APPENDIX 20

SPECIFIC LABELLING REQUIREMENTS

22.	ATORVASTATIN
23.	AZACITIDINE
24.	AZATHIOPRINE
25.	AZITHROMYCIN
26.	BEE POLLEN
27.	BENZODIAZEPINE
28.	BENZOYL PEROXIDE
29.	BENZYL ALCOHOL
30.	BERBERINE ALKALOIDS – NATURAL OCCURING BERBERINE E.G. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA ETC.
31.	BETA-LACTAM ANTIBIOTICS (INCLUDING COMBINATION PRODUCTS)
32.	BISPHOSPHONATE (ALENDRONATE, CLODRONATE, IBANDRONIC ACID, PAMIDRONATE, RISEDRONATE, ZOLEDRONIC ACID)
33.	BLACK COHOSH (*CIMICIFUGA RACEMOSA*)
34.	BORTEZOMIB
35.	BOSWELLIA SPP.
36.	BROMHEXINE
37.	BROMPHENIRAMINE
38.	CAMPHOR
39.	CANAGLIFLOZIN (INCLUDING COMBINATION PRODUCTS)
40.	CARBAMAZEPINE
41.	CARBIMAZOLE OR METHIMAZOLE (THIAMAZOLE)
42.	CARBOCISTEINE
43.	CEFTRIAXONE
44.	CETIRIZINE
45.	*CHELIDONIUM MAJUS*
46.	CHITOSAN

177.	PENICILLIN
178.	PHENIRAMINE
179.	PHENYLEPHRINE
180.	PIPERACILLIN (INCLUDING COMBINATION PRODUCTS)
181.	PIROXICAM
182.	PRAVASTATIN
183.	PREDNISONE AND PREDNISOLONE
184.	PROMETHAZINE HCL
185.	PROPAFENONE
186.	PROPOFOL
187.	PROPOLIS (ORAL)
188.	PROPOLIS (TOPICAL)
189.	PROPYLTHIOURACIL
190.	PSEUDOEPHEDRINE
191.	PROTON PUMP INHIBITORS (PPI)
192.	PSYCHOTROPIC PRODUCTS
193.	PSYLLIUM/ PLANTAGO (SEED/ HUSK)
194.	RED YEAST RICE (MONASCUS PURPUREUS)
195.	RETINOID (ORAL)
196.	RETINOIDS (ORAL) INDICATED FOR TREATMENT OF SKIN DISEASES
197.	RETINOIDS (TOPICAL)
198.	RHUBARB (e.g. *Radix et Rhizoma Rhei / Rheum Palmatum / Rheum Officinalis*) – root part
199.	RISPERIDONE
200.	RITUXIMAB
201.	RIVASTIGMINE
202.	ROCURONIUM

203.	ROSIGLITAZONE
204.	ROSUVASTATIN
205.	ROXITHROMYCIN
206.	ROYAL JELLY
207.	SACCHAROMYCES BOULARDII
208.	SALBUTAMOL
209.	SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)
210.	SEDATIVE – HYPNOTIC PRODUCTS
211.	SELENIUM SULPHIDE
212.	SENNA (CASSIA SPP.) – fruit/ pod/ semen / leaf
213.	SERTRALINE
214.	SIMVASTATIN
215.	SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS
216.	SODIUM METABISULPHITE (EXCIPIENT)
217.	SODIUM VALPROATE
218.	ST. JOHN'S WORT *(Hypericum perforatum)*
219.	STATINS
220.	STRONTIUM RANELATE
221.	SUCCINYLATED GELATIN (MODIFIED FLUID GELATIN)
222.	SULFASALAZINE
223.	SULPHONAMIDES/ TRIMETHOPRIM
224.	SYNTHETIC SALMON CALCITONIN
225.	TABEBUIA SPP. (PAU D'ARCO)
226.	TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 (EXCIPIENT)
227.	TEMOZOLAMIDE
228.	TERBUTALINE

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
1.	**5-ALPHA REDUCTASE INHIBITOR (5-ARI)** The following statement shall be included in the package inserts of products containing 5-ARI: **1. PRODUCT CONTAINING FINASTERIDE 5MG** **WARNINGS AND PRECAUTIONS** **Increased Risk of High-Grade Prostate Cancer** Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo). 5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. **Increased Risk of Breast Cancer** Breast cancer has been reported in men taking finasteride 5 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS: POST MARKETING EXPERIENCE** Male breast cancer **2. PRODUCT CONTAINING FINASTERIDE 1MG** **WARNINGS AND PRECAUTIONS** **Increased Risk of High-Grade Prostate Cancer** Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of [Brand Name]) in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	another 5-alpha reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo). 5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. **Increased Risk of Breast Cancer** Breast cancer has been reported in men taking finasteride 1 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS: POST MARKETING EXPERIENCE** Male breast cancer **3. <u>PRODUCT CONTAINING DUTASTERIDE</u>** **WARNINGS AND PRECAUTIONS** **Increased Risk of High-Grade Prostate Cancer** In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus placebo 0.5%). In a 7-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (finasteride 5 mg, PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%). 5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. **References:** **Directive No. 9, 2011**. ***Bil. (19) dlm. BPFK/PPP/01/03 Jilid 1***. *Direktif Untuk Memuatkan Kenyataan Amaran Berkaitan Dengan Risiko High-Grade Prostate Cancer dalam Sisip Bungkusan Semua Produk 5-Alpha Reductase Inhibitor (5-ARI)* **Directive No. 3, 2012. *Bil. (64) dlm. BPFK/PPP/01/03 Jilid 1***. *Direktif Untuk Mengemaskini Sisip Bungkusan Produk Yang Mengandungi Finasteride Dengan Memuatkan Amaran Berkaitan dengan Risiko Kanser Payudara Di Kalangan Pesakit Lelaki*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
2.	**ABIRATERONE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Abiraterone; **Package Insert** **a) Warnings and Precautions** Hypoglycaemia Cases of hypoglycaemia have been reported when [product name] was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide; therefore, blood sugar should be measured frequently in patients with diabetes. **b) Interactions:** In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1000mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Taking other medicines Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is important because [product name] may increase the effects of a number of medicines including some medicines for diabetes. Your doctor may want to change the dose of these medicines. **Reference: Directive No. 2, 2021.** ***NPRA.600-1/9/13 (12)*** *Direktif Untuk Semua Produk Yang Mengandungi Abiraterone: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hypoglycaemia Akibat Interaksi Ubat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
3.	**ACE INHIBITORS** The following statement shall be included in the package inserts of products containing ACE inhibitors: **WARNINGS AND PRECAUTIONS** • INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY **USE IN PREGNANCY** • INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY **Reference:** ***Circular Bil. (65) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Sisip Bungkusan Bagi Semua Produk yang Mengandungi ACE Inhibitors Sebagai Bahan Tunggal Atau Kombinasi*
4.	**ACETAZOLAMIDE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Acetazolamide; **Package Insert** **a) Warnings and Precautions:** Adverse reactions common to all sulfonamide derivatives may occur such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP). If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation. **b) Adverse Effects / Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known: Severe skin reactions [including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP)] **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	[Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 16, 2018.** ***BPFK/PPP/07/25 (16) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Acetazolamide: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*
5.	**ACETYLCYSTEINE** 1. The following warning shall be included in the package inserts of products containing Acetylcysteine : **CONTRAINDICATIONS** Contraindicated in children below two (2) years of age. **Reference: Directive No. 11, 2010.** ***Bil. (7) dlm. BPFK/PPP/01/03 Jilid 1*** *Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip Bungkusan Semua Produk Carbocysteine, Acetylcysteine Dan Methylcarbocysteine (Mecysteine)* 2. The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) for products containing acetylcysteine; **2.1 Injectable products with the indication as antidote for paracetamol overdose** **Package Insert** **a) Warnings and Precautions:** Hypersensitivity Reactions Serious acute hypersensitivity reactions during acetylcysteine administration including rash, hypotension, wheezing, and/or shortness of breath, have been observed in patients receiving intravenous acetylcysteine for paracetamol overdose and occurred soon after initiation of the infusion (see Adverse Effects/ Undesirable Effects). If a severe hypersensitivity reaction occurs, immediately stop the infusion of acetylcysteine and initiate appropriate treatment.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Acute flushing and erythema of the skin may occur in patients receiving acetylcysteine intravenously. These reactions usually occur 15 to 60 minutes after initiating the infusion and often resolve spontaneously despite continued infusion of acetylcysteine. If a reaction to acetylcysteine involves more than simply flushing and erythema of the skin, it should be treated as a hypersensitivity reaction. Management of less severe hypersensitivity reactions should be based upon the severity of the reaction and include temporary interruption of the infusion and/or administration of antihistaminic drugs. The acetylcysteine infusion may be carefully restarted after treatment of the hypersensitivity symptoms has been initiated; however, if the hypersensitivity reaction returns upon re-initiation of treatment or increases in severity, acetylcysteine should be discontinued and alternative patient management should be considered. **b) Adverse Effects / Undesirable Effects:** <u>Immune System Disorders:</u> Anaphylactic/ anaphylactoid reaction <u>Skin and Subcutaneous Tissue Disorders:</u> Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects. **2.2 All other products (not include Injectable products for treatment of paracetamol overdose)** **<u>Label</u>** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **<u>Package Insert</u>** **Adverse Effects / Undesirable Effects:** <u>Immune System Disorders:</u> Anaphylactic / anaphylactoid reaction

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Skin and Subcutaneous Tissue Disorders: Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects. **Consumer Medication Information Leaflet (RiMUP)** **Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **Reference: Directive No. 14, 2018.** ***BPFK/PPP/07/25 (14) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine dan Acetylcysteine: Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Anaphylactic/ Anaphylactoid Reaction dan Severe Cutaneous Adverse Reactions (SCARs)*
6.	**ACETYLSALICYLIC ACID (ASPIRIN)** For products containing Acetylsalicylic acid, the following warning shall be included on the labels in two languages (*Bahasa Malaysia* and English): ***AMARAN*** *TIDAK BOLEH DIBERI KEPADA KANAK-KANAK BERUMUR KURANG DARIPADA 16 TAHUN.* **WARNING** NOT TO BE GIVEN TO CHILDREN UNDER 16 YEARS OF AGE.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
7.	**ACTIVATED CHARCOAL/ ATTAPULGITE** 1. The following boxed warning shall be included on the labels of products containing Activated charcoal/ attapulgite: **NOT RECOMMENDED FOR TREATMENT OF DIARRHOEA IN CHILDREN UNDER 6 YEARS OF AGE** 2. The following statements shall be included in the package inserts of products containing Activated charcoal/ attapulgite: **Not recommended for treatment of diarhoea in children under 6 years of age** **WARNINGS AND PRECAUTIONS** Activated charcoal/ attapulgite may interfere with the absorption of other drugs, including antibiotics, when administered concurrently. Appropriate fluid and electrolyte therapy should be given to protect against dehydration. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative.
8.	**ALBENDAZOLE & BENZIMIDAZOLE ANTIHELMINTICS** The following statement shall be included on the labels and in the package inserts of products containing Albendazole or Benzimidazole antihelmintics: **SHOULD NOT BE ADMINISTERED DURING CONFIRMED OR SUSPECTED PREGNANCY**
9.	**ALFALFA (*MEDICAGO SATIVA*)** The following boxed warning shall be included on the labels of products containing Alfalfa (*Medicago sativa*): This product contains **Alfalfa** (*Medicago sativa*). Individual with a predisposition to **systemic lupus erythematosus** should consult their physician before consuming this product.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
10.	**ALLOPURINOL** The following statement shall be included in the package inserts of products containing Allopurinol: **WARNINGS AND PRECAUTIONS** Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction. Hypersensitivity to allopurinol usually appears after some weeks of therapy, and more rarely immediately after beginning treatment. In some instances, a skin rash may be followed by more severe reactions such as exfoliative, urticarial and purpuric lesion as well as Stevens-Johnson syndrome, and/or generalized vasculitis, irreversible hepatotoxicity and even death.
11.	**ALPHA LIPOIC ACID** The following statement shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) for health supplement products containing alpha lipoic acid; **Warning** Please consult your doctor/pharmacist before using this product if you are on other medicines. There may be a potential for interactions or side effects. **Reference: Directive No. 2, 2022.** *NPRA.600-1/9/13 (2)Jld.1 Direktif Berkenaan Penambahan Pernyataan Amaran Bagi Produk Suplemen Kesihatan Yang Mengandungi Bahan Aktif Alpha Lipoic Acid*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
12.	**AMBROXOL** The following warning shall be included in the package insert, label and Consumer Medication Information Leaflet (RiMUP) of products containing Ambroxol: **Package Insert** **a) Warnings and Precautions:** Very rare cases of chronically associated severe skin impairments such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported. In most cases, these could be explained by the severity of the underlying disease or concomitant administration of another drug. In the early stages of such severe skin reactions, initially only nonspecific flu-like symptoms appear, e.g. fever, arthralgia, runny nose, cough, and sore throat. If skin or mucous membrane damage occurs, seek medical advice immediately and discontinue treatment as a precaution. **b) Adverse Effects/Undesirable Effects:** Immune System Disorders Frequency not known: Anaphylactic reactions including anaphylactic shock. Skin and Subcutaneous Skin Disorders Frequency not known: Severe skin reactions (including Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP). **Label and Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: 1) severe allergy: breathing difficulties, light headedness, skin swellings or rash 2) severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 1, 2018.** ***BPFK/PPP/07/25 (1) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Ambroxol dan Bromhexine: Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Anafilaksis dan Severe Cutaneous Adverse Reactions (SCARs)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
13.	**AMIODARONE** The following <u>boxed warning</u> shall be <u>included on the package inserts</u> of products containing Amiodarone: This product is to be used only by a registered medical practitioner with experience in cardiology. The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing amiodarone; **<u>Package Insert</u>** **a) Warnings & Precautions:** <u>Transplantation</u> In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of primary graft dysfunction (PGD). PGD is a life-threatening complication of heart transplantation that presents as left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see section Adverse Effects). Severe PGD may be irreversible. For patients who are on the heart transplant waiting list, consideration should be given to use an alternative antiarrhythmic drug as early as possible before transplant. **b) Adverse Effects/ Undesirable Effects:** <u>Injury, poisoning and procedural complications</u> Frequency 'not known': Potentially fatal primary graft dysfunction post cardiac transplant (See section Warnings and Precautions) **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** <u>Before you start to use it:</u> If you are on a heart transplant waiting list, your doctor may change your treatment. This is because taking amiodarone before heart transplantation has shown an increased risk of a life-threatening complication (primary graft dysfunction) in which the transplanted heart stops working properly within the first 24 hours after surgery.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Side effects: Frequency not known: • Life-threatening complication after heart transplantation (primary graft dysfunction) in which the transplanted heart stops working properly **Reference: Directive No. 22, 2025.** ***NPRA.600-1/9/13 (69)Jld.1*** *Direktif untuk semua produk yang mengandungi amiodarone: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Penguna (RiMUP) dengan maklumat keselamatan berkaitan risiko primary graft dysfunction (PGD) selepas pemindahan jantung (heart transplantation)*
14.	**AMOXICILLIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Amoxicillin (including combination products); **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Skin and subcutaneous tissue disorders: Frequency 'very rare': Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Stop taking [product name] and contact your doctor immediately if you experience any of the following: • Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature and enlarged lymph nodes. **Reference: Directive No. 8, 2018.** ***BPFK/PPP/07/25 (8) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Amoxicillin Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Memperkukuhkan Maklumat Berkaitan Severe Cutaneous Adverse Reactions (SCARs) Pada Bahagian Warnings & Precautions dan Amaran Berkaitan Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Pada Bahagian Side Effects*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
15.	**ANASTROZOLE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing anastrozole: **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Psychiatric disorders Frequency 'very common': Depression **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Frequency 'very common': Depression **Reference: Directive No. 21, 2021**. ***NPRA.600-1/9/13(31)*** *Direktif Untuk Semua Produk Yang Mengandungi Anastrozole: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Depression*
16.	**ANTIDEPRESSANTS** The following statement shall be included in the package inserts of products used as antidepressants: **WARNINGS AND PRECAUTIONS** Suicidality in Children and Adolescents • Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. • Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need. • Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. • Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber. • The indication(s) approved in paediatric for the particular drug should be clearly

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	stated / included. **Reference:** ***Bil.(41)dlm. BPFK/02/5/1.3*** *Keputusan Pihak Berkuasa Kawalan Dadah (PBKD) Berhubung Tambahan Amaran Berkaitan Dengan "Suicidality In Children and Adolescents Treated With Antidepressants"* **CITALOPRAM, DESVENLAFAXINE, DULOXETINE, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VENLAFAXINE AND VORTIOXETINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine and vortioxetine; **Package Insert** **a) Pregnancy and lactation:** Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth. *An additional statement should also be included in the package insert of vortioxetine: Although no studies have investigated an association between vortioxetine treatment and postpartum haemorrhage, there is a potential risk, taking into account the related mechanism of action. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use <product name>:** Before you start to use it: If you take <product name> near the end of your pregnancy there may be an increased risk of heavy vaginal bleeding shortly after birth, especially if you have a history of bleeding disorders. Your doctor should be aware that you are taking <product name> so they can advise you. **Reference: Directive No. 23, 2021.** ***NPRA.600-1/9/13 (33)*** *Direktif Untuk Semua Produk Yang Mengandungi Citalopram, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Venlafaxine dan Vortioxetine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Postpartum Haemorrhage (PPH)* **CITALOPRAM, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VENLAFAXINE, DESVENLAFAXINE AND DULOXETINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine,

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	desvenlafaxine and duloxetine; **<u>Package Insert</u>** **a) Warnings & Precautions:** Sexual dysfunction Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) While you are using it:** Medicines like [Product name] (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction. In some cases, these symptoms have continued after stopping treatment. **Reference: Directive No. 23, 2025.** ***<u>NPRA.600-1/9/13 (70)Jld.1</u>*** *Direktif untuk semua produk yang mengandungi Selective Serotonin Reuptake Inhibitor (SSRI) dan Serotonin-Norepinephrine Reuptake Inhibitor (SNRI): Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko sexual dysfunction berterusan*
17.	**ANTIEPILEPTICS** The following <u>statement</u> shall be <u>included in the package inserts</u> of products used as antiepileptics: **WARNINGS AND PRECAUTIONS** Potential for an increase in risk of suicidal thoughts or behaviors. **Reference:** ***<u>Bil. (43) dlm. BPFK/PPP/01/03</u>*** *Kenyataan Amaran Berkaitan Dengan "Potential for an Increase in Risk of Suicidal Thoughts or Behaviours" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Antiepileptik*
18.	**ANTIPSYCHOTIC AGENTS** **1. <u>ALL ANTIPSYCHOTIC AGENTS</u>** The following statement shall be <u>included in the package inserts</u> of products containing antipsychotic: **PREGNANCY AND LACTATION** Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation. [BRAND NAME] should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. **Reference:** ***Bil. (16) dlm. BPFK/PPP/01/03 Jilid 1*** *Directif Kenyataan Amaran Berkaitan Dengan Risiko Extrapyrimidal and/or Withdrawal Symptoms Bagi Neonat Yang Terdedah Kepada Produk Antipsikotik Semasa Trimester Ketiga Kehamilan Pada Sisip Bungkusan Semua Produk Antipsikotik* **2. ATYPICAL ANTIPSYCHOTIC AGENTS** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Atypical Antipsychotic Agent; **Package Insert** **a) Warnings and Precautions:** **[replace *Direktif Bil. (31) dlm BPFK/02/5/1.3: Tambahan amaran berkaitan dengan hyperglycemia bagi keluaran 'atypical antipsychotic agents' bertarikh 20 Julai 2004*]** Hyperglycaemia and Diabetes Mellitus: Hyperglycaemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity,

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. **b) Adverse Effects/Undesirable Effects:** <u>Nervous System Disorders:</u> Restless legs syndrome <u>Respiratory, Thoracic and Mediastinal Disorders:</u> Sleep apnoea* *Atypical antipsychotic drugs, such as <active ingredient>, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, [product name] should be prescribed with caution. <u>Renal and Urinary Disorders:</u> Urinary retention **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** <u>Before you start to use it</u> Talk to your doctor or pharmacist if you: • have or are at a risk of having diabetes (e.g. being overweight or a family history of diabetes). Your doctor should check your blood sugar before you start taking [product name] and regularly during treatment. **b) Side Effects:** Talk to your doctor or pharmacist if you experience: • Increases in blood sugar level and/or symptoms of high blood sugar (e.g. increased thirst, increased hunger, and frequent urination) • Unpleasant leg sensations and an intense urge to move the legs (restless legs syndrome) • Trouble breathing during sleep (sleep apnoea)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• Difficulty or inability to pass urine (urinary retention) **Reference: Directive No. 26, 2018.** ***BPFK/PPP/07/25 (26) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Atypical Antipsychotic Agent: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RIMUP) Dengan Maklumat Berkaitan Risiko Restless Legs Syndrome, Sleep Apnoea, Urinary Retention, Hyperglycaemia dan Diabetes Mellitus*
19.	**ARGININE** The following statement shall be included on the labels and in the package inserts of oral preparations containing Arginine for **health supplement products**: **WARNINGS AND PRECAUTIONS** Arginine is not recommended for patients following a heart attack. **Reference:** ***Bil. (64) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Lebal dan Sisip Bungkusan Produk Suplemen Kesihatan Oral Yang Mengandungi Arginine Berkaitan Dengan "Arginine is not recommended for patients following a heart attack"*
20.	**ARIPIPRAZOLE** The following statements shall be included in the package insert and RiMUP of products containing Aripiprazole: **Package Insert** **a) Warnings and Precautions:** Pathological gambling and impulse-control problems Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, or other urges, while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases urges were reported to have stopped when the dose was reduced or the medication was discontinued. Patients who are at higher risk for impulse-control problems (e.g. personal or family history of obsessive-compulsive disorder, impulse-control disorder, bipolar disorder, impulsive personality, alcoholism, drug abuse or other addictive behaviours) would require closer monitoring for new or worsening of uncontrollable urges. Impulse-control problems may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Adverse Effects/Undesirable Effects: Psychiatric disorders Pathological gambling, hypersexuality, impulse-control problems (See Section Warnings and Precautions). **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]** Before you start to use it Talk to your doctor or pharmacist if you have: • a history of excessive gambling or other unusual urges (e.g. increased sexual urges, binge or compulsive eating, and compulsive shopping). **b) Side effects:** Side effects may include: • Excessive gambling or other unusual urges, such as increased sexual urges, binge or compulsive eating, and compulsive shopping. If you or your family members notice that you are having unusual urges or behaviours, talk to your doctor or pharmacist. **Reference: Directive No. 22, 2017.** ***BPFK/PPP/07/25 (27) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Aripripazole: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Pathological Gambling dan Impulse-Control Problems*
21.	**ASPARTAME** The following statement shall be included on the labels and in the package inserts of products containing Aspartame: **WARNING** Unsuitable for phenylketonurics.
22.	**ATORVASTATIN** The following statement shall be included in the package inserts of products containing Atorvastatin: **DOSAGE AND ADMINISTRATION** Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with [Product Name] should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing [Product Name] and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with [Product Name] should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with [Product Name] should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. **WARNINGS AND PRECAUTIONS** Skeletal Muscle Effects Physicians considering combined therapy with atorvastatin and fibrates, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin (≥1g/day) should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy. All generic products containing Atorvastatin should update their package inserts respectively according to the innovator's information such as parts for Interactions, Pharmacokinetics and other parts deemed relevant. **Reference: Directive No. 10, 2014.** ***Bil. (17) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Atorvastatin: Mengehadkan Dos Penggunaan Atorvastatin Untuk Mengurangkan Risiko Kecederaan Otot*
23.	**AZACITIDINE** The following statements shall be included in the package insert for products containing azacitidine; **Package Insert**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	a) Warnings & Precautions: Differentiation syndrome Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving injectable azacitidine. Differentiation syndrome may be fatal and symptoms and clinical finding include respiratory distress, pulmonary infiltrates, fever, rash, pulmonary oedema, peripheral oedema, rapid weight gain, pleural effusions, pericardial effusions, hypotension and renal dysfunction. Treatment with high-dose IV corticosteroids and haemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation of injectable azacitidine should be considered until resolution of symptoms and if resumed, caution is advised. **b) Adverse Effects/ Undesirable Effects:** Neoplasms benign, malignant and unspecified (including cysts and polyps) Frequency 'Not known': Differentiation syndrome* *= rarely fatal cases have been reported Skin & subcutaneous tissue disorders Frequency 'not known': Cutaneous vasculitis **References:** **Directive No. 5, 2023.** *NPRA.600-1/9/13 (23)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Azacitidine: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Differentiation Syndrome (DS)* **Directive No. 13, 2024.** *NPRA.600-1/9/13 (44)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Azacitidine (Sediaan Injeksi Sahaja) : Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Cutaneous Vasculitis*
24.	**AZATHIOPRINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing azathioprine; **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Immune system disorders Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following

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	administration of azathioprine. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhea, fever, rigors, exanthema, rash, **erythema nodosum**, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis. In many cases, rechallenge has confirmed an association with azathioprine. Immediate withdrawal of azathioprine and institution of circulatory support where appropriate have led to recovery in the majority of cases. Other marked underlying pathology has contributed to the very rare deaths reported. Following a hypersensitivity reaction to azathioprine, the necessity for continued administration of azathioprine should be carefully considered on an individual basis. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects:** Tell your doctor or pharmacist if you notice any of the following serious side effects. Allergic reactions, the signs may include: • general tiredness, dizziness, feeling sick (nausea), being sick (vomiting), diarrhoea, fever, chills • redness of the skin, skin nodules or a skin rash (including blisters, itching or peeling skin) • Pain in the muscles or joints • Drop in blood pressure • Changes in urine volume and color (kidney problems) • Yellowing of the skin or the whites of the eyes (jaundice) **Reference: Directive No. 7, 2022.** *NPRA.600-1/9/13 (7)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Azathioprine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Erythema Nodosum dan Menyelaraskan Maklumat Keselamatan Lain Berkenaan Reaksi Hipersensitiviti*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
25.	**AZITHROMYCIN** 1. The following statement shall be included in the <u>package insert and RIMUP</u> of **all products containing Azithromycin**: **<u>Package Insert</u>** **a) Warnings and Precautions** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/ Undesirable Effects** <u>Skin and Subcutaneous Tissue Disorders:</u> Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation 2. The following statement shall be <u>included in the package insert and RiMUP</u> of **products containing azithromycin (except topical/ external and ophthalmic preparations);** **<u>Package Insert</u>** **a) Warnings and Precautions:** **<u>Prolongation of the QT interval</u>** Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see section 4.8). Prescribers should consider

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including:

- Patients with congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in infants (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs.

b) Adverse Effects/Undesirable Effects:

Postmarketing Experience:

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see **Warnings and Precautions**).

Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis.

Consumer Medication Information Leaflet (RiMUP)

Side Effects

If you notice that the child vomits and/or irritability with feeding occurs, contact doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS).

References:

Directive No. 3, 2016. ***Bil. (34) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Azithromycin (Formulasi Sistemik): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Kesan Advers QT Prolongation Dan Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)*

Directive No. 28, 2017. ***BPFK/PPP/07/25 (33) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin Dan Erythromycin Kecuali Persediaan Topikal/ Eksternal Dan Ubat Untuk Kegunaan Mata: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)*

Directive No. 22, 2018. ***Bil. (22) dlm. BPFK/PPP/07/25 Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin dan Roxithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Berkaitan Severe Cutaneous Adverse Reactions (SCARs)
26.	**BEE POLLEN** The following statement shall be included on the labels and in the package inserts of products containing bee pollen: This product contains Bee Pollen and may cause severe allergic reactions, including fatal anaphylactic reactions in susceptible individuals. Asthma and allergy sufferers may be at greater risks.
27.	**BENZODIAZEPINE** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing benzodiazepine: **Package Insert** **a) Warnings and Precautions:** Risks from Concomitant Use with Opioids Profound sedation, respiratory depression, coma, and death may result from the concomitant use of [product name] with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use. If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when [product name] is used with opioids. Advise

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (See Drug Interactions). **b) Interactions:** Opioids Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death. The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation. **Consumer Medication Information Leaflet (RiMUP)** **a) Taking other medicines:** Taking [product name] with an opioid medicine (medicine to relieve pain) can depress your central nervous system. Inform your doctor if you are currently taking any opioid medicine. Seek medical attention immediately if you or the person taking this medication experience(s) symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness. **Reference: Directive No. 23, 2017.** ***BPFK/PPP/07/25 (28) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Opioid dan Benzodiazepin : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
28.	**BENZOYL PEROXIDE** The following statement shall be included on the labels and in the package inserts of products containing Benzoyl peroxide: **WARNING** Do not use this medication if you have sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possible swelling.
29.	**BENZYL ALCOHOL** The following statement shall be included on label and in package insert of parenteral products containing Benzyl alcohol: **As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age.** **Not to be used in neonates.**
30.	**BERBERINE ALKALOIDS – NATURALLY OCCURING BERBERINE e.g. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA etc.** The following statement shall be included on the label and in the package insert of products containing berberine alkaloid: **WARNING** Not to be taken by babies, children under 12 years of age, pregnant women or lactating mothers. Consult your practitioner if you have conditions such as: -Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency -Haemolytic anemia -Glaucoma -Diabetes -High Blood Pressure -History of cardiovascular disease -If you are using Paclitaxel, Cyclosporin, or other chemotherapeutic agents. **Reference:** ***Bil.(22)dlm.BPFK/PPP/06/12 Jld.26*** *Kawalan Produk Mengandungi Bahan Aktif Yang Mempunyai Berberine Secara Semulajadi*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
31.	**BETA-LACTAM ANTIBIOTICS (INCLUDING COMBINATION PRODUCTS)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing beta-lactam antibiotics (including combination products); **Package Insert** **a) Warnings and Precautions:** Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with [product name], careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, [product name] must be discontinued immediately and appropriate alternative therapy instituted. **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 2, 2019.** ***BPFK/PPP/07/25 (2) Jld.3*** *Direktif Untuk Semua Produk Antibiotik Kumpulan Beta-Lactam Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*
32.	**BISPHOSPHONATE (ALENDRONATE, CLODRONATE, IBANDRONIC ACID, PAMIDRONATE, RISEDRONATE, ZOLEDRONIC ACID)** The following statement shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Bisphosphonate (Alendronate, Clodronate, Ibandronic acid, Pamidronate, Risedronate, Zoledronic acid): **Package Insert** **WARNINGS AND PRECAUTIONS:** Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections. **ADVERSE EFFECTS / UNDESIRABLE EFFECTS:** Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction). **Consumer Medication Information Leaflet (RiMUP)** **SIDE EFFECTS:** Very rare • Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear. **Reference: Directive No. 7, 2016.** ***BPFK/PPP/07/25(38)*** *Direktif Bagi Semua Produk Yang Mengandungi Bisphosphonate (Alendronate, Clodronate, Ibandronic Acid, Pamidronate, Risedronate, Zoledronic Acid) Dengan Risiko Kesan Advers Berkaitan Osteonecrosis of the External Auditory Canal*
33.	**BLACK COHOSH (*CIMICIFUGA RACEMOSA*)** The following statement shall be included on the labels and in the package inserts of products containing Black Cohosh (*Cimicifuga Racemosa*): **WARNING** Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine and consult your doctor immediately. Patients using herbal medicinal products should tell their doctor about it. **Reference:** ***Bil. (61) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk Tradisional/Semulajadi Yang Mengandungi Black Cohosh (Cimicifugae Racemosae) Berkaitan Dengan "Serious Hepatic Reactions"*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
34.	**BORTEZOMIB** The following statements shall be <u>included in the package insert</u> for products containing bortezomib: **<u>Package Insert</u>** **a) Adverse Effects/ Undesirable Effects:** <u>Nervous system disorders</u> Frequency 'rare': Guillain-Barré syndrome, Demyelinating polyneuropathy **Reference: Directive No. 20, 2021.** ***NPRA.600-1/9/13(30)*** *Direktif Untuk Semua Produk Yang Mengandungi Bortezomib: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Guillain-Barré Syndrome dan Demyelinating Polyneuropathy*
35.	**BOSWELLIA SPP.** The following statement shall be <u>included on label and package inserts</u> of oral products containing *Boswellia spp:* **WARNING:** Please consult your doctor/pharmacist before using this product if you are on other medicines. **Reference: Directive No. 10, 2018.** ***BPFK/PPP/07/25(10)Jld.2*** *Direktif Penambahan Kenyataan Amaran Bagi Semua Produk Yang Mengandungi Boswellia Spp.*
36.	**BROMHEXINE** The following <u>warning</u> shall be <u>included in the package insert, label and Consumer Medication Information Leaflet (RiMUP)</u> of products containing Bromhexine : **<u>Package Insert</u>** **a) Warnings and Precautions:** Very rare cases of chronically associated severe skin impairments such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported. In most cases, these could be explained by the severity of the underlying disease or concomitant administration of another drug. In the early stages of such severe skin reactions, initially only nonspecific flu-like symptoms appear, e.g. fever, arthralgia, runny nose, cough, and sore throat. If

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	skin or mucous membrane damage occurs, seek medical advice immediately and discontinue treatment as a precaution. **b) Adverse Effects/Undesirable Effects:** Immune System Disorders Frequency not known: Anaphylactic reactions including anaphylactic shock. Skin and Subcutaneous Skin Disorders Frequency not known: Severe skin reactions (including Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP). **Label and Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: 1) severe allergy: breathing difficulties, light headedness, skin swellings or rash 2) severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 1, 2018.** ***BPFK/PPP/07/25 (1) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Ambroxol dan Bromhexine : Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Anafilaksis dan Severe Cutaneous Adverse Reactions (SCARs)*
37.	**BROMPHENIRAMINE** The following statement shall be included on the labels and in the package inserts of liquid oral products containing Brompheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
38.	**CAMPHOR** 1. The following <u>boxed warning</u> shall be <u>included on the labels</u> of products containing Camphor: CAN CAUSE CONVULSION **CONTRAINDICATED** IN CHILDREN BELOW 2 YEARS OF AGE. CAUTION MUST BE EXERCISED WHEN OLDER CHILDREN ARE TREATED **AVOID DIRECT** APPLICATION INTO THE NOSTRILS 2. The following <u>warnings and precautions</u> shall be <u>included in the package insert</u> of products containing Camphor: **WARNINGS AND PRECAUTIONS** This product is contraindicated in **children** below 2 years of age. Caution must be exercised when older children are treated. It is dangerous to place any camphor containing product into the nostril of children. A small amount applied this way may cause immediate collapse.
39.	**CANAGLIFLOZIN (INCLUDING COMBINATION PRODUCTS)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing canagliflozin (including combination products): **<u>Package Insert</u>** **a) Interactions:** <u>Lithium</u> The concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more closely during treatment with canagliflozin, especially during initiation and dosage changes. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]- taking other medicines** In particular, tell your doctor if you are taking any of the following medicines: • lithium (a medicine used to treat bipolar disorder) **Reference: Directive No. 9, 2024.** *<u>NPRA.600-1/9/13 (40)Jld.1</u> Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	(Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat
40.	**CARBAMAZEPINE** The following statement shall be included in the package insert of products containing Carbamazepine: Severe dermatologic reactions including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) have been reported with carbamazepine. Patients treated with carbamazepine should closely be monitored for signs of hypersensitivity reactions, particularly during the first month of therapy. Immediate discontinuation of therapy should be made when cutaneous reactions occur.
41.	**CARBIMAZOLE OR METHIMAZOLE (THIAMAZOLE)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing carbimazole or methimazole (thiamazole): **Package Insert** **a) Contraindications:** Patients with a history of acute pancreatitis after administration of carbimazole or active metabolite, methimazole (thiamazole). **b) Warnings and Precautions:** Carbimazole may cause white cell disorders such as neutropenia and agranulocytosis, which may be fatal if treatment with carbimazole is not stopped promptly. These reactions usually occur during the first 3 months of therapy, and in most cases, are reversible on stopping treatment. Since agranulocytosis can develop very rapidly, periodic leucocyte counts alone may not be effective in the early detection of these reactions. There have been post-marketing reports of acute pancreatitis in patients receiving carbimazole or its active metabolite, methimazole (thiamazole). In case of acute pancreatitis, carbimazole or methimazole (thiamazole) should be discontinued immediately. Carbimazole or methimazole (thiamazole) must not be given to patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite methimazole (thiamazole). Re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Women of childbearing potential and pregnancy Women of childbearing potential have to use effective contraceptive measures during treatment. The use of carbimazole or methimazole (thiamazole) in pregnant women must be based on the individual benefit/risk assessment. If carbimazole or methimazole (thiamazole) is used during pregnancy, the lowest effective dose without additional administration of thyroid hormones should be administered. Close maternal, foetal and neonatal monitoring is warranted. **c) Fertility, Pregnancy and Lactation:** Women of childbearing potential and pregnancy Women of childbearing potential have to use effective contraceptive measures during treatment (see Section Warnings and Precautions). Pregnancy Carbimazole or methimazole (thiamazole) crosses the placenta but, provided the mother's dose is within the standard range and her thyroid status is monitored; there is no evidence of neonatal thyroid abnormalities. Studies have shown that the incidence of congenital malformations is greater in the children of mothers whose hyperthyroidism has remained untreated than in those who have been treated with carbimazole or methimazole (thiamazole). However, cases of congenital malformations have been observed following the use of carbimazole or its active metabolite, methimazole (thiamazole) during pregnancy. A causal relationship of these malformations, especially choanal atresia and aplasia cutis congenita (congenital scalp defects), to transplacental exposure to carbimazole and methimazole (thiamazole) cannot be excluded. Therefore, the use of carbimazole or methimazole (thiamazole) in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section Warnings and Precautions). Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported. Therefore, carbimazole or methimazole (thiamazole) should be used in pregnancy only when propylthiouracil is not suitable. If carbimazole or methimazole (thiamazole) is used in pregnancy, the dose must be regulated by the patient's clinical condition. The lowest dose possible should be used, and this can often be discontinued three or four weeks before term, in order to reduce the risk of neonatal complications. The blocking-replacement regimen should not be used during pregnancy since very little thyroxine crosses the placenta in the last trimester.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications. Carbimazole or methimazole (thiamazole) is able to cross the human placenta. Based on human experience from epidemiological studies and spontaneous reporting, carbimazole or methimazole (thiamazole) is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses. Reported malformations include aplasia cutis congenita, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly, and ventricular septal defect. Carbimazole or methimazole (thiamazole) must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. If carbimazole or methimazole (thiamazole) is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended (see section Warnings and Precautions). **d) Adverse Effects / Undesirable Effects:** SOC Gastrointestinal disorders Frequency "Not Known": Acute pancreatitis **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [Product Name]:** When you must not use it: - Do not use [Product name] if you had inflammation of the pancreas (acute pancreatitis) after administration of carbimazole or thiamazole in the past. Before you start to use it: - [Product name] can cause harm to an unborn baby. If you can get pregnant, use reliable contraception from the time you start treatment and during treatment. - If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor straight away. Your treatment with [product name] may need to be continued during pregnancy if the potential benefit outweighs the potential risk to you and your unborn baby. **b) While you are using it:** Things to be careful of:

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	- Tell your doctor straight away if you develop fever or abdominal pain, which may be signs of inflammation of the pancreas (acute pancreatitis). [Product name] may need to be discontinued. **c) Side Effects:** - Inflammation of the pancreas (acute pancreatitis) **Reference: Directive No. 19, 2019.** ***BPFK/PPP/07/25 (19) Jld. 3*** *Direktif Untuk Semua Produk Yang Mengandungi Carbimazole atau Methimazole (Thiamazole): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RIMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Pankreatitis Akut (Acute Pancreatitis) dan Pengukuhan Maklumat Keselamatan Berkaitan Risiko Kecacatan Kongenital (Congenital Malformation)*
42.	**CARBOCISTEINE** The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) of products containing carbocisteine: **Label** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Immune System Disorders: Anaphylactic / anaphylactoid reaction Skin and Subcutaneous Tissue Disorders: Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects. **b) Contraindications** Contraindicated in children below two (2) years of age. **Reference: Directive No. 11, 2010.** ***Bil. (7) dlm. BPFK/PPP/01/03 Jilid 1*** *Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Bungkusan Semua Produk Carbocysteine, Acetylcysteine dan Methylcarbocysteine (Mecysteine) **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:**]Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **Reference: Directive No. 14, 2018.** ***BPFK/PPP/07/25 (14) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine dan Acetylcysteine: Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Anaphylactic/ Anaphylactoid Reaction dan Severe Cutaneous Adverse Reactions (SCARs)*
43.	**CEFTRIAXONE** The following statements shall be included in the package insert for products containing Ceftriaxone: **Package Insert** **CONTRAINDICATION** Ceftriaxone is contraindicated in neonates (≤28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium. **WARNINGS AND PRECAUTIONS** • In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. • Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur. **Reference:** ***Bil. (48) dlm. BPFK/PPP/01/03*** *Pindaan Pada Kenyataan Amaran Berkaitan Dengan*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	"Potential Risk Associated with Concomitant Use Of Ceftriaxone With Calcium - Containing Intravenous Solutions" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Ceftriaxone **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** *Nervous system disorders* *Frequency 'not known': Encephalopathy** **Reversible encephalopathy has been reported with the use of ceftriaxone, particularly when high doses are administered in patients with renal impairment and additional predisposing factors such as older age, pre-existing central nervous system disorders.* **Reference: Directive No. 14, 2021**. ***NPRA.600-1/9/13(24)*** *Direktif Untuk Semua Produk Yang Mengandungi Ceftriaxone: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Encephalopathy*
44.	**CETIRIZINE** The following statement shall be included in the package insert of products containing Cetirizine: **WARNINGS AND PRECAUTIONS** Activities Requiring Mental Alertness: In clinical trials the occurrence of somnolence has been reported in some patients taking Cetirizine: due caution should therefore be exercised when driving a car or operating potentially dangerous machinery.
45.	***CHELIDONIUM MAJUS*** The following statement shall be included on the label of products containing *Chelidonium majus* in 2 languages (*Bahasa Melayu* and English) in bold font: **WARNING** This product may cause adverse reaction to the liver. ***AMARAN*** *Produk ini mungkin boleh menyebabkan kesan sampingan pada hepar (hati).* **Reference:** ***Bil. 17 dlm. BPFK/02/5/1.3*** *Label Amaran Tentang Penggunaan Bahan Chelidonium majus*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
46.	**CHITOSAN** The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of products containing chitosan. **"DERIVED FROM SEAFOOD"** **Reference:** ***Bil. (52) dlm. BPFK/02/5/1.3*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan Aktif Adalah Dari Sumber Laut*
47.	**CHLORHEXIDINE** The following statements shall be <u>included in the package insert, label and RiMUP</u> of pharmaceutical products containing Chlorhexidine: **<u>Package Insert</u>** **a) Warnings and Precautions:** [Product Name] contains chlorhexidine. Chlorhexidine is known to induce hypersensitivity, including generalised allergic reactions and anaphylactic shock. The prevalence of chlorhexidine hypersensitivity is unknown, but available literature suggests this is likely to be very rare. [Product Name] should not be administered to anyone with a possible history of an allergic reaction to chlorhexidine. If any signs or symptoms of a suspected hypersensitivity reaction such as itching, skin rash, redness, swelling, breathing difficulties, light headedness, and rapid heart rate develop, immediately stop using the product. Appropriate therapeutic countermeasures must be instituted as clinically indicated. **b) Adverse Effects/ Undesirable Effects:** Immune system disorders Frequency not known: Hypersensitivity including anaphylactic shock **<u>Label and Consumer Medication Information Leaflet (RiMUP)</u>** [Product Name] contains chlorhexidine. Inform your healthcare provider if you have a known allergy to chlorhexidine. Stop using this product and seek immediate medical assistance if you experience rash, itching, swelling, breathing difficulties, light-headedness or rapid heartbeat.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 8, 2017. ***BPFK/PPP/07/25 (13) Jld. 1*** *Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Chlorhexidine: Pengemaskinian Sisip Bungkusan, Label dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Reaksi Hipersensitiviti*
48.	**CHLOROQUINE AND HYDROXYCHLOROQUINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing chloroquine and hydroxychloroquine; **Package Insert** **a) Warnings and Precautions:** **Chloroquine** Suicidal behaviour and psychiatric disorders Cases of suicidal behaviour and psychiatric disorders have been reported in patients treated with chloroquine, including in patients with no prior history of psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment. **Hydroxychloroquine** Suicidal behaviour and psychiatric disorders Suicidal behaviour and psychiatric disorders have been reported in some patients treated with hydroxychloroquine. Psychiatric side effects typically occur within the first month after the start of treatment with hydroxychloroquine and have been reported also in patients with no prior history of psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment. Drug Induced Phospholipidosis Cases of hydroxychloroquine induced phospholipidosis have been reported during use of [product name] (see section Adverse Effects). Drug-induced phospholipidosis may occur in different organ systems such as cardiac, renal, or muscle. Monitoring for toxicity is advised. Discontinue [product name] if cardiac, renal, or muscle toxicity related to drug induced phospholipidosis is suspected or demonstrated by tissue biopsy. Aggravation of Myasthenia Gravis

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Aggravation of symptoms of myasthenia gravis (generalized weakness including shortness of breath, dysphagia, diplopia, ptosis etc.) have been reported in myasthenic patients receiving hydroxychloroquine therapy. Discontinue [product name] if aggravation of symptoms related to myasthenia gravis is suspected. **b) Adverse Effects/ Undesirable Effects:** **Chloroquine** SOC Psychiatric disorders Very common: insomnia Common: depression Rare: psychiatric disorders such as anxiety, agitation, confusion, hallucinations, delirium Not known: suicidal behaviour, psychosis, aggression, delusion, paranoia, mania, attention deficit, sleep disorders **Hydroxychloroquine** SOC Psychiatric disorders Common: Affect lability Uncommon: Nervousness Not known: suicidal behaviour, psychosis, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders. Skin and subcutaneous tissue disorders Frequency 'not known': Sweet's syndrome Metabolism and nutrition disorders Frequency 'not known': phospholipidosis* *Cases of hydroxychloroquine induced phospholipidosis have been reported. Drug-induced phospholipidosis may occur in different organ systems such as cardiac, renal, or muscle causing toxicity (see section Warnings and Precautions). **c) Pregnancy:** **Hydroxychloroquine** Data from a population-based cohort study including 2045 hydroxychloroquine exposed pregnancies suggests a small increase in the relative risk (RR) of congenital malformations associated with hydroxychloroquine exposure in the

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	first trimester (n = 112 events). For a daily dose of ≥ 400 mg the RR was 1.33 (95% CI, 1.08 – 1.65). For a daily dose of < 400 mg the RR was 0.95 (95% CI, 0.60 – 1.50). **Consumer Medication Information Leaflet (RiMUP)** **a) While you are using [product name]:** **Chloroquine** Some people being treated with [product name] can experience mental health problems such as irrational thoughts, hallucinations, feeling confused, aggressiveness, paranoia, feeling depressed or have thoughts of self-harm or suicide, even those who have never had similar problems before. If you or others around you notice any of these side effects seek medical advice straight away. **Hydroxychloroquine** Some people being treated with [product name] can experience mental health problems such as irrational thoughts, anxiety, hallucinations, feeling confused or feeling depressed, including thoughts of self-harm or suicide, even those who have never had similar problems before. If you or others around you notice any of these side effects seek medical advice straight away. **b) Side Effects:** **Chloroquine** Very common: sleeping difficulty (insomnia) Common: depression Rare: anxiety, agitation, confusion, seeing/feeling things that are not there (hallucinations), disturbance in mental abilities that results in confused thinking and reduced awareness of the environment (delirium) Not known: feeling depressed or having thoughts of self-harm or suicide, feeling anxious, feeling confused, aggressiveness, having irrational thoughts, paranoia, feeling elated or overexcited, lack of concentration, sleep disorders. **Hydroxychloroquine** Common: mood swings Uncommon: nervousness Not known: Feeling depressed or having thoughts of self-harm or suicide, feeling nervous or anxious, feeling confused, hallucinations, agitated, feeling elated or

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	overexcited, difficulty sleeping. Skin reaction including plum-colored, raised, painful sores, particularly on your arms, hands, fingers, face and neck, which may also be accompanied by fever. This could be a condition called Sweet's syndrome Accumulation of a type of fat in tissues causing harm. The doctor may decide to stop the treatment with [product name]. **c) Before you use [product name]:** **<u>Hydroxychloroquine</u>** <u>When you must not use it:</u> • [Product name] may be associated with a small increased risk of malformations and should not be used during pregnancy unless your doctor considers the benefits outweigh the risks. <u>Before you start to use it:</u> Take special care and check with your doctor if: • You have or have had myasthenia (a disease with general muscle weakness including in some cases muscles used for breathing). You may notice aggravation of symptoms such as muscle weakness, difficulty in swallowing, double vision, drooping of the upper eyelid etc. • Hydroxychloroquine may cause heart, kidney or muscle disorders. Please ask your doctor to inform you of signs and symptoms of drug induced phospholipidosis. Hydroxychloroquine may need to be stopped. **References:** **Directive No. 8, 2022.** ***NPRA.600-1/9/13 (8)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Chloroquine dan Hydroxychloroquine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Risiko Psychiatric Disorders* **Directive No. 14, 2024.** ***NPRA.600-1/9/13 (45)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Hydroxychloroquine : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Acute Febrile Neutrophilic Dermatosis (Sweet's Syndrome)* **Directive No. 17, 2025.** ***NPRA.600-1/9/13 (64)Jld.1*** *Direktif untuk semua produk yang mengandungi hydroxychloroquine: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko major congenital malformation di kalangan kanak-kanak yang terdedah kepada hydroxychloroquine dalam kandungan, drug-induced phospholipidosis dan aggravation of myasthenia gravis (MG)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
49.	**CHLORPHENIRAMINE** The following statement shall be included on the labels and package inserts of liquid oral products containing Chlorpheniramine: **WARNING** When used for treatment of cough and cold; (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
50.	**CHORIONIC GONADOTROPHIN** The following statement shall be included in the package inserts of products containing Chorionic gonadotrophin: **The ovulation cycle should be monitored with oestriol levels and ultrasonography**
51.	**CHROMIUM** The following statement shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) for health supplement products containing *Chromium;* **Warning:** Please consult your doctor/pharmacist before using this product. If you are on other medicines, there may be a potential for interactions or side effects. **Reference: Directive No. 7, 2023.** ***NPRA.600-1/9/13(25)Jld.1*** *Direktif Berkenaan Penambahan Pernyataan Amaran Bagi Produk Suplemen Kesihatan yang Mengandungi Bahan Aktif Chromium*
52.	**CIPROFLOXACIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing ciprofloxacin for systemic use (oral and injection dosage forms):

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Package Insert **a) Warnings & Precautions:** Psychiatric reactions Psychiatric reactions may occur even after the first administration of fluoroquinolones, including [Product name]. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, [Product name] should be discontinued and appropriate measures instituted. Caution is recommended if [Product name] is to be used in psychotic patients or in patients with a history of psychiatric disease. **b) Adverse Effects/ Undesirable Effects:** Psychiatric disorders Rare: Depression (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) **Consumer Medication Information Leaflet (RiMUP)** **a) While you are using it:** You may experience mental health problems even when taking/ using fluoroquinolone antibiotics, including [Product name] for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts. If you develop such reactions, stop taking/ using [Product name] and inform your doctor immediately. **b) Side effects:** Rare: Depression (potentially leading to thoughts of suicide, suicide attempts, or completed suicide), or hallucinations Very rare: Psychotic reactions potentially leading to thoughts of suicide, suicide attempts, or completed suicide **Reference: Directive No. 8, 2024.** *NPRA.600-1/9/13 (39)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
53.	**CLEMASTINE** The following statement shall be included on the labels and package inserts of liquid oral products containing Clemastine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
54.	**CLARITHROMYCIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Clarithromycin: **Package Insert** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/ Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **c) Contraindications:** Concomitant administration of Clarithromycin and the following drugs is contraindicated: Domperidone as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	torsades de pointes (See Section Interactions). **d) Interactions:** Co-administration of Clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. The following drugs or drug classes are known or suspected to be metabolized by CYP3A isozyme: Domperidone **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **b) Before you use [Product name]:** Do not take [product name] if you are taking any of the following medicines: domperidone (used for nausea & vomiting) **References:** ***Directive No. 22, 2018.*** *BPFK/PPP/07/25 (22) Jld.2 Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin dan Roxithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)* ***Directive No. 32, 2018.*** *BPFK/PPP/07/25 (32) Jld. 2 Direktif Untuk Semua Produk Yang Mengandungi Clarithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat Yang Mengakibatkan Peningkatan Risiko QT Interval Prolongation*
55.	**CLINDAMYCIN** The package insert must emphasize the possibility of pseudomembranous colitis with the use of the drug. The package insert must include the **following boxed or emphasized statements/ warning:** • Clindamycin therapy has been associated with severe colitis which may end fatally.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. • It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. • Its use in newborns is contraindicated. **CLINDAMYCIN (ORAL & INJECTION)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for oral and injection products containing clindamycin; **<u>Package Insert</u>** **a) Warnings & Precautions:** Clindamycin is potentially nephrotoxic. Acute kidney injury including acute renal failure has been reported. Therefore, monitoring of renal function should be considered during therapy of patients with pre-existing renal dysfunction or taking concomitant nephrotoxic drugs and monitoring of renal function should be performed if therapy is prolonged. **b) Adverse Effects/ Undesirable Effects:** <u>Renal and urinary disorders</u> Frequency 'not known': Acute kidney injury **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** <u>Before you start to use it</u> Tell your doctor if you have any of the following conditions to help him or her decide if <product name> is suitable for you: • you suffer from problems with kidneys <u>Taking other medicines</u> Tell your doctor if you are taking any other medicines. **b) Side effects:** If you develop decreased urine output, fluid retention causing swelling in your legs, ankles or feet, shortness of breath or nausea you should contact your doctor immediately.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	CLINDAMYCIN (ORAL CAPSULE FORM) The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing clindamycin (oral capsule form); **<u>Package Insert</u>** **a) Route of Administration** To avoid the possibility of oesophageal irritation, clindamycin hydrochloride capsules should be taken with a full glass of water and no less than 30 minutes before lying down. **b) Warnings & Precautions:** Due to the risk of oesophagitis and oesophageal ulcer, it is important to ensure compliance with administration guidance (see Sections Route of administration and Adverse Effects/ Undesirable Effects). **c) Adverse Effects/ Undesirable Effects:** <u>Gastrointestinal disorders</u> Frequency 'not known': Oesophageal ulcer, oesophagitis **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) How to use [product name]:** [Product name] should be taken with a full glass of water and no less than 30 minutes before lying down. **b) While you are using it:** Due to the risk of stomach and throat irritation, it is important to ensure compliance with administration guidance (see How to use [product name]). **c) Side effects:** Inflammation/ ulcer from the throat to the stomach tube lining **References:** **Directive No. 8, 2023.** ***NPRA.600-1/9/13 (26)Jld.1*** *Direktif untuk semua produk yang mengandungi clindamycin bagi kegunaan sistemik (sediaan oral dan injeksi): Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko Acute Kidney Injury (AKI)* **Directive No. 4, 2026.** ***NPRA.600-1/9/13 (75)Jld.1*** *Direktif untuk semua produk yang mengandungi clindamycin dalam sediaan oral kapsul: Pengemaskinian sisip bungkusan dan RiMUP bagi*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	memperkukuhkan maklumat keselamatan berkaitan risiko oesophagitis dan oesophageal ulcer
56.	**CLOPIDOGREL** The following statement shall be included in the package inserts of products containing Clopidogrel: **WARNINGS AND PRECAUTIONS** Pharmacogenetics: Based on literature data, patients with genetically reduced CYP2C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function. **INTERACTION** Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g proton pump inhibitors) should be discouraged. **PHARMACOKINETIC PROPERTIES** The oxidative step is regulated primarily by Cytochrome P450 ISOENZYMES 2B6, 3A4, 1A1, 1A2 and 2C19. **Reference:** ***Bil (42) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Berkaitan Dengan "Possible Interaction Between Clopidogrel and Proton Pump Inhibitors" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Clopidogrel*
57.	**CLOZAPINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Clozapine; **Package Insert** **a) Contraindications** Paralytic ileus **b) Warnings and Precautions** Clozapine exerts anticholinergic activity, which may produce undesirable effect throughout the body. Probably on account of its anticholinergic properties, [product name] has been associated with varying degrees of impairment of

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, paralytic ileus, megacolon and intestinal infarction/ischaemia. On rare occations these cases have proved fatal. Careful monitoring during treatment with [product name] to identify early, the onset of constipation, followed by effective management of constipation are recommended to prevent complications. **c) Adverse Effects/ Undesirable Effects:** Gastrointestinal disorders: (very rare) intestinal obstruction, ileus, faecal impaction Post-marketing: megacolon*, intestinal infarction/ischaemia*, intestinal necrosis*, intestinal ulceration*, intestinal perforation*, colitis (*These adverse drug reactions were sometimes fatal) **d) Interactions** Due to the possibility of additive effects, caution is essential when substances possessing anticholinergic effects are given concomitantly with [product name]. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) When you must not use it:** Do not take [product name] if you suffer or have ever suffered from severe constipation, obstruction of the bowel or any other condition which has affected your large bowel. **b) Taking other medicines:** Tell your doctor or pharmacist if you are taking or have recently taken medicines which cause constipation (such as anticholinergic, which are used to relieve stomach cramps, spasms and travel sickness). **c) While you are using [product name]:** Tell your doctor or pharmacist if you have experienced constipation, abdominal pain, abdominal tenderness, fever, bloating and/or bloody diarrhea. Your doctor will need to examine you. **d) Side effects:** Abdominal pain, cramping, swollen abdomen, vomiting, constipation and failure to pass gas which may be signs and symptoms of bowel obstruction.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 3, 2021. ***NPRA.600-1/9/13 (13)*** *Direktif Untuk Semua Produk Yang Mengandungi Clozapine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Komplikasi Usus Yang Serius Akibat Sembelit*
58.	**COBICISTAT** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Cobicistat: **Package Insert** **a) Interactions:**

Medicinal product by therapeutic areas	***Effects on medicinal product levels.***	***Recommendation concerning co-administration with [product name]***
All corticosteroids excluding cutaneous products		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).	*Interaction not studied with any of the components of [product name].* *Plasma concentrations of these medicinal products may be increased when co-administered with [product name], resulting in reduced serum cortisol concentrations.*	*Concomitant use of [product name] and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.* *Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long-term use.*

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

It is important to tell your doctor if you are taking corticosteroids such as betamethasone, budesonide, fluticasone, mometasone, prednisone and triamcinolone. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 2, 2018. ***BPFK/PPP/07/25 (2) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Cobicistat dan Kortikosteroid (Kecuali Produk Untuk Kegunaan Luar): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat*
59.	**CODEINE** The following safety information/ statements shall be included in the package inserts of products containing Codeine: **Indications** [Product name] is indicated for the relief of painful disorders such as headache, dysmenorrhea, conditions involving musculoskeletal pain, myalgias and neuralgias. It is also indicated as an analgesic and antipyretic in conditions accompanied by discomfort and fever, such as the common cold and viral infections. [Product name] is an effective analgesic after dental work and tooth extractions. Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone). **Dosing and Administrations** Paediatric population: • Children aged less than 12 years: Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine. [Product name] is contraindicated in children below the age of 12 years for the symptomatic treatment of cold. • Children aged 12 years to 18 years: [Product name] is not recommended for use in children aged 12 years to 18 years with compromised respiratory function. **Contraindications** • In children below the age of 12 years for the symptomatic treatment of colds due to an increased risk of developing serious and life-threatening adverse reactions. • In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to increased risk of developing serious and life-threatening adverse reactions. • In women who are breastfeeding. • In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Warnings and Precautions

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4 to 6.5%
Asian	1.2 to 2.0%
Caucasian	3.6 to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1.0 to 2.0%

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however, there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Pregnancy and Lactation

Pregnancy

Careful consideration should be given before prescribing the product for pregnant patients. Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	As a precautionary measure, use of [Product name] should be avoided during the third trimester of pregnancy and during labor. Breastfeeding [Product name] is contraindicated in women during breastfeeding. At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal. **Reference: Directive No. 16, 2016.** ***BPFK/PPP/07/25 (2) Jld. 1*** *Direktif Bagi Semua Produk Yang Mengandungi Codeine Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Respiratory Depression*
60.	**COLCHICINE** The following statement shall be included in the package inserts of products containing Colchicines: **INTERACTIONS** Potential risk of severe drug interactions, including death, in certain patients treated with colchicine and concomitant P-glycoprotein or strong CYP3A4 inhibitors such as clarithromycin, cyclosporin, erythromycin, calcium channel antagonists (e.g Verapamil and Diltiazem), telithromycin, ketoconazole, itraconazole, HIV protease inhibitors and nefazodone. P-Glycoprotein or strong CYP3A4 inhibitors are not to be used in patients with renal or hepatic impairment who are taking colchicine. A dose reduction or interruption of colchicine treatment should be considered in patients with normal renal and hepatic function if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required. Avoid consuming grapefruit and grapefruit juice while using colchicine. **Reference:** ***Bil (45) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Berkaitan Dengan "Severe Drug Interaction Between Colchicine and P-Glycoprotein or Strong CYP3A4 Inhibitors" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Colchicine*
61.	**CORTICOSTEROID** 1. The following statements shall be included in the package insert and RiMUP of inhaled corticosteriod used for treatment of Chronic Obstructive Pulmonary Disease (COPD) such as **budesonide** and **fluticasone** (product containing single

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	active ingredient and in combination) and **beclomethasone** (only for combination product): **<u>Package Insert</u>** **a) Warnings and Precautions:** <u>Pneumonia in patients with COPD</u> An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. Physicians should remain vigilant for the possible development of pneumonia in patient with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking status, older age, low body mass index (BMI) and severe COPD. **b) Adverse Effects / Undesirable Effects:** "Pneumonia (in COPD patients)" to be listed as "Common" adverse drug reaction in the "Infections and Infestations" SOC. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects** <u>Pneumonia (infection of the lung) in COPD patients (common side effect)</u> • Tell your doctor if you have any of the following while taking [product name] they could be symptoms of a lung infection: - Fever or chills; - Increased mucus production or change in mucus colour; - Increased cough or increased breathing difficulties. 2. The following statements shall be <u>included in the package insert and RiMUP</u> of products containing corticosteroid (except products for external use): **(i) Products containing Beclomethasone:** **<u>Package Insert</u>**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	a) Interactions with Other Medicaments: Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** Some medicines may increase the effects of [product name] and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV such as cobicistat). **(ii) Products containing corticosteroids other than Beclomethasone:** **<u>Package Insert</u>** **a) Interactions:** Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** Some medicines may increase the effects of [product name] and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV such as cobicistat). 3. **CORTICOSTEROIDS FOR SYSTEMIC USE (ORAL AND INJECTION DOSAGE FORMS)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing corticosteroids for systemic use (oral and injection dosage forms); **<u>Package Insert</u>**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	a) Warnings and Precautions: Pheochromocytoma crisis, which may be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it Talk to your doctor or pharmacist if you: • have pheochromocytoma (a tumour of the adrenal gland) **References:** **Directive No. 9, 2017.** ***BPFK/PPP/07/25 (14) Jld. 1*** *Direktif Untuk Semua Produk Inhalasi Kortikosteroid Yang Digunakan Untuk Rawatan Chronic Obstructive Pulmonary Disease (COPD): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Tambahan Berkenaan Peningkatan Risiko Pneumonia* **Directive No. 2, 2018.** ***BPFK/PPP/07/25 (2) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Cobicistat dan Kortikosteroid (Kecuali Produk Untuk Kegunaan Luaran): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat* **Directive No. 6, 2022.** ***NPRA.600-1/9/13 (6)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Kortikosteroid Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Pheochromocytoma Crisis*
62.	**CO-TRIMOXAZOLE (SULFAMETHOXAZOLE, TRIMETHOPRIM)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing co-trimoxazole (sulfamethoxazole, trimethoprim); **Package Insert** **a) Warnings and Precautions:** Respiratory toxicity Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates, and

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, co-trimoxazole should be discontinued and appropriate treatment given. Circulatory shock Cases of circulatory shock, often accompanied by fever and not responding to standard treatment for hypersensitivity, have been reported with sulfamethoxazole + trimethoprim, mainly in immunocompromised patients. **b) Adverse Effects/ Undesirable Effects:** Vascular disorders Frequency 'not known': circulatory shock **Consumer Medication Information Leaflet (RiMUP)** **a) While you are using [product name]:** Tell your doctor or pharmacist immediately if you develop an unexpected worsening of cough and shortness of breath. **b) Side effects:** Serious side effects Call the emergency department immediately if you experience multiple signs and symptoms such as fever, very low blood pressure or increased heart rate after taking this drug as it may be a sign of shock. **References:** **Directive No. 3, 2022.** *NPRA.600-1/9/13 (3)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Co-trimoxazole (Sulfamethoxazole, Trimethoprim): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Acute Respiratory Distress Syndrome (ARDS)* **Directive No. 5, 2026.** *NPRA.600-1/9/13 (76)Jld.1 Direktif untuk semua produk yang mengandungi kombinasi sulfamethoxazole dan trimethoprim (cotrimoxazole): Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko circulatory shock*
63.	**COX-2 INHIBITORS** The following statement shall be included in the package insert of COX-2 Inhibitors products containing Celecoxib and Etoricoxib: • Contraindication for patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke). • Warning to prescriber when prescribing COX-2 Inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia,

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	diabetes, smoking patient and patient with peripheral arterial disease. • Statement on limiting the period and dosing is written as 'Given the association between cardiovascular risk and exposure to COX-2 Inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment'. • Contraindication for patient using Etoricoxib is written as 'Contraindication for Etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control'. **Reference:** ***Bil. (46) dlm. BPFK/02/5/1.3*** *Keputusan Mesyuarat PBKD - Tindakan-tindakan Regulatori Terhadap COX-2 Inhibitors: Celecocib dan Etoricoxib*
64.	**CYPROTERONE ACETATE** The following statement shall be included in the package inserts of products containing Cyproterone acetate: **WARNINGS AND PRECAUTIONS** Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 100mg or more of cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.
65.	**CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION** **CYPROTERONE ACETATE 2MG AND ETHINYLESTRADIOL 0.035MG** The following statement shall be included in the package inserts of products containing Cyproterone acetate 2mg and Ethinylestradiol 0.035mg **INDICATIONS** - Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age. - For the treatment of acne, [product name] should only be used after topical therapy or systemic antibiotic treatments have failed. - Since [product name] is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives. **DOSAGE AND METHOD OF ADMINISTRATION** (At the beginning part with **bold** formatting)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Note: [Product name] should not be prescribed for the purpose of contraception alone. However, when taken as recommended, [product name] will provide reliable contraception in patients treated for the above clinical conditions. If patient compliance is uncertain and contraception is necessary, then a supplementary non-hormonal contraceptive method should be considered. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS:** - Vascular Disorders - Rare: Thromboembolism
66.	**CYTOTOXIC AGENT** The following boxed statement shall be included on the label of products containing Cytotoxic agents: **CAUTION : CYTOTOXIC AGENT** ***Note:*** *The label caution should be printed prominently on the label.*
67.	**DAPAGLIFLOZIN (INCLUDING COMBINATION PRODUCTS)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing dapagliflozin (including combination products): **Package Insert** **a) Interactions:** Concomitant use of dapagliflozin and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]- taking other medicines** Especially tell your doctor: • if you are taking lithium because [product name] can lower the amount of lithium in your blood. **Reference: Directive No. 9, 2024.** *NPRA.600-1/9/13 (40)Jld.1 Direktif Untuk Semua Produk Yang*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat
68.	**DECITABINE** The following statements shall be <u>included in the package insert</u> for products containing decitabine; **<u>Package Insert</u>** **a) Warnings and Precautions:** Differentiation syndrome Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving decitabine. Differentiation syndrome may be fatal. Treatment with high dose IV corticosteroids and hemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation should be considered until resolution of symptoms and if resumed, caution is advised. **b) Adverse Effects/ Undesirable Effects:** <u>Neoplasms benign, malignant and unspecified (including cysts and polyps)</u> Frequency 'Very rare': Differentiation syndrome **Reference: Directive No. 24, 2021.** ***<u>NPRA.600-1/9/13 (34)</u>*** *Direktif Untuk Semua Produk Yang Mengandungi Decitabine: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Differentiation Syndrome*
69.	**DEXBROMPHENIRAMINE** The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of liquid oral products containing Dexbrompheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***<u>Bil. (34) dlm. BPFK/PPP/01/03</u>*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
70.	**DEXTROMETHORPHAN** The following statement shall be included on the labels and package inserts of liquid oral products containing Dextromethorphan: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
71.	**DICLOFENAC SODIUM** The following statement shall be included in the package inserts of products containing Diclofenac sodium: **WARNINGS AND PRECAUTIONS** Severe cutaneous reactions, including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs. Adverse effects: Dermatological: Occasional - rashes or skin eruptions Cases of hair loss, bullous eruptions, erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported.
72.	**DICLOFENAC (SYSTEMIC FORMULATION)** The following statement shall be included in the package inserts of products containing Diclofenac: **DOSAGE AND ADMINISTRATION** **DOSAGE** As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section WARNINGS AND PRECAUTIONS). **ESTABLISHED CARDIOVASCULAR DISEASE OR SIGNIFICANT CARDIOVASCULAR RISK FACTORS**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes melilitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily if treated for more than 4 weeks (see section WARNINGS AND PRECAUTIONS). **CONTRAINDICATIONS** Severe cardiac failure (see section WARNINGS AND PRECAUTIONS). **WARNINGS AND PRECAUTIONS** **Cardiovascular Effects** Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, maybe associated with an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke). Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes melilitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks. Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event. **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** **Cardiac Disorders** Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain. * The frequency reflects data from long-term treatment with a high dose (150 mg/day). **Description of Selected Adverse Drug Reactions**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Arteriothrombotic events Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see section WARNINGS AND PRECAUTIONS). **Reference: Directive No. 7, 2015.** ***Bil. (30)dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Diclofenac (Formulasi sistemik): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Kesan Advers Kardiovaskular*
73.	**DICLOFENAC (ALL PRODUCTS EXCEPT PRODUCTS FOR CUTANEOUS USE)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Diclofenac (except products for cutaneous use); **Package Insert** **a) Warnings & Precautions** Gastrointestinal effects NSAIDs, including diclofenac, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastrointestinal surgery. **b) Adverse Effects/Undesirable Effects:** Cardiac disorders: Kounis syndrome: Frequency "not known" **Consumer Medication Information Leaflet (RiMUP)** **a) Before you start to use it:** Tell your doctor if you recently had or you are going to have a surgery of the stomach or intestinal tract before receiving/taking/using [product name], as [product name] can sometimes worsen wound healing in your gut after surgery. **b) Side Effects:** Frequency "not known": Chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome. **Reference: Directive No. 4, 2020.** ***BPFK/PPP/07/25 (4) Jld. 4*** *Direktif Untuk Semua Produk Yang Mengandungi Diclofenac (Kecuali Sediaan Untuk Kegunaan Pada Kulit): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Keselamatan Berkaitan Risiko Anastomotic Leakage Dan Kounis Syndrome
74.	**DICYCLOMINE** The following boxed warning shall be included on the labels and in the package inserts of products containing Dicyclomine: **WARNING** Dicyclomine is not recommended for use in infants under the age of six month
75.	**DIPHENHYDRAMINE** The following statement shall be included on the labels and in the package inserts of products containing Diphenhydramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
76.	**DIPHENOXYLATE** 1. The following boxed warning shall be included on the labels of products containing Diphenoxylate: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE.** 2. The following statement shall be included in the package insert of products containing Diphenoxylate: **WARNING** **Not recommended for children under 6 years of age.**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	PRECAUTION Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid detention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes, especially in young children. If severe dehydration of electrolyte imbalance is present, diphenoxylate should be withheld until appropriate corrective therapy has been initiated.
77.	**DIURETICS** **HYDROCHLOROTHIAZIDE, INDAPAMIDE, CHLORTHALIDONE AND ACETAZOLAMIDE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing hydrochlorothiazide, indapamide, chlorthalidone and acetazolamide (including combination products); **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Eye disorders: Frequency 'not known': Choroidal effusion, acute myopia, acute angle-closure glaucoma **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Frequency 'not known': • Choroidal effusion: an abnormal building of liquid in your eye that may result in vision changes; • Acute myopia: sudden nearsightedness or blurred vision; • Acute angle-closure glaucoma: a rapid increased pressure in your eyes, eye pain. If left untreated, it may lead to permanent vision loss. **Reference: Directive No. 5, 2022.** *NPRA.600-1/9/13 (5)Jld.1 Direktif Untuk Semua Produk (Termasuk Kombinasi) Yang Mengandungi Hydrochlorothiazide, Indapamide, Chlorthalidone*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	dan Acetazolamide: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Choroidal Effusion, Acute Myopia dan Acute Angle-Closure Glaucoma
78.	**DOMPERIDONE** The following statement shall be included on the package inserts and RiMUP of products containing Domperidone: **Package insert** **INDICATIONS** Domperidone is indicated for the relief of the symptoms of nausea and vomiting. This includes: • Nausea and vomiting of functional, organic, infectious or dietary origin. • Nausea and vomiting induced by: - radiotherapy or drug therapy. - dopamine agonists (such as L-dopa and bromocriptine) used in the treatment of Parkinson's disease. **DOSAGE AND ADMINISTRATION** It is recommended to take [product name] 15-30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed. Adults and adolescents ≥ 12 years of age and weighing ≥35 kg & children <12 years of age and weighing ≥ 35 kg The dose of [product name] should be the lowest effective dose for the individual situation (typically 30 mg/day) and can be increased if necessary to a maximum daily oral dose of 40 mg. Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. If nausea and vomiting persists for longer than one week, patients should consult their physician. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be re-evaluated and the need for continued treatment reassessed.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Tablets (10 mg/tablet)	1 tablet three to four times per day	40 mg (4×10 mg tablet).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Oral suspension (1 mg/ml)	10 mL three to four times per day	40 mg (40 mL of 1 mg/mL oral suspension)

Adults and adolescents (≥ 12 years of age) weighing < 35 kg

The dose of [product name] should be the lowest effective dose. The total daily dose is dependent on weight (see table below).

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed. Due to the need for accurate dosing, tablets are unsuitable for use in adults and adolescents weighing less than 35 kg.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Oral suspension (1 mg/mL)	0.25 mg/kg three to four times per day	1 mg/kg but no more than 35 mL (35mg)

Infants and children < 12 years of age and weighing < 35 kg

The efficacy of [product name] has not been established in infants and children < 12 years of age and weighing < 35 kg.

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L), the dosing frequency of [product name] should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Patients with severe renal impairment should be reviewed regularly.

Hepatic impairment

[Product name] is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh >9) hepatic impairment. Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment.

CONTRAINDICATIONS

[Product name] is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see Warnings and Precautions). • co-administration with QT-prolonging drugs • co-administration with potent CYP3A4 inhibitors regardless of their QT-prolonging effects (See Section Interactions). • Whenever stimulation of gastric motility might be dangerous, e.g., in the presence of gastro-intestinal haemorrhage, mechanical obstruction or perforation. • In patients with moderate or severe hepatic impairment). **INTERACTIONS** The main metabolic pathway of domperidone is through CYP3A4. In vitro and human data show that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Co-administration of domperidone with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation is contraindicated (See Section Contraindications). **WARNINGS AND PRECAUTIONS** **Cardiovascular effects** Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT-prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see Adverse Reactions). Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see Adverse Reactions). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors. Domperidone should be used at the lowest effective dose in adults and children. Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see Contraindications). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS
{information to be included}
Postmarketing:
Cardiac Disorders
Frequency: Very rare
Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, Sudden cardiac death (see Warnings and Precautions)

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [Product name]:

Do not take [product name] if you are taking any of the following medicines: clarithromycin (antibiotic)

b) How to use [product name]:

You should always take the lowest amount of [product name] that works for you and you should not take it for longer than is necessary. Although the amount of [product name] you should usually take is described below, your doctor may adjust your dose to your personal needs.

[Product name] is most effective if taken 15-30 minutes before meals.

Adults and adolescents (12 years of age and over) weighing 35 kg or more; children weighing 35kg or more:

Tablets: Take 1 tablet 3 to 4 times a day. Do not take more than 4 tablets per day (40 mg/day).
Oral suspension: Take 10mL of oral suspension 3 or 4 times a day. Do not take more than 40mL per day (40 mg/day).

Adults and adolescents weighing less than 35 kg:

Oral suspension: Give 0.25 milliliters of the oral suspension per kilogram of body weight 3 or 4 times a day. The maximum dose per day is 1 mg/kg but do not exceed 35 mg per day.

Infants and children less than 12 years of age and weighing less than 35kg:

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	The effectiveness of [product name] has not been established in infants and children under 12 years of age with a body weight of <35 kg. **References:** **Directive No. 4, 2015.** ***Bil. (28) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Domperidone Untuk Mengehadkan Penggunaan Berikutan Risiko Kesan Advers Jantung* **Directive No. 31, 2018.** ***BPFK/PPP/07/25 (31) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Domperidone: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat Yang Mengakibatkan Peningkatan Risiko QT Interval Prolongation* **Directive No. 6, 2020.** ***BPFK/PPP/07/25 (6) Jld. 4*** *Direktif Untuk Semua Produk Yang Mengandungi Domperidone: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Penggunaan Dalam Kalangan Golongan Pediatrik*
79.	**DONEPEZIL** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing donepezil; **Package Insert** **a) Warnings & Precautions:** Cardiovascular Conditions There have been post-marketing reports of QT interval prolongation and Torsade de Pointes. Caution is advised in patients with pre-existing or family history of QT prolongation, in patients treated with drugs affecting the QT interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required. **b) Interactions:** Cases of QT interval prolongation and Torsade de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QT interval and clinical monitoring (ECG) may be required. Examples include: • Class IA antiarrhythmics (e.g. quinidine). • Class III antiarrhythmics (e.g. amiodarone, sotalol). • Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline). • Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone). • Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin). **c) Adverse Effects/ Undesirable Effects:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Cardiac disorders Frequency 'not known': polymorphic ventricular tachycardia including Torsade de Pointes; Electrocardiogram QT interval prolonged. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Tell the doctor about all your present or past health problems. Including: • Any heart problems including problems with irregular, slow or fast heartbeats. • A heart condition called 'prolonged QT interval' or a history of certain abnormal heart rhythms called Torsade de Pointes or if anyone in your family have 'prolonged QT interval'. • Low levels of magnesium or potassium in your blood. **b) Taking other medicines:** Be particularly sure to tell the doctor if you are taking any of the following types of medicines: • Medicines for heart rhythm problems e.g. amiodarone, sotalol and quinidine. • Medicines for depression e.g. citalopram, escitalopram, amitriptyline. • Medicines for psychosis e.g. pimozide, sertindole, ziprasidone. • Medicines for bacterial infections e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin. **c) Side Effects:** Unknown (frequency cannot be estimated): • Fast, irregular heart beat and fainting, which could be symptoms of a life-threatening condition known as Torsade de Pointes. • Changes in the heart activity which can be seen on an electrocardiogram (ECG) called 'prolonged QT interval'. **Reference: Directive No. 18, 2022.** ***NPRA.600-1/9/13 (18)Jld.1*** *Direktif untuk semua produk yang mengandungi donepezil: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko QT prolongation dan Torsade de Pointes*
80.	**DOPAMINERGIC INGREDIENT** The following warning/ statement related to "Sudden sleep onset" shall be included in the package insert and product literature of products containing dopaminergic ingredients

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	WARNINGS AND PRECAUTIONS ……. has been associated with somnolence and episodes of sudden onset, particularly in patients with Parkinson's diseases. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ……. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES** Patients being treated with ……. and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also section on warnings and precautions). **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** ……. is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes. **Reference:** ***Bil. 14 dlm. BPFK/02/5/1.3*** *Keputusan Mesyuarat PBKD - Keluaran Yang Mengandungi Bahan Aktif Dopaminergik: Tambahan Amaran Berkaitan Dengan 'Sudden Sleep Onset'*
81.	**DOXYCYCLINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Doxycycline; **Package Insert** **a) Warnings and Precautions:** Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline treatment is started. Patients should be reassured that this is a usually self-limiting consequence of antibiotic treatment of spirochete infections. **b) Adverse Effects/Undesirable Effects:** Immune system disorders Frequency not known: Jarisch-Herxheimer reaction (see Section Warnings and Precautions)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Skin and subcutaneous tissue disorders: Frequency 'rare': Fixed eruption **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause Jarisch-Herxheimer reaction which usually consists of fever, chills, headache, muscle pain, and skin rash. The reaction occurs shortly after starting [product name] for spirochete infections and is often self-limiting. Round or oval patches of redness and swelling of the skin which reappear at the same site each time the medicine is taken (fixed eruption) **Reference:** **Directive No. 19, 2018.** ***BPFK/PPP/07/25 (19) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Doxycycline: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Jarisch-Herxheimer Reaction* **Directive No. 18, 2025.** ***NPRA.600-1/9/13 (65)Jld.1*** *Direktif untuk semua produk yang mengandungi doxycycline: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko Fixed Eruption (FE)/ Fixed Drug Eruption (FDE)*
82.	**EFAVIRENZ** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Efavirenz: **Package Insert** **a) Warnings and Precautions:** - QTc prolongation has been observed with the use of efavirenz (see Section Pharmacodynamics and Section Interaction with Other Medicaments). Consider alternatives to [Product name] when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes. - Nervous System Symptoms: Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms, which are associated with increased efavirenz levels despite standard dosing of [product name]. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of [product name] is warranted.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Pharmacodynamics: Cardiac Electrophysiology The effect of [Product name] on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days. (see Section Warnings and Precautions & Section Interaction with Other Medicaments). **c) Interactions:** QT Prolonging Drugs There is limited information available on the potential for a pharmacodynamic interaction between [Product name] and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of efavirenz (see Section Pharmacodynamics and Section Warnings and Precautions). Consider alternatives to [Product name] when coadministered with a drug with a known risk of Torsade de Pointes. **d) Adverse Effects/ Undesirable Effects:** Postmarketing experiences: encephalopathy **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before You Use [product name]:** Before you start to use it: Tell your doctor if you have any heart disorder. **b) Side effects:** Some nervous system symptoms [e.g. confusion, slow thoughts and physical movement and delusions (false beliefs) or hallucinations (seeing or hearing things that others do not see or hear)] may occur months to years after beginning [product name] therapy. Always notify your doctor or pharmacist if you have

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	these symptoms or any side effects while taking [product name]. **References:** **Directive No. 18, 2018.** ***BPFK/PPP/07/25 (18) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Efavirenz: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan QTc Prolongation* **Directive No. 4, 2021.** ***NPRA.600-1/9/13 (14)*** *Direktif Untuk Semua Produk Yang Mengandungi Efavirenz (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Late Onset Neurotoxicity*
83.	**EMPAGLIFLOZIN (INCLUDING COMBINATION PRODUCTS)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing empagliflozin (including combination products): **Package Insert** **a) Interactions:** Lithium Concomitant use of SGLT2 inhibitors, including empagliflozin, with lithium may decrease blood lithium levels through increased renal lithium elimination. Therefore, serum lithium concentration should be monitored more frequently with empagliflozin initiation or following dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]- taking other medicines** It is important to tell your doctor: • if you are taking lithium because [product name] can lower the amount of lithium in your blood. **Reference: Directive No. 9, 2024.** ***NPRA.600-1/9/13 (40)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
84.	**EPHEDRINE** The following statement shall be included on the labels and in the package inserts of products containing Ephedrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
85.	**ERYTHROMYCIN** 1. The following statement shall be included in the package insert and RiMUP of products containing erythromycin; **Package Insert** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **Consumer Medication Information Leaflet (RiMUP)** **Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you

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	experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive Bil 22, 2018.** ***Bil. (22) dlm BPFK/PPP/07/25 Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin dan Roxithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)* 2. The following statement shall be included in the package insert and RiMUP of products containing erythromycin (except topical/ external and ophtalmic preparations); **Package Insert** **a) Warnings and Precautions:** There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs. **b) Adverse Effects/Undesirable Effects:** Postmarketing Experience: Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis. **Consumer Medication Information Leaflet (RiMUP)** **Side Effects** If you notice that the child vomits and/or irritability with feeding occurs, contact doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS). **Reference: Directive No. 28, 2017.** ***BPFK/PPP/07/25 (33) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin dan Erythromycin Kecuali Persediaan Topikal/ Eksternal dan Ubat Untuk Kegunaan Mata: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
86.	**ETHINYLESTRADIOL** The following statements shall be <u>included in the package insert</u> and <u>Consumer Medication Information Leaflet (RiMUP)</u> of products containing ethinylestradiol; **<u>Package Insert</u>** **a) Contraindications:** [Product name] is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interactions with Other Medicaments). **b) Warnings and Precautions:** ALT elevations During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir/ ritonavir and dasabuvir therapy (See Section Contraindications and Section Interactions with Other Medicaments). **c) Interactions:** Concomitant use with the medicinal products containing ombitasvir/ paritaprevir/ ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. [Product name] can be restarted 2 weeks following completion of treatment with this combination drug regimen. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before You Use [product name]:** When you must not use it: Do not use [product name] if you have Hepatitis C and are taking the

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir. Taking other medicines: Do not use [product name] if you have Hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir. Your doctor will prescribe another type of contraceptive before starting the treatment with these medicinal products. **Reference: Directive No. 13, 2018.** ***BPFK/PPP/07/25 (13) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Ethinylestradiol: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Risiko Peningkatan Paras Alanine Transaminase (ALT) Akibat Interaksi Dengan Produk Kombinasi Ombitasvir / Paritaprevir / Ritonavir dan Dasabuvir*
87.	**ETORICOXIB** The following statements shall be <u>included in the package insert and RiMUP</u> of pharmaceutical products containing Etoricoxib: **<u>Package Insert</u>** **Dosage and Administration:** <u>Rheumatoid arthritis</u> The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered. <u>Ankylosing spondylitis</u> The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **How Much to Use:** <u>Rheumatoid arthritis</u> The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. <u>Ankylosing spondylitis</u> The recommended dose is 60 mg once a day, and may increase to 90 mg once a day

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	if needed. **Reference: Directive No. 13, 2017.** ***BPFK/PPP/07/25 (18) Jld. 1*** *Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Etoricoxib: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Perubahan Dos Permulaan Bagi Rawatan Rheumatoid Arthritis dan Ankylosing Spondylitis*
88.	**FAMOTIDINE** The following statement shall be included in the package inserts of products containing Famotidine: **DOSAGE** Dosage adjustment is required for patients with moderate to severe renal insufficiency. Since CNS adverse effects have been reported in patients with moderate to severe renal insufficiency, to avoid excess accumulation of the drug, the dose of famotidine may be reduced to half the recommended dose or the dosing interval may be prolonged to 36 - 48 hours as indicated by the patient's clinical response. **WARNINGS AND PRECAUTIONS** As elderly patients are more likely to have decreased clearance of famotidine, care should be taken in dose selection and it may be useful to monitor renal function.
89.	**FIBRATES** The following statement shall be included in the package inserts of products containing Fibrates: **INTERACTION** Concurrent use of fibrates with HMG-CoA reductase inhibitors may cause severe myositis and myoglobinuria.
90.	**FILGRASTIM** The following statement shall be included in the package inserts of ALL biosimilar products containing FILGRASTIM **WARNINGS AND PRECAUTIONS** Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

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	Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** Clinical Trials **In Cancer Patients** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥1/1000 to < 1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony stimulating factors. **In Normal Donors undergoing peripheral blood progenitor cell mobilization** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony stimulating factors. Post Marketing **Vascular disorders** Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. Frequency "rare": Aortitis **References:** **Directive No. 13, 2014.** ***Bil. (20) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim dan Pegfilgrastim: Amaran Berkaitan Risiko Capillary Leak Syndrome (CLS) Bagi Pesakit Kanser dan Healthy Donor (Filgrastim) dan Bagi Pesakit Kanser (Pegfilgrastim)* **Directive No. 30, 2018.** ***Bil. (30) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim, Pegfilgrastim dan Lenograstim: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Aortitis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
91.	**FLUCLOXACILLIN** The following warning shall be included in the package insert of products containing Flucloxacillin: **WARNING** Liver Toxicity Flucloxacillin can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in older patients and those who take the drug for prolonged periods (see Precaution, Adverse Reactions)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
92.	**FLUCONAZOLE** The following statements shall be <u>included in the package insert and RiMUP</u> of pharmaceutical products containing Fluconazole: **<u>Package Insert</u>** **a) Pregnancy and Lactation:** <u>Use During Pregnancy</u> There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150mg of fluconazole as a single or repeated dose in the first trimester. Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom [product name] may be used if the anticipated benefit outweighs the possible risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus. Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400mg/day to 800mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high-dose levels associated with maternal toxicity. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 times the recommended human dose) to 320 mg/kg, embryolethality in rats were increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification. Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high dose (400-800mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

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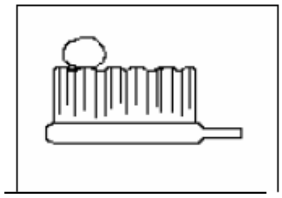
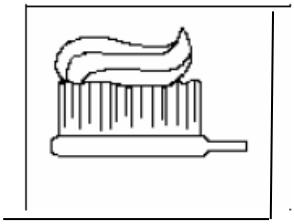
	Use During Lactation Fluconazole is found in human breast milk at concentrations similar to plasma. Breast-feeding may be maintained after a single dose of 150mg fluconazole. Breast-feeding is not recommended after repeated use or after high-dose fluconazole. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]** Inform your doctor if you have such conditions: • Pregnant or planning to become pregnant [Product name] may cause harm to your unborn baby. You should not take [product name] while you are pregnant unless your doctor has told you to. Inform your doctor if you are pregnant or planning to become pregnant. If you are a woman of child-bearing potential, avoid becoming pregnant during treatment. Use effective contraception during treatment and for 1 week after treatment. • Breast-feeding [Product name] is excreted in human breast milk, hence its use in nursing mothers is not recommended.However, breast-feeding may be maintained if you took a single dose of [product name] 150mg. Breast-feeding is not recommended after a high dose (more than 150 mg) or repeated use of [product name]. **Reference: Directive No. 24, 2017.** ***BPFK/PPP/07/25 (29) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Fluconazole: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Baharu Berkaitan Risiko Spontaneous Abortion Serta Memperkukuhkan Maklumat Keselamatan Berkaitan Multiple Congenital Abnormalities dan Penggunaan Dalam Kalangan Ibu Menyusu*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
93.	**FLUORIDE** All toothpastes containing Fluorides should be labeled with the following additional information: a. **DIRECTIONS ON USE** • Do not swallow – spit and rinse after use. b. **FOR CHILDREN BELOW 6 YEARS** • Use a pea-sized amount of toothpaste (less than 5mm). • Supervise child's brushing. c. **DIRECTIONS ON DENTAL HEALTH** • Brush at least twice a day. • Restrict the amount and frequency of sugary food. • Visit your dentist at least once a year. d. **GRAPHICS AS SHOWN** • *Child's use* • *Adult's use*  *Child's use*  *Adult's use*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
94.	**1. <u>FLUOROQUINOLONE</u>** The following statement shall be <u>included in the package inserts</u> of **oral and parenteral** products containing Fluoroquinolone: **WARNINGS AND PRECAUTIONS** <u>Exacerbation of myasthenia gravis</u> Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with flouroquinolones use in persons with myasthenia gravis. Avoid flouroquinolones in patients with known history of myasthenia gravis **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** <u>Exacerbation of myasthenia gravis</u> Post Marketing Experience **2. <u>FLUOROQUINOLONE (SYSTEMIC FORMULATIONS INCLUDING ORAL AND INJECTION DOSAGE FORMS)</u>** The following statement shall be included in the **<u>package inserts</u>**: **<u>Package Insert</u>** **a) Indication:** **(i) The following statement should be included:** Consideration should be given to official guidance on the appropriate use of antibacterial agents. **(ii) The following indication(s), if relevant, should be deleted:** • Acute bronchitis • Laryngitis • Pharyngitis-tonsillitis • Prophylaxis of infectious gastroenteritis / traveller's diarrhoea • Selective decontamination of gastrointestinal tract in patients with compromised immune system • Vaginal infections

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(iii) The following indication(s), if relevant, should be restricted:

- Acute bacterial rhinosinusitis*
- Acute exacerbation of chronic obstructive pulmonary disease including chronic bronchitis*
- Nosocomial pneumonia / Hospital-acquired pneumonia*
- Acute otitis media*
- External otitis*
- Endocarditis*
- Infection of cerebrospinal fluid*
- Meningitis*
- Septicaemia*
- Uncomplicated acute cystitis / uncomplicated cystitis*
- Prevention of exacerbations in women with recurring urinary tract infections*
- Prevention of infection in surgical procedures in the urogenital system*,#
- Pre-operative preparations for chronic cholesteatomatous otitis and chronic otitis spreading to bone*

(iv) The following text should be added after the restricted indications in part (iii):

*[Product name] should be only used :

- When Pseudomonas is considered AND patient is allergic to antipseudomonal penicillins/cephalosporins;
- For resistant organisms with no other alternative antibiotics available.

#[Product name] should not be used >24 hours post operation.

b) Warnings and Precautions:

The use of [INN] should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolones containing products (see section Adverse Effects/Undesirable Effects). Treatment of these patients with [INN] should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Aortic aneurysm and dissection Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department. Prolonged, disabling and potentially irreversible serious adverse drug reactions Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. [INN] should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice. Tendinitis and tendon rupture Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids*. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with [INN] should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur. *[For systemically administered levofloxacin-containing products, the listing of risk factors should additionally include: "in patients receiving daily doses of 1000 mg levofloxacin".] Peripheral neuropathy Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with [INN] should be advised to inform their doctor and pharmacist prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	(see section Adverse Effects/Undesirable Effects). **c) Adverse Effects/Undesirable Effects:** Musculoskeletal and connective tissue disorders* Nervous system disorders* General disorders and administrative site conditions* Psychiatric disorders* Eye disorders* Ear and labyrinth disorders* *Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see section Warnings and Precautions). The following statements shall be included in the **Consumer Medication Information Leaflet (RiMUP)**: **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it: - Tell your healthcare providers if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm). - Tell your healthcare providers if you have experienced a previous episode of aortic dissection (a tear in the aorta wall). - Tell your healthcare providers if you have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet´s disease, high blood pressure, or known atherosclerosis). - You should not take fluoroquinolone antibacterial medicines, including [product name], if you have experienced any serious adverse reaction in the past when taking a fluoroquinolone (see section Things to be careful of and Side effects). In

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	this situation, you should inform your healthcare providers as soon as possible. **b) While you are using it:** Things to be careful of: If you feel sudden, severe pain in your abdomen, chest or back, go immediately to the emergency department. <u>Prolonged, disabling and potentially irreversible serious side effects</u> Fluoroquinolone antibacterial medicines, including [product name], have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible. Stop taking your fluoroquinolone antibiotic and contact your healthcare providers immediately if you have the following signs of a side effect: • Tendon pain or swelling, often beginning in the ankle or calf. If this happens, rest the painful area until you can see your healthcare providers. • Pain in your joints or swelling in your shoulder, arms, or legs. • Abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in your body, especially in the legs or arms, or difficulty walking. • Severe tiredness, depressed mood, anxiety, problems with your memory, or severe problems sleeping. • Changes in your vision, taste, smell, or hearing. Tell your healthcare providers if you have had one of the above effects during or shortly after taking a fluoroquinolone – this means you should avoid them in the future. You and your healthcare providers will decide on continuing the treatment considering also an antibiotic from another class. <u>Tendinitis and tendon rupture</u> Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping of [product name] therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking [product name], contact your healthcare providers and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture. <u>Peripheral neuropathy</u> You may rarely experience symptoms of nerve damage (neuropathy) such as pain,

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	burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking [product name] and inform your healthcare providers immediately in order to prevent the development of potentially irreversible condition. **c) Side Effects:** Fluoroquinolones have been reported to cause serious side effects involving tendons, muscles, joints, and the nerves – in a small proportion of patients, these side effects caused long-lasting or permanent disability (see section Before you start to use it and Things to be careful of). **References:** **Directive No. 10, 2011.** ***Bil. (20) dlm. BPFK/PPP/01/03 Jilid 1*** *Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Exacerbation of Myasthenia Gravis dalam Sisip Bungkusan Semua Produk Antibiotik dalam Kumpulan Fluoroquinolones* **Directive No. 9, 2019.** ***BPFK/PPP/07/25 (9) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Antibiotik Kumpulan Fluoroquinolone (Sediaan Oral Dan Injeksi Sahaja): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Aortic Aneurysm dan Aortic Dissection* **Directive No. 12, 2019.** ***BPFK/PPP/07/25 (12) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Fluoroquinolone (Sediaan Oral Dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berikut: a) Membatalkan dan Menghadkan Indikasi Antibiotik Kumpulan Fluoroquinolone b) Amaran Berkaitan Disabling and Potentially Permanent Side Effects (Tendinitis, Tendon Rupture, Peripheral Neuropathy & Central Nervous System/ Neuropsychiatric Effects)*
95.	**GABAPENTIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Gabapentin; **Package Insert** **a) Warnings and Precautions:** Respiratory depression Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients. **b) Adverse Effects/ Undesirable Effects:** Respiratory, thoracic and mediastinal disorders Frequency 'rare': Respiratory depression

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	Post-marketing experience: Dysphagia **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** <u>Before you start to use it</u> If you have kidney problems, nervous system disorders, respiratory disorders or you are more than 65 years old, your doctor may prescribe a different dosing regimen. Tell your doctor or pharmacist if you are taking or have been recently taking any medicines for convulsions, sleeping disorders, depression, anxiety, or any other neurological or psychiatric problems. **b) Side Effects:** Contact your doctor immediately or go to the Emergency Department of your nearest hospital if you experience breathing problems such as slow, shallow or weak breathing after taking this medicine as this can be a sign of respiratory depression. **References:** **Directive No. 9, 2018**. ***BPFK/PPP/07/25 (9) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Gabapentin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Respiratory Depression* **Directive No. 5, 2020**. ***BPFK/PPP/07/25 (5) Jld. 4*** *Direktif Untuk Semua Produk Yang Mengandungi Gabapentin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Dysphagia*
96.	**GADOBENIC ACID** **Indication** of products containing gadobenic acid shall be amended as follows: a) [Product name] is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) of the liver for the detection of focal liver lesions in patients with known or suspected primary liver cancer (e.g. hepatocellular carcinoma) or metastatic disease. [Product name] should be used only when diagnostic information is essential and not available with unenhanced MRI and when delayed phase imaging is required. b) Other indications including use in MRI of the brain and spine, as contrast-enhanced MR- angiography & MRI of the breast shall be removed.

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97.	**GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING**
	
	The following boxed warning and warning shall be included in the package inserts of products containing Gadolinium Based Contrast Medium for Magnetic Resonance Imaging:
	
	BOXED WARNING
	
	- Exposure to gadolinium – based contrast agents (GBCAs) increases the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with:
	  • acute or chronic severe renal insufficiency (glomerular filtration rate < 30mL/min/1.73m^2), or
	  • acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
	
	- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs
	
	- Avoid use of GBCAs unless the diagnotic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).
	
	- Screen all patients for renal dysfunction by obtaining a history and/ or laboratory tests.
	
	- When administering a GBCA, do not exceed the dose recommended in product labelling. Allow sufficient time for elimination of the GBCA prior to any readministration.
	
	WARNINGS AND PRECAUTIONS
	• Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA.
	
	• For patients receiving haemodialysis, healthcare professionals may consider prompt haemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if haemodialysis prevents NSF.
	
	• Determine the renal function of patients by obtaining a medical history of conducting laboratory tests that measure renal function prior to using GBCA.
	
	• The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.
	
	• Post-marketing reports have identified the development of NSF following

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	single and multiple administrations of GBCAs. **Reference:** ***Bil. (2) dlm. BPFK/PPP/01/03 Jld. 1*** *Keputusan Mesyuarat PBKD - Penambahan Amaran Berkotak dan Amaran Terkini Ke Dalam Sisip Bungkusan Semua Agen 'Contrast Medium' Yang Berasaskan 'Gadolinium' (Gadolinium Based) Untuk Tujuan 'Magnetic Resonance Imaging'*
98.	**GAMAT/ STICHOPUS spp.** For products containing Gamat/ Stichopus spp. for **ORAL USE ONLY**, please state: **"Please consult your pharmacist, doctor, or other healthcare providers about any other supplements/ medications you are taking and other health care problems. There may be a potential for interactions or side effects."**
99.	**GENTAMICIN TOPICAL PREPARATIONS** The following boxed statement shall be included in the package inserts of topical Gentamicin preparations: Use of topical gentamicin preparations in closed hospital settings is actively discouraged
100.	**GINKGO BILOBA/ GINKGO EXTRACT** The following statements shall be included on the labels and in the package inserts of products containing *Gingko biloba*/ Gingko extract: As the use of Ginkgo may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/dental procedure. (*Memandangkan Ginkgo boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau akan menggunakan ubat lain dan sebelum prosedur pembedahan / dental dijalankan*). **Reference:** ***Bil. (47) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Ginkgo Biloba / Ginkgo Ekstrak*

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101.	**GINSENG** The following statements shall be included on the labels and in the package inserts of products containing Ginseng (including all Panax genus): • Contraindicated in pregnant women. • Safe use in lactating women and children has not been established. • Do not exceed the stated dose. • Safety on long term use has not been established.
102.	**GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISTS** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists; **Package Insert** **a) Warnings & Precautions:** Aspiration in association with general anaesthesia or deep sedation Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying should be considered prior to performing procedures with general anaesthesia or deep sedation. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it: If you know that you are due to have surgery where you will be under anaesthesia (sleeping), please tell your doctor that you are taking [product name]. **Reference: Directive No. 19, 2025.** *NPRA.600-1/9/13 (66)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Aspiration dan Pneumonia Aspiration Semasa Anestesia Umum (General Anaesthesia) atau Sedasi Penuh (Deep Sedation)*

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103.	**GLUCOSAMINE** The following statement shall be included on the labels and package inserts of products containing Glucosamine (derived from seafood); **"DERIVED FROM SEAFOOD"** The following statement shall be included in the package inserts of products containing Glucosamine: **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS:** • Cardiovascular Peripheral oedema, tachycardia were reported in a few patients following larger clinical trials investigating oral administration in osteoarthritis. Causal relationship has not been established. • Central nervous system Drowsiness, headache, insomnia have been observed rarely during therapy (less than 1%). • Gastrointestinal Nausea, vomiting, diarrhoea, dyspepsia or epigastric pain, constipation, heartburn and anorexia have been described rarely during oral therapy with glucosamine. • Skin Skin reactions such as erythema and pruritus have been reported with therapeutic administration of glucosamine. **References:** ***Bil. (52) dlm. BPFK/02/5/1.3*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Daripada Sumber Laut* ***Bil. (72) dlm. BPFK/02/5/1.3*** *Keputusan Mesyuarat PBKD - Mengemaskini dan Menyelaraskan Maklumat Mengenai Kesan Sampingan Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Glucosamine*
104.	**GRISEOFULVIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing griseofulvin; **Package Insert** **a) Warnings & Precautions:** Severe cutaneous adverse reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms,

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	acute generalised exanthematous pustulosis) and erythema multiforme have been reported with griseofulvin use. These reactions may be serious and may result in hospitalisation or death. If severe skin reactions occur, griseofulvin should be discontinued. **b) Adverse Effects/ Undesirable Effects:** Skin and subcutaneous tissue disorders Frequency 'not known': Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis, erythema multiforme. **Consumer Medication Information Leaflet (RiMUP)** **a) While You Are Using It:** If you experienced a severe skin reaction, including bumps under the skin, blisters, redness and peeling with or without fever, swollen glands and abnormal blood test results, see your doctor straight away. **b) Side effects:** Rare skin reactions which may be serious: widespread rash with blisters and peeling of the skin, especially around the mouth, nose and in the genital area causing severe skin peeling, fever, enlargement of the lymph nodes, or abnormal blood test (elevated eosinophil level or liver enzyme level). If you have such signs, consult your doctor immediately. **Reference: Directive No. 4, 2023.** *NPRA.600-1/9/13 (22)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Griseofulvin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Severe Cutaneous Adverse Reactions (SCARs)*
105.	**HIV PROTEASE INHIBITORS** The following statement shall be included in the package inserts of products containing HIV Protease inhibitors: **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS:** Although a causal relationship has not been definitively established, protease inhibitors may contribute to increase in blood sugar levels and even diabetes in HIV patients. Close monitoring of blood glucose level is recommended.

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106.	**HYDROCHLOROTHIAZIDE (INCLUDING COMBINATION PRODUCTS)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> of products containing hydrochlorothiazide (including combination products); **<u>Package Insert</u>** **a) Warnings and Precautions:** <u>Non-melanoma skin cancer</u> An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC. <u>Acute Respiratory Toxicity</u> Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, [product name] should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake. **b) Adverse Effects/ Undesirable Effects:** <u>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</u> Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma) Description of selected adverse reactions Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

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Respiratory, thoracic and mediastinal disorders
Frequency 'very rare': Acute respiratory distress syndrome (ARDS)

c) Pharmacodynamic:

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg).

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Inform your healthcare providers before taking [product name] if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking [product name].

Before taking [product name], tell your doctor:

- if you experience breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking [product name], seek medical attention immediately.

b) Side Effects:

Frequency 'not known': Skin and lip cancer (Non-melanoma skin cancer)

Very Rare:

- Acute respiratory distress (signs include severe shortness of breath, fever, weakness and confusion).

Reference: Directive No. 11, 2019. ***BPFK/PPP/07/25 (11) Jld.3*** *Direktif Untuk Semua Produk Yang*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Mengandungi Hydrochlorothiazide Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Non-Melanoma Skin Cancer **Directive No. 12, 2024.** ***NPRA.600-1/9/13 (43)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Hydrochlorothiazide (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Acute Respiratory Distress Syndrome (ARDS)*
107.	**HYDROQUINONE** The following warning shall be included on the outer labels of products containing Hydroquinone: **WARNING:** Some users of this product may experience skin irritations. Should this occur, stop using and consult a medical doctor. For hydroquinone products that do not contain any sun screening agent, a statement should be included in the package insert to advise users to either use a sun screening agent or protect themselves from sunlight or to use the products only at night. **Reference:** ***Bil. (26) dlm.BPFK/02/5/1.2*** *Amaran bagi Produk Mengandungi Hydroquinone*
108.	**HYOSCINE (FOR INJECTION ONLY)** The following statements shall be included in the package insert of products containing Hyoscine: **Package Insert** **a) Contraindications:** [Product name] should not be administered to patients with tachycardia. **b) Warnings and Precautions:** [Product name] can cause tachycardia, hypotension and anaphylaxis, therefore use with caution in patients with cardiac conditions such as cardiac failure, coronary heart disease or cardiac arrhythmia and patients with cardiovascular disease (e.g. acute myocardial infarction, hypertension and conditions associated with tachycardia or hypertension, and in cardiac surgery). Monitoring of these patients is advised. Emergency equipment and personnel trained in its use must be readily available. **c) Adverse Effects/Undesirable Effects:** Immune system disorders

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Not known: anaphylactic shock including cases with fatal outcome, anaphylactic reactions. Cardiac disorders Common: tachycardia **Reference: Directive No. 17, 2017.** ***BPFK/PPP/07/25 (22) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Hyoscine (Bentuk Dos Injeksi Sahaja): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Serius Pada Pesakit Jantung dan Kardiovaskular*
109.	**IMATINIB** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing imatinib; **Package Insert** **a) Warnings & Precautions:** Thrombotic microangiopathy BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA), including individual case reports for Imatinib. If laboratory or clinical findings associated with TMA occur in a patient receiving Imatinib, treatment should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If antiADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with Imatinib should not be resumed. **b) Adverse Effects/ Undesirable Effects:** Blood and lymphatic system disorders Frequency 'rare': thrombotic microangiopathy **Consumer Medication Information Leaflet (RiMUP)** **a) Before you start to use [product name]:** Before taking [product name], tell your doctor: • if you experience bruising, bleeding, fever, fatigue and confusion when taking [product name]. This may be a sign of damage to blood vessels known as thrombotic microangiopathy (TMA). **b) Side effects:** Rare: • blood clots in small blood vessels (thrombotic microangiopathy). **Reference: Directive No. 2, 2024.** ***NPRA.600-1/9/13 (33)Jld.1*** *Direktif Untuk Semua Produk Yang*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Mengandungi Imatinib: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Thrombotic Microangiopathy (TMA)
110.	**IMMUNOSUPPRESANTS** The following information shall be included in the package inserts of products containing immunosuppressants: **WARNINGS AND PRECAUTIONS** Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes. **Reference:** ***Bil. (44) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Berkaitan Dengan "Increased Risk for Opportunistic Infections Such As Activation of Latent Viral Infections Including BK Virus – Associated Nephropathy" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Immunosuppressant*
111.	**INSULIN (INCLUDING COMBINATION PRODUCTS)** The label of the product shall state clearly the source of insulin. The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing insulin (including combination products); **Package Insert** **a) Posology and Method of Administration:** Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. **b) Warnings and Precautions:** Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	c) Adverse Effects/ Undesirable Effects: Skin and subcutaneous tissue disorders Frequency "not known": Cutaneous amyloidosis Description of selected adverse reactions Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it Skin changes at the injection site: The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area. Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose. **b) Side effects:** Frequency 'not known': Changes at the injection site (Cutaneous amyloidosis) **Reference: Directive No. 18, 2021**. ***NPRA.600-1/9/13(28)*** *Direktif Untuk Semua Produk Yang Mengandungi Insulin (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Cutaneous Amyloidosis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
112.	**INGREDIENTS DERIVED FROM SEAFOOD** The following statement shall be included on the labels and package inserts of products containing ingredients derived from seafood. **"DERIVED FROM SEAFOOD"** **Reference:** ***Bil. (52) dlm. BPFK/02/5/1.3*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan Aktif Adalah Daripada Sumber Laut*
113.	**INTERFERON ALPHA** The following statements shall be included in the package insert and RiMUP of products containing Interferon Alpha: **Package Insert** **a) Adverse Effects/ Undesirable Effects:** **Respiratory, thoracic and mediastinal disorders:** Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alpha products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alpha. **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects** Tell your doctor immediately if you experience: • Shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen. These may indicate pulmonary arterial hypertension (high blood pressure in the arteries that supply the lungs). **Reference: Directive No. 1, 2017.** ***BPFK/PPP/07/25 (6) Jld. 1*** *Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa dan Interferon Beta: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Pulmonary Arterial Hypertension (PAH)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
114.	**INTERFERON BETA** The following statements shall be <u>included in the package insert and RiMUP</u> of products containing Interferon Beta: **<u>Package Insert</u>** **a) Adverse Effects/ Undesirable Effects:** **Respiratory, thoracic and mediastinal disorders:** Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects** Tell your doctor immediately if you experience: • Shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen. These may indicate pulmonary arterial hypertension (high blood pressure in the arteries that supply the lungs). **Reference: Directive No. 1, 2017.** ***<u>BPFK/PPP/07/25 (6) Jld. 1</u>*** *Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa dan Interferon Beta: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Pulmonary Arterial Hypertension (PAH)*
115.	**IODINATED CONTRAST MEDIA** The following statements shall be <u>included in the package insert</u> for products containing Iodinated Contrast Media; **<u>Package Insert</u>** **a) Warnings & Precautions:** <u>Thyroid Dysfunction</u> Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported in pediatric patients 0-3 years of age after exposed to iodinated contrast media. Younger age, very low birth weight, prematurity and other conditions are associated with an increased risk. If thyroid dysfunction is detected, treat and monitor thyroid function as

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	clinically needed. **b) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Severe cutaneous adverse reactions {e.g. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP)} have been reported in post-marketing experience of iodinated contrast media. Post-marketing Experience Endocrine disorders Frequency 'not known': hypothyroidism **References:** **Directive No. 24, 2018.** ***Bil. (24) dlm. BPFK/PPP/07/25 (24) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Iodinated Contrast Media: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)* **Directive No. 11, 2022.** ***NPRA.600-1/9/13 (11)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Iodinated Contrast Media: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Hypothyroidism (Terutamanya Dalam Kalangan Bayi)*
116.	**ISONIAZID** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Isoniazid: **Package Insert** **a) Adverse Effects/Undesirable Effects:** Gastrointestinal Disorders: Pancreatitis **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Inflammation of the pancreas, which causes severe pain in the abdomen and back (pancreatitis) **Reference : Directive No. 27, 2018.** ***BPFK/PPP/07/25 (27) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Isoniazid: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RIMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Pancreatitis*

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117.	**ISOTRETINOIN** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing isotretinoin; **<u>Package Insert</u>** **a) Warnings & Precautions:** <u>Musculo-skeletal and connective tissue disorders</u> Sacroiliitis has been reported in patients exposed to [product name]. To differentiate sacroiliitis from other causes of back pain, in patients with clinical signs of sacroiliitis, further evaluation may be needed including imaging modalities such as MRI. In cases reported post-marketing, sacroiliitis improved after discontinuation of [product name] and appropriate treatment. **b) Adverse Effects/ Undesirable Effects:** <u>Musculo-skeletal system disorders</u> Cases of sacroiliitis have been observed in patients treated with isotretinoin (see section Warnings and Precautions) <u>Renal and urinary disorders</u> Cases of urethritis have been reported. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **b) While you are using it:** <u>Things you must do:</u> Talk to your doctor if you experience persistent pain in your lower back or buttocks during treatment with [product name]. These symptoms may be signs of sacroiliitis, a type of inflammatory back pain. Your doctor may discontinue treatment with [product name] and refer you to a specialist for treatment of inflammatory back pain. Further evaluation may be needed including imaging modalities such as MRI. **b) Side effects:** - persistent pain in the lower back or buttocks - inflammation of the urethra **Reference: Directive No. 7, 2025.** *NPRA.600-1/9/13 (54)Jld.1 Direktif untuk semua produk yang mengandungi isotretinoin: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko sacroiliitis dan urethritis*

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118.	**KAOLIN, PECTIN, KAOLIN-PECTIN** The following boxed warning shall be included on the labels: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE.** The following statement shall be included in the package inserts of products containing kaolin and/ or pectin: **WARNING** **Not recommended for children under 6 years of age.** Severe constipation, which may lead to faecal impaction, may rarely occur in children and the elderly patients taking kaolin and pectin. Kaolin and pectin may interfere with the absorption of other drugs, including antibiotics, administered concurrently. **PRECAUTION** Appropriate fluid and electrolyte therapy should be given to protect against dehydration. Oral rehydration therapy with the use of appropriate fluids including oral rehydration salts - remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative.
119.	**KETOCONAZOLE** **1. Indication of products containing oral ketoconazole is restricted as follows, and the package insert of the product shall be amended accordingly:** [BRAND NAME] (ketoconazole) Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks. [BRAND NAME] (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. [BRAND NAME] (ketoconazole) Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid.

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Reference: Directive No. 3, 2014. ***Bil. (9)dlm.BPFK/PPP/07/25*** *Direktif Untuk Memperketatkan Indikasi Semua Produk Ketoconazole Oral Dan Mengehadkan Penggunaan Di Hospital Sahaja Berikutan Risiko Kesan Advers Hepatotoksisiti*

2. The following statement shall be included in the package inserts of products containing oral ketoconazole:

CONTRAINDICATIONS

In patients with acute or chronic liver disease.

WARNINGS AND PRECAUTIONS

Because of the risk for serious hepatotoxicity, [BRAND NAME] should be used only when the potential benefits are considered to outweigh the potential risks, taking into consideration the availability of other effective antifungal therapy.

Assess liver function, prior to treatment to rule out acute or chronic liver disease, and monitor at frequent and regular intervals during treatment, and at the first signs or symptoms of possible hepatotoxicity.

Hepatotoxicity

Very rare cases of serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation have occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Cases have been reported that occurred within the first month of treatment, including some within the first week.

The cumulative dose of the treatment is a risk factor for serious hepatotoxicity. Factors which may increase the risk of hepatitis are prolonged treatment with ketoconazole tablets, females over 50 years of age, previous treatment with griseofulvin, a history of liver disease, known drug intolerance and concurrent use of medication which compromises liver function. A period of one month should be allowed between cessation of griseofulvin treatment and commencement treatment with ketoconazole tablets because of an apparent association between recent griseofulvin therapy and hepatic reactions to ketoconazole tablets.

Monitor liver function in all patients receiving treatment with ketoconazole tablets (see Monitoring of hepatic function).

Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. In these patients, treatment should be stopped immediately and liver function should be conducted.

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	Monitoring of hepatic function Monitor liver function in all patients receiving treatment with ketoconazole tablets. Monitor liver function prior to treatment to rule out acute or chronic liver disease (see CONTRAINDICATIONS), after two weeks of treatment and then on a monthly basis and at the first signs or symptoms of possible hepatic toxicity. When the liver function tests indicate liver injury, the treatment should be stopped immediately. A risk and benefit evaluation should be made before oral ketoconazole is used in cases of non-life threatening diseases requiring long treatment periods. In patients with elevated liver enzymes, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases, close monitoring of the liver enzymes is necessary. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** **Post-marketing Experience** ***Hepato-biliary Disorders*** Very rare: serious hepatotoxicity, including hepatitis cholestatic, biopsy-confirmed hepatic necrosis, cirrhosis, hepatic failure including cases resulting in transplantation or death (see WARNINGS AND PRECAUTIONS). **Reference: Directive No. 12, 2011.** ***Bil. (22)dlm.BPFK/PPP/01/03 Jilid 1*** *Direktif Memperkukuhkan Amaran Berkaitan Dengan Risiko Hepatotoksisiti Yang Teruk Dalam Sisip Bungkusan Semua Produk Oral Ketoconazole*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
120.	**KETOROLAC TROMETHAMOL (KETOROLAC TROMETHAMINE)** The following statements shall be included in the package inserts of products containing Ketorolac tromethamol: **THE PRODUCT SHALL BE INDICATED FOR THE FOLLOWING** For short-term management of moderate to severe acute post-operative pain following surgical procedures associated with low risk of haemorrhage. **DOSAGE AND DURATION OF TREATMENT** Parenteral administration: The starting dose should be 10mg with subsequent doses of 10-30mg four to six hourly as required. The lowest effective dose should be used. The total daily dose of 90mg for the non-elderly and 60mg for the elderly should not be exceeded. Maximum duration of parenteral treatment is 2 days for all age groups. In patients who have received parenteral ketorolac and are converted to oral tablets, the total combined daily dose of all forms of ketorolac should not exceed 90mg for non-elderly and 60mg for the elderly. Maximum duration of treatment for the oral formulation is 7 days. **CONTRAINDICATIONS** • A history of peptic ulceration or gastrointestinal bleeding • A history of haemorrhagic diathesis • A history of confirmed or suspected cerebrovascular bleeding • Operations associated with a high risk of haemorrhage • A history of asthma • Moderate or severe renal impairment (serum creatinine > 160□mol/L) • Hypovolaemia or dehydration from any cause • Hypersensitivity to NSAIDs or aspirin • During pregnancy, labour, delivery or lactation • Concomitant administration with other NSAIDs, anticoagulant including low dose heparin

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
121.	**LABETALOL** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing labetalol; **<u>Package Insert</u>** **a) Pregnancy and Lactation:** Nipple pain and Raynaud's phenomenon of the nipple have been reported. **b) Adverse Effects/ Undesirable Effects:** <u>Reproductive System and Breast Disorders</u> Frequency 'not known': Nipple pain, Raynaud's phenomenon of the nipple **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects:** Nipple pain and intermittent decrease in blood flow to your nipples, which may cause your nipples to go numb, pale and painful have been reported, but the frequency cannot be estimated from the available data. **Reference: Directive No. 15, 2022.** ***<u>NPRA.600-1/9/13 (15)Jld.1</u>*** *Direktif Untuk Semua Produk Yang Mengandungi Labetalol: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Memperkukuhkan Maklumat Keselamatan Berkaitan Risiko Kesakitan Pada Puting Payudara Disebabkan Oleh Fenomena Raynaud*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
122.	**LAMOTRIGINE** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing lamotrigine; **<u>Package Insert</u>** **a) Warnings and Precautions:** Hemophagocytic lymphohistiocytosis (HLH) has occurred in patients taking lamotrigine (see section Adverse Effects/Undesirable Effects). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lympha-denopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation. Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be discontinued unless an alternative aetiology can be established. **Brugada-type ECG** A very rare association with Brugada-type ECG has been observed, although a causal relationship has not been established. Therefore, careful consideration should be given before using [product name] in patients with Brugada syndrome. **b) Adverse Effects/Undesirable Effects:** <u>Skin and subcutaneous tissue disorders</u> Frequency 'rare': erythema multiforme **Post-marketing** Blood and lymphatic system disorders Very rare: Hemophagocytic lymphohistiocytosis (see section Warnings and Precautions) **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** Before you start to use it Talk to your healthcare providers before taking [product name]: • If you have a condition called Brugada syndrome (a genetic disease that

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	affects the heart) **b) Side Effects:** Hemophagocytic lymphohistiocytosis (HLH) There have been reports of a rare but very serious immune system reaction, in patients taking lamotrigine. - Contact your doctor or pharmacist immediately if you experience any of the following symptoms while taking lamotrigine: fever, rash, neurological symptoms (e.g. shaking or tremor, confusional state). Skin rashes or redness, which may develop into severe skin reactions including red spots or patches that may look like a target or "bulls-eye" with a dark red centre surrounded by paler red rings (Erythema multiforme) **References:** **Directive No. 3, 2019.** ***BPFK/PPP/07/25 (3) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Lamotrigine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hemophagocytic Lymphohistiocytosis (HLH)* **Directive No. 14, 2019.** ***BPFK/PPP/07/25 (14) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Lamotrigine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Brugada-Type ECG* **Directive No. 16, 2025.** ***NPRA.600-1/9/13 (63)Jld.1*** *Direktif untuk semua produk yang mengandungi Lamotrigine: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko Erythema Multiforme (EM)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
123.	**LENOGRASTIM** The following statements shall be <u>included in the package insert</u> of products containing Lenograstim; **a) Warnings and Precautions:** Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. **b) Adverse Effects/Undesirable Effects:** <u>Vascular disorders</u> Frequency "rare": Aortitis **Reference: Directive No. 30, 2018.** ***<u>Bil. (30) dlm. BPFK/PPP/07/25 Jld.2</u>*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim, Pegfilgrastim dan Lenograstim: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Aortitis*
124.	**LEVETIRACETAM** The following statements shall be <u>included in the package insert</u> and <u>Consumer Medication Information Leaflet (RiMUP)</u> of products containing Levetiracetam; **<u>Package Insert</u>** **a) Warnings and Precautions:** Acute kidney injury The use of levetiracetam has been rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months. **b) Adverse Effects / Undesirable Effects:** Renal and urinary disorders: Frequency rare: acute kidney injury. Musculoskeletal and connective tissue disorders: Frequency rare: rhabdomyolysis and blood creatine phosphokinase increased.* * Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects:** Tell your doctor immediately if you notice any of the following: • Symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, may be a sign of sudden decrease of kidney function. • Signs or symptoms including muscleache, feeling of weakness and dark urine may indicate the side effect of rhabdomyolysis (breakdown of muscle tissue). • If someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements, these could be symptoms of an encephalopathy. **Reference: Directive No. 3, 2018.** ***BPFK/PPP/07/25 (3) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Levetiracetam: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Acute Kidney Injury, Rhabdomyolysis/ Blood Creatine Phosphokinase Increased dan Encephalopathy*
125.	**LEVOFLOXACIN** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing levofloxacin for systemic use (oral and injection dosage forms): **<u>Package Insert</u>** **a) Warnings & Precautions:** <u>Psychiatric reactions</u> Psychiatric reactions may occur even after the first administration of fluoroquinolones, including [Product name]. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, [Product name] should be discontinued and appropriate measures instituted. Caution is recommended if [Product name] is to be used in psychotic patients or in patients with a history of psychiatric disease. **b) Adverse Effects/ Undesirable Effects:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Psychiatric disorders Rare: Psychotic reactions (with e.g. hallucination, paranoia), Depression Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) Not known (cannot be estimated from available data): Psychotic disorders with self-endangering behavior including suicidal ideation or suicide attempt **Consumer Medication Information Leaflet (RiMUP)** **a) While you are using it:** You may experience mental health problems even when taking/ using fluoroquinolone antibiotics, including [Product name] for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts. If you develop such reactions, stop taking/ using [Product name] and inform your doctor immediately. **b) Side effects:** Rare: Change in your opinion and thoughts (psychotic reactions) with a risk of having suicidal thoughts or actions, hallucination, depression Very rare: Psychotic behaviour Not known (frequency cannot be estimated from the available data): Psychotic reactions with a risk of having suicidal thoughts or actions **Reference: Directive No. 8, 2024.** *NPRA.600-1/9/13 (39)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour*
126.	**LEVONORGESTREL** The following statements shall be included in the package insert, label and RiMUP of emergency contraceptives containing Levonorgesteral: **Package Insert** **a) Recommended Dose:** Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to use a non-hormonal emergency contraceptive, i.e. Cu-IUD or take a double dose of levonorgestrel (i.e. <number of> tablets taken together) for those women unable or unwilling to use Cu-IUD.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

b) Interactions:

The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers, mainly CYP3A4 enzyme inducers. Concomitant administration of efavirenz has been found to reduce plasma levels of levonorgestrel (AUC) by around 50%.

Drugs suspected of having similar capacity to reduce plasma levels of levonorgestrel include barbiturates, phenytoin, carbamazepine, herbal medicines containing Hypericum perforatum (St. John's wort), rifampicin, ritonavir, and griseofulvin.

For women who have used enzyme-inducing drugs in the past 4 weeks and need emergency contraception, the use of non-hormonal emergency contraception (i.e. a Cu-IUD) should be considered. Taking a double dose of levonorgestrel (i.e. 3 mg within 72 hours after the unprotected intercourse) is an option for women who are unable or unwilling to use a Cu-IUD, although this specific combination (a double dose of levonorgestrel during concomitant use of an enzyme inducer) has not been studied.

Label

*If you have used certain **other medicines in the last 4 weeks**, in particular treatment for epilepsy, tuberculosis, for HIV infection or herbal medicines containing St. John´s wort (see leaflet), [product name] may work less effectively. If you use these medicines take <number of> tablets of [product name]. If you are unsure or to ask for an alternative treatment speak to your doctor or pharmacist before using [product name].*

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]

Taking other medicines

If you have used any of the medicines below during the last 4 weeks, [product name] may work less effectively.Your doctor may prescribe another type of (non-hormonal) emergency contraceptive, i.e. a copper intrauterine device (Cu-IUD). If this is not an option for you or if you are unable to see your doctor promptly, you can take a double dose (i.e. <number of> tablets) of [product name]:

- medicines used to treat epilepsy (e.g. phenobarbitone, phenytoin, carbamazepine)
- medicines used to treat tuberculosis (e.g. rifampicin)
- medicines used to treat HIV (e.g. ritonavir, efavirenz)
- medicines used to treat fungal infections (e.g. griseofulvin)
- herbal remedies containing St. John's wort (Hypericum perforatum)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Speak to your doctor or pharmacist if you need further advice on the correct dose for you. Consult your doctor as soon as possible after taking the tablets for further advice on a reliable form of regular contraception and to exclude a pregnancy. **Reference: Directive No. 11, 2017.** ***BPFK/PPP/07/25 (16) Jld.1*** *Direktif Untuk Semua Produk Kontraseptif Kecemasan Yang Mengandungi Levonorgestrel Dengan Maklumat Berkaitan Interaksi Antara Ubat-Ubatan Yang Dikelaskan Sebagai Hepatic Enzyme Inducer Dan Keberkesanan Kontrasepsi*
127.	**LINCOMYCIN** For all products containing Lincomycin: The package insert must emphasize the possibility of pseudomembranous colitis with the use of the drug and must include the following boxed or emphasized statement/ warning: a. Lincomycin therapy has been associated with severe colitis which may end fatally. b. It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. c. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. d. Its use in newborns is contraindicated.
128.	**LINEZOLID** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing linezolid; **Package Insert** **a) Warnings & Precautions:** Rhabdomyolysis has been reported with the use of linezolid. If signs or symptoms of rhabdomyolysis are observed, linezolid should be discontinued and appropriate therapy initiated. **b) Adverse Effects/ Undesirable Effects:** System Organ Class (SOC): Musculoskeletal and connective tissue disorders Frequency 'rare': Rhabdomyolysis* *ADR identified post-marketing **Consumer Medication Information Leaflet (RiMUP) (for oral dosage form only)** **a) While you are using it:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	If signs or symptoms of rhabdomyolysis (breakdown of damaged muscle) are observed, you should stop using [Product name] and tell your doctor immediately. **b) Side effects:** Rhabdomyolysis (breakdown of damaged muscle) - muscle pain, tenderness or weakness and dark urine Reference: **Directive No. 3, 2026.** *NPRA.600-1/9/13 (74)Jld.1 Direktif untuk semua produk yang mengandungi linezolid: Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko rhabdomyolysis*
129.	**LIQUID PARAFFIN** The following statement shall be included on the labels of products containing Liquid paraffin as laxative: • Not recommended for use in children below 3 years of age; • Not recommended for use in pregnant women; • Repeated use is not advisable; • Consult your doctor if laxatives are needed every day, if you have persistent abdominal pain or have a condition which makes swallowing difficult.
130.	**LITHIUM** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing lithium (for treatment purpose only): **Package Insert** **a) Interactions:** SGLT2 inhibitors may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after initiation and dose changes of SGLT2 inhibitors. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]- taking other medicines** The following medication interacts with Lithium Carbonate: • Medication of the class 'sodium-glucose co-transporter 2 (SGLT2) inhibitors' such as empagliflozin (medication for type 2 diabetes or heart failure), dapagliflozin (medication for type 2 diabetes, heart failure or chronic kidney disease), canagliflozin (medication for type 2 diabetes,

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	heart failure or chronic kidney disease). **Reference: Directive No. 9, 2024.** *NPRA.600-1/9/13 (40)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat*
131.	**LOPERAMIDE** 1. The following boxed warning shall be included on the labels of products containing Loperamide: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE** 2. The following statement shall be included in the package inserts of products containing Loperamide: **a) WARNING** Not recommended for children under 6 years of age. Its use has been associated with fatal episodes of paralytic ileus in infants and young children. **b) PRECAUTION** Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes. If severe dehydration or electrolyte imbalance is present Loperamide should be withheld until appropriate corrective therapy has been initiated. **c) Warnings and Precautions** The use of higher than the recommended doses for control of the diarrhea may cause abnormal heart rhythms and serious cardiac events leading to death. However, in adult patients receiving the recommended dosage of loperamide, cases of syncope and ventricular tachycardia have been reported. Some of these patients were taking other drugs or had other risk factors that may have increased their risk of cardiac adverse reactions. Abuse and misuse of loperamide, as an opioid substitute, have been described

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	in individuals with opioid addiction (see Overdose). **d) Adverse Effects/ Undesirable Effects** Post-marketing Experience Cardiac Disorders: QT/QTc interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death (see Warnings and Precautions) <u>Gastrointestinal disorders</u> Frequency 'not known': Acute pancreatitis **e) Overdose** In individuals who have intentionally ingested overdoses (reported in doses from 40 mg up to 792 mg per day) of loperamide HCL, prolongation of the QT/QTc interval, Torsades de Pointed, other ventricular arrhythmias and cardiac arrest, have been observed (see Warnings and Precautions). Fatal cases have also been reported. Abuse, misuse and/or overdose with excessively large doses of loperamide, may unmask Brugada syndrome. 3. The following <u>statement</u> shall be <u>included in the RiMUP</u> of products containing Loperamide: **a) Side effects** Upper abdominal pain, abdominal pain that radiates to back, tenderness when touching the abdomen, fever, rapid pulse, nausea, vomiting, which may be symptoms of inflammation of the pancreas. **b) If you use too much (overdose)** If you have taken more than the recommended dose of [product name], immediately contact your doctor or go to the Emergency Department of your nearest hospital for advice. Symptoms may include : • changes to your heartbeat such as increased heart rate and irregular heart rhythm (these symptoms can have potentially serious, life-threatening consequences) • muscle stiffness • uncoordinated movements • drowsiness • difficulty urinating

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• weak breathing **References:** **Directive No. 14, 2017.** ***BPFK/PPP/07/25 (19) Jld.1*** *Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Loperamide: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Pada Jantung Yang Serius Susulan Pengambilan Loperamide Melebihi Dos Yang Disyorkan dan Isu Penyalahgunaan* **Directive No. 18, 2019.** ***BPFK/PPP/07/25 (18) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Loperamide: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Unmasking Brugada Syndrome Dengan Pengambilan Dos Berlebihan* **Directive No. 10, 2023**. ***NPRA.600-1/9/13 (28) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Loperamide: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Pankreatitis Akut (Acute Pancreatitis)*
132.	**LOVASTATIN** The following statement shall be included in the package inserts of products containing Lovastatin: **1. Contraindications:** • Concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone). • Concomitant administration of cyclosporine. **2. Dosage and Administration:** Concomitant Therapy The combined use of lovastatin with gemfibrozil should be avoided. In patients taking danazol, verapamil, diltiazem, fibrates (except gemfibrozil) or lipid-lowering dose of niacin (≥1g/day) concomitantly with [Product Name], the dose of [Product Name] should not exceed 20mg/day. In patients taking amiodarone concomitantly with [Product Name], the dose of [Product Name] should not exceed 40mg/day. **3. Warnings and Precautions:** Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine. **4. Interactions:** Contraindicated Drugs

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Strong inhibitors of CYP3A4: Concomitant use with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) is contraindicated. Cyclosporine: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine. Concomitant use of this drug with lovastatin is contraindicated. <u>Other Drugs</u> • Gemfibrozil, other fibrates, niacin ≥1g/day: These drugs increase the risk of myopathy when given concomitantly with lovastatin, probably because they can produce myopathy when given alone. There is no evidence to suggest that these agents affect the pharmacokinetics of lovastatin. Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of lovastatin with fibric acid derivatives or niacin. • Danazol, verapamil, diltiazem: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, verapamil, or diltiazem particularly with higher doses of lovastatin. • Amiodarone: The risk of myopathy/rhabdomyolysis is increased when amiodarone is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class. • Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine.
133.	***MAGNOLIA OFFICINALIS*** The label and package insert shall include the following boxed statement:- • Contraindicated in pregnant women. Insufficient reliable data in breastfeeding women. • Safety on long-term use has not been established. • For Registered Traditional Chinese Medicine Practitioner Use only. **Reference:** *NPRA.600-1/9/12 (11) Pekeliling Berkenaan Pengemaskinian Status Bahan Aktif Magnolia Officinalis Dalam Drug Registration Guidance Document (DRGD)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
134.	**MEDROXYPROGESTERONE ACETATE** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing medroxyprogesterone acetate (all injectable and oral preparations with dosage ≥ 100mg); **<u>Package Insert</u>** **a) Contraindication:** Patient with meningioma or history of meningioma (for non-oncological indications) **b) Warnings & Precautions:** <u>Meningioma</u> Cases of meningioma (single and multiple) have been reported in patients treated with medroxyprogesterone acetate for a prolonged time (several years). Patients treated with medroxyprogesterone acetate should be monitored for signs and symptoms of meningioma in accordance with clinical practice. In some cases, shrinkage of meningioma was observed after treatment discontinuation of depot medroxyprogesterone acetate. If a patient treated for a non-oncological indication is diagnosed with meningioma, medroxyprogesterone acetate must be stopped, as a precautionary measure. If a patient treated for an oncological indication is diagnosed with meningioma, the need for further treatment with medroxyprogesterone acetate should be carefully considered on a case-by-case basis taking into account individual benefits and risks. **c) Adverse Effects/ Undesirable Effects:** <u>Neoplasms benign, malignant & unspecified</u> Frequency (Unknown): meningioma **d) Pharmacodynamics:** Based on results from a French epidemiological case-control study, an association between medroxyprogesterone acetate and meningioma has been observed. This study was based on data from the French National health data system (SNDS – Système National des Données de Santé) and included a population of 18,061 women who had intracranial surgery for meningioma and 90,305 women without meningioma. The exposure to medroxyprogesterone acetate 150 mg/3ml injectable was compared between women who had intracranial surgery for meningioma and women without meningioma. Analyses showed an excess risk of meningioma with the use of medroxyprogesterone acetate 150 mg/3 ml

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	(9/18,061 (0.05%) v 11/90, 305 (0.01%), OR 5.55 (95%CI 2.27 to 13.56)). This excess risk seems to be driven primarily by prolonged use (≥3 years) of medroxyprogesterone acetate. **<u>Consumer Medication Information Leaflet (RiMUP) (oral preparations with dosage ≥ 100mg only)</u>** **a) Before you use [product name]:** <u>When you must not use it:</u> Do not use [product name], if you have meningioma or have ever been diagnosed with a meningioma (a usually benign tumour of the tissue layer surrounding the brain and spinal cord) unless you use [product name] for cancer. <u>Before you start to use it:</u> <u>Meningioma</u> Use of medroxyprogesterone acetate has been linked to the development of a usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma). The risk increases especially when you use it for longer duration (several years). If you are diagnosed with meningioma, your doctor will reconsider your treatment with [product name]. If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway. **b) Side effects:** Usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma) with a frequency not known. **Reference: Directive No. 14, 2025.** ***<u>NPRA.600-1/9/13 (61)Jld.1</u>*** *Direktif untuk semua produk yang mengandungi medroxyprogesterone acetate (MPA) bagi sediaan injeksi dan oral (dengan dos ≥100mg) : Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko meningioma*
135.	**MEFENAMIC ACID** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing mefenamic acid: **<u>Package Insert</u>** **a) Warnings & Precautions:** <u>Skin Reactions</u> Serious skin reactions such as Generalised bullous fixed drug eruption (GBFDE) have been reported very rarely in association with the use of mefenamic acid.

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	Mefenamic acid should be discontinued at the first appearance of the skin rash, mucosal lesions or any other sign of hypersensitivity. **b) Adverse Effects/ Undesirable Effects:** Skin and subcutaneous tissue disorders: Generalised bullous fixed drug eruption (GBFDE) **Consumer Medication Information Leaflet (RiMUP)** **a) While you are using it:** If you suffer from skin rash and blisters during your treatment, inform your doctor immediately. **b) Side effects:** Skin rash sometimes with blisters. **Directive No. 10, 2024.** *NPRA.600-1/9/13 (41)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Mefenamic Acid: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Generalised Bullous Fixed Drug Eruption (GBFDE)*
136.	**MEFLOQUINE** The following statement shall be included in the package inserts of products containing Mefloquine as single ingredient or in combination with other active ingredients: **1. WARNINGS AND PRECAUTIONS** a) Products containing Mefloquine as single ingredient**:** In chemoprophylaxis the safety profile of mefloquine is characterized by a predominance of neuropsychiatric adverse reactions. If acute anxiety, depression, restlessness or confusion occur during prophylactic use, **[Brand name] (mefloquine)** should be discontinued and an alternative prophylactic agent should be recommended. Because of the long half-life of mefloquine, adverse reactions to **[Brand name] (mefloquine)** may occur or persist up to several weeks after discontinuation of the drug. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug. Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with **[Brand name] (mefloquine)**.

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b) Products containing Mefloquine in combination with other active ingredientas (mefloquine/artesunate):

If acute anxiety, depression, restlessness or confusion occur during treatment, **[Brand name] (mefloquine/artesunate)** should be discontinued and an alternative agent should be recommended. Because of the long half-life of mefloquine, adverse reactions to **[Brand name] (mefloquine/artesunate)** may occur or persist up to several weeks after discontinuation of the drug. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with **[Brand name] (mefloquine/artesunate).**

2. POSTMARKETING ADVERSE EVENT

Nervous system disorders	
Common	Dizziness, headache
Not known	Balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy (including paraesthesia, tremor and ataxia), encephalopathy
Eye disorders	
Common	Visual impairment
Not known	Vision blurred, cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment

Reference: ***Bil. (13) dlm.BPFK/PPP/01/03 Jld.3*** *Pengemaskinian Sisip Bungkusan Semua Produk Antimalaria Yang Mengandungi Mefloquine (Termasuk Produk Kombinasi) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Pada Sistem Saraf (Neurologik) Yang Berpanjangan dan Gangguan Penglihatan*

137. **MELALEUCA LEUCADENDRA**

The following statement shall be included on the labels of products containing Melaleuca Leucadendra (cajeput oil) in topical dosage form:

a) Malay language:

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	AMARAN **Produk ini tidak boleh disapu pada muka, khususnya di kawasan hidung bayi dan kanak-kanak. Ia mungkin boleh menyebabkan masalah pernafasan/ kesukaran bernafas.** b) English language: **WARNING** **This product should not be applied to the facial area, in particular around the nose of infants and small children. It might cause breathing problem / shortness of breath.** **Reference: Directive No. 13, 2016.** ***Bil. (44) dlm.BPFK/PPP/07/25*** *Direktif Bagi Semua Produk Yang Mengandungi Bahan Aktif Minyak Cajeput (Melaleuca Leucadendra) Dalam Bentuk Dos Topikal Dengan Menambah Kenyataan Amaran Berkaitan Risiko Masalah Pernafasan/ Kesukaran Bernafas*
138.	**MESALAZINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing mesalazine; **Package Insert** **a) Warnings and Precautions:** • Photosensitivity More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema. • Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment. **b) Adverse Effects/ Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency "rare": Photosensitivity Renal and urinary disorders Frequency 'not known' : Nephrolithiasis **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td></td><td>
- Kidney stones may develop with the use of [product name]. Symptoms may include pain in the sides of the abdomen and blood in the urine. Take care to drink a sufficient amount of liquid during treatment with [product name].

b) Side Effects:

• Photosensitivity: Itchy eruption and exaggerated sunburn on patches of sun-exposed skin
• Kidney stones and associated pain

References:
Directive No. 12, 2018. <u>BPFK/PPP/07/25 (12) Jld.2</u> Direktif Untuk Semua Produk Yang Mengandungi Mesalazine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Photosensitivity
Directive No. 1, 2021. <u>NPRA.600-1/9/13 (11)</u> Direktif Untuk Semua Produk Yang Mengandungi Mesalazine dan Sulfasalazine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Nephrolithiasis
</td></tr>
<tr><td>139.</td><td>
METFORMIN

The following statements shall be <u>included in the package insert and RiMUP</u> of pharmaceutical products containing Metformin:

<u>Package Insert</u>

1. Recommended Dosage:

a) <u>Products containing Metformin as a single active ingredient:</u>

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

<table>
<tr><th>GFR mL/min</th><th>Total maximum daily dose (to be divided into 2-3 daily doses)*</th><th>Additional considerations</th></tr>
<tr><td>60-89</td><td>3000 mg</td><td>Dose reduction may be considered in relation to declining renal function.</td></tr>
<tr><td>45-59</td><td>2000 mg</td><td rowspan="2">Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.</td></tr>
<tr><td>30-44</td><td>1000 mg</td></tr>
</table>
</td></tr>
</table>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

<30	-	Metformin is contraindicated.

* The text "to be divided into 2-3 daily doses" should be omitted for extended release products containing metformin as single agent.

b) Combination products containing Metformin:

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR <60 ml/min.

If no adequate strength of [Product name] is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	Metformin	[other monocomponent]
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated.	

2. Contraindications:

- Severely reduced kidney function (GFR <30 mL/min)
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

3. Warnings and Precautions:

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly there after [See Section Recommended Dosage]. Metformin is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function [See Section Contraindications].

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

4. Adverse Effects / Undesirable Effects:

Metabolism and nutrition disorders

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Common: Vitamin B12 decrease/deficiency

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

When you must not use it:

- If you have severely reduced kidney function.
- If you have lactic acidosis [too much lactic acid in the blood (see "Risk of lactic acidosis" below)] or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms of acidosis may include stomach pain, abnormal breathing and drowsiness (if severe).

Before you start to use it:

Risk of lactic acidosis

[Product name] may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration, liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). If any of the above apply to you, talk to your doctor for further instructions.

Stop taking [roduct name] for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking [product name] and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.

Symptoms of lactic acidosis include:

- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing

Lactic acidosis is a medical emergency and must be treated in a hospital.

During treatment with [product name], your doctor will check your kidney

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	function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function. **b) Side effects:** Common side effects (may affect up to 1 in 10 people): • Decreased or low vitamin B12 levels in the blood (symptoms may include extreme tiredness (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin). Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems. **References:** **Directive No. 25, 2017.** ***BPFK/PPP/07/25 (30) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Metformin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Penggunaan Dalam Kalangan Pesakit Yang Mempunyai Moderately Reduced Kidney Function Dan Pengukuhan Amaran Lactic Acidosis* **Directive No. 1, 2024.** ***NPRA.600-1/9/13 (32)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Metformin (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Risiko Kekurangan Vitamin B12 (Vitamin B12 Deficiency)*
140.	**METHADONE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing methadone; **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Post-marketing Experience Metabolic and nutritional disorders Frequency 'not known': hypoglycaemia **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Low blood sugar **Reference: Directive No. 12, 2022.** ***NPRA.600-1/9/13 (12)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Methadone: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hipoglisemia*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
141.	**METHYL SALICYLATE** The following statements shall be included in the package inserts and product literature of topical preparations containing methyl salicylate ≥5%: **WARNINGS AND PRECAUTIONS** This product contains methyl salicylate and when applied or rub on to the skin, can be absorbed through the skin into the blood. For patients taking warfarin, excessive application on to the skin for muscle or joint pains may increase the chances of bleeding.
142.	**METHYLCARBOCYSTEINE (MECYSTEINE)** The following warning shall be included in the package inserts of products containing Methylcarbocysteine (Mecysteine): **CONTRAINDICATIONS** Contraindicated in children below two (2) years of age. **Reference: Directive No. 11, 2010.** ***Bil. (7) dlm. BPFK/PPP/01/03 Jilid 1*** *Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip Bungkusan Semua Produk Carbocysteine, Acetylcysteine dan Methylcarbocysteine (Mecysteine)*
143.	**METHYLPHENIDATE** The following boxed statement shall be included on the labels and in the package insert of products containing Methylphenidate HCl: **FOR SPECIALIST'S USE ONLY** The following statement shall be included in the package insert of products containing Methylphenidate: **WARNINGS AND PRECAUTIONS** **Priapism** Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	immediate medical attention. **Reference: Directive No. 12, 2014.** ***Bil. (19) dlm.BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Methylphenidate: Amaran Berkaitan Risiko Priapism (Kesan Ereksi Yang Berpanjangan) Di Kalangan Lelaki*
144.	**METOCLOPRAMIDE** The following statements shall be included in the package inserts of products containing Metoclopramide: **DOSAGE** Total daily dose of metoclopramide, especially for children and young adults, should not normally exceed 0.5mg/kg body weight. **WARNINGS AND PRECAUTIONS** • Avoid doses exceeding 0.5mg/kg/day. • Extrapyramidal effects, especially dystonic reaction of metoclopramide are more likely to occur in children shortly after initiation of therapy, and usually with doses higher than 0.5mg per kg of body weight per day. The following route of products containing Metoclopramide shall update its package inserts according to Directive No. 17, 2014, ***Bil. (24) dlm.BPFK/PPP/07/25*** as below: **1) PARENTERAL ROUTE** • **Indication** • **Dose and Administration** • **Contraindication** • **Warnings and Precautions** **2) ORAL ROUTE (Tablet/ Syrup)** • **Indication** • **Dose and Administration** • **Contraindication** • **Warnings and Precautions** **3) RECTAL ROUTE (Suppository)** • **Indication** • **Dose and Administration** • **Contraindication** • **Warnings and Precautions**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 17, 2014. ***Bil. (24) dlm.BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Metoclopramide: Memperketatkan Indikasi dan Mengehadkan Dos Penggunaan Berikutan Risiko Kesan Advers Neurologik*
145.	**METRONIDAZOLE (ALL PRODUCTS EXCEPT FOR EXTERNAL USE)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products (except for external use) containing Metronidazole: **Package Insert** **a) Warnings and Precautions:** Cases of severe hepatotoxicity/ acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Inform your doctor if you are affected by Cockayne syndrome. Cases of severe liver toxicity/ acute liver failure in patients with Cockayne syndrome have been reported with products containing metronidazole. Stop taking [product name] and tell your doctor immediately if you develop: stomach pain, decreased appetite, nausea, vomiting, fever, unusual tiredness, yellowing of the skin and the whites of the eyes, dark-coloured urine, light or clay-coloured stools or itching. **Reference: Directive No. 18, 2017**. ***BPFK/PPP/07/25 (23) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Metronidazole (Kecuali Produk Untuk Kegunaan Luar): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko Hepatotoxicity Dalam Kalangan Pesakit Cockayne Syndrome*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

146. **MICONAZOLE**

1. Intravaginal preparations

The following boxed warning shall be included on the label and in the package insert of intravaginal preparations containing Miconazole:

> Sila dapatkan nasihat doktor atau ahli farmasi sebelum menggunakan keluaran ini jika anda mengambil ubat warfarin, iaitu sejenis ubat antipembekuan darah, kerana lebam/ pendarahan pada gusi/ hidung boleh berlaku secara spontan.
>
> (Please consult your physician/ pharmacist before using this product if you are on the anticoagulant medicine warfarin, because bleeding from nose/ gums or bruising may accur spontaneously).

Reference: ***Bil. (45) dlm. BPFK/02/5/1.2*** *Keputusan Mesyuarat Pihak berkuasa Kawalan Dadah (PBKD) ke 122 Berhubung Amaran Berkaitan Interaksi Ubat Bagi Semua Keluaran Antifungal Intravaginal Yang Mengandungi Miconazole*

2. Oral gel preparations

The following statements shall be included in the package insert and RiMUP of oral gel preparations containing Miconazole:

Package Insert

a) Contraindications

Use of miconazole oral gel in combination with the following drug that is subjected to metabolism by CYP2C9 (see Interactions):

- Warfarin

b) Interactions

Miconazole can inhibit the metabolism of drugs metabolized by the CYP2C9 enzyme system. This can result in an increase and/or prolongation of their effects, including adverse effects.

Miconazole oral gel is contraindicated with the co-administration of the following drug that is subjected to metabolism by CYP2C9 (see Contraindications):

- Warfarin

Consumer Medication Information Leaflet (RiMUP)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	a) Before you use [product name] When you must not use it Do not use [product name] if you are on warfarin therapy. **3. Preparations other than oral gel** The following statements shall be <u>included in the package insert and RiMUP</u> of preparations (other than oral gel) containing Miconazole: **<u>Package Insert</u>** **a) Warnings and Precautions** In patients on warfarin, caution should be exercised and the anticoagulant effect should be monitored (see Interactions). **b) Interactions** Miconazole administered systemically is known to inhibit CYP2C9 enzyme system. Due to the limited systemic availability after topical application, clinically relevant interactions occur very rarely. In patients on warfarin which is subjected to metabolism by CYP2C9, caution should be exercised and the anticoagulant effect should be monitored (see Warnings and Precautions). **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before You Use [Product Name]** Before you start to use it You must tell your doctor if you: • are on warfarin therapy **Reference: Directive No. 10, 2017.** ***<u>BPFK/PPP/07/25 (15) Jld. 1</u>*** *Direktif Untuk Semua Produk Yang Mengandungi Miconazole: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
147.	**MIDAZOLAM** The following statements shall be included in the package inserts of IV preparations containing Midazolam: **WARNINGS AND PRECAUTIONS** IV Midazolam has been associated with severe respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy resulted. IV Midazolam should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory and cardiac functions. Assure immediate availability of resuscitative drugs, equipments, appropriate antidote and personnel trained in their use. Dosage of IV Midazolam must be individualized for each patient. Lower doses are usually required for elderly, debilitated or higher risk surgical patients. When Midazolam is administered intravenously for conscious sedation, it should be injected slowly (over at least 2 minutes); it should not be administered by rapid or single bolus IV injection because of respiratory depression and/or arrest, especially in elderly or debilitated patients. The initial dose may be as little as 1mg, but should not exceed 2.5mg in a normal healthy adult; administer over at least 2 minutes and allow additional 2 or more minutes to fully evaluate sedative effect. If further titration is necessary, use small increments to the appropriate level of sedation, allowing an additional 2 or more minutes after each increment to fully evaluate sedative effect. See Dosage and Administration for complete dosing information.
148.	**MINOCYCLINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Minocycline: **Package Insert** **a) Warnings and Precautions:** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) including fatal cases have been reported with minocycline use. DRESS, which often occurs several weeks after initiation of treatment, consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy, and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue minocycline if DRESS is suspected.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Adverse Effects/ Undesirable Effects: Skin and subcutaneous tissue disorders: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects:** Stop taking [product name] and contact your doctor immediately if you experience any of the following: • Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature and enlarged lymph nodes. **Reference: Directive No. 6, 2018.** ***BPFK/PPP/07/25 (6) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Minocycline: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)*
149.	**MINOXIDIL** The label and the package insert shall include the following statement: **To be supplied only on the prescription of a registered medical practitioner.** ***<u>Note:</u>*** <u>exempted for external use preparation</u> containing not more than 5% of Minoxidil; its salts; its derivatives *(Please refer to the latest Poison List: Preparations for external use containing not more than 5% of Minoxidil; its salts; its derivatives, which is under Group C)*
150.	**MIRTAZAPINE** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Mirtazapine; **<u>Package Insert</u>** **a) Adverse Effects/ Undesirable Effects:** <u>Nervous system disorders</u> Frequency 'common': Amnesia

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Skin and subcutaneous tissue disorders Frequency 'not known': Drug reaction with eosinophilia and systemic symptoms (DRESS) **Consumer Medication Information Leaflet (RiMUP)** **a) Side effects:** Frequency 'common': Memory problems Frequency 'not known': Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature and enlarged lymph nodes. **Reference: Directive No. 12, 2021**. *NPRA.600-1/9/13(22) Direktif Untuk Semua Produk Yang Mengandungi Mirtazapine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Amnesia dan Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)*
151.	**MOMORDICA CHARANTIA** For product containing Momordica Charantia, please state: - **"Shall not be used in pregnant and breast-feeding women."** - **"Be sure to tell your pharmacist, doctor, or other healthcare providers about any other supplements you are taking. There may be a potential for interactions or side effects."**
152.	**MONTELUKAST** The following statement shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products that contains Montelukast: **Package Insert** **a) Adverse Effects/Undesirable Effects:** Postmarketing Experience Blood and lymphatic system disorders: thrombocytopenia Psychiatric disorders: obsessive-compulsive symptoms

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Side Effects:** Tell your healthcare provider right away if you notice any of the following behavior and mood-related changes: • Obsessive-compulsive symptoms **References:** **Directive No. 6, 2015.** ***Bil. (31) dlm.BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Montelukast: Pengemaskinian Sisip Bungkusan Dengan Maklumat Kesan Advers Berkaitan Thrombocytopenia* **Directive No. 8, 2019.** ***BPFK/PPP/07/25 (8) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Montelukast: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Obsessive-Compulsive Symptoms*
153.	**MOXIFLOXACIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing moxifloxacin for systemic use (oral and injection dosage forms): **Package Insert** **a) Warnings & Precautions:** Psychiatric reactions Psychiatric reactions may occur even after the first administration of fluoroquinolones, including [Product name]. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, [Product name] should be discontinued and appropriate measures instituted. Caution is recommended if [Product name] is to be used in psychotic patients or in patients with a history of psychiatric disease. **b) Adverse Effects/ Undesirable Effects:** Psychiatric disorders Rare: Depression (in very rare cases potentially culminating in self- injurious behaviour, such as suicidal ideation/ thoughts or suicide attempts), Hallucination Very Rare: Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideation/ thoughts or suicide attempts) **Consumer Medication Information Leaflet (RiMUP)**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	a) While you are using it: You may experience mental health problems even when taking/ using fluoroquinolone antibiotics, including [Product name] for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts. If you develop such reactions, stop taking/ using [Product name] and inform your doctor immediately. **b) Side effects:** Rare: Depression (in very rare cases leading to self-harm, such as suicidal ideations/ thoughts (desire to kill oneself), or suicide attempts), hallucinations Very rare: Psychotic reactions (potentially leading to self-harm, such as suicidal ideations/ thoughts (desire to kill oneself), or suicide attempts) **Reference: Directive No. 8, 2024.** *NPRA.600-1/9/13 (39)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour*
154.	**MYCOPHENOLATE (MYCOPHENOLATE MOFETIL AND MYCOPHENOLIC ACID)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing mycophenolate (mycophenolate mofetil and mycophenolic acid): **Package Insert** **CONTRAINDICATIONS** • [Product name] is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see Use in Special Populations: Pregnancy). • [Product name] is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see Use in Special Populations: Pregnancy). • [Product name] is contraindicated in women who are breastfeeding (see Use in Special Populations: Breastfeeding). **USE IN SPECIAL POPULATIONS** **Pregnancy** [Product name] is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. (see Contraindications). Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	malformations and must be counseled regarding pregnancy prevention, and planning. Prior to starting therapy with [product name], female patients of childbearing potential must have **two negative serum or urine pregnancy tests** with a sensitivity of at least 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting [product name]. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant. Due to the mutagenic and teratogenic potential of mycophenolate, **women of child bearing potential** should use **two reliable forms of contraception** simultaneously, including at least one highly effective method, before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception. **Sexually active men** are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, **female partners of male patients** are recommended to use highly effective during treatment and for total of 90 days after the last dose of [product name]. Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported: • Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits; • Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos); • Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly); • Cardiac abnormalities such as atrial and ventricular septal defects; • Oesophageal malformations (e.g. oesophageal atresia); • Nervous system malformations (such as spina bifida). In the medical literature, malformations in children from mycophenolate-exposed pregnancies have been reported in 23% to 27% of live births. For comparison, the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosuppressants other than mycophenolate. Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate, mainly in the first trimester. In the medical literature, the risk has

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	been reported at 45% to 49% following mycophenolate exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants. Studies in animals have shown reproductive toxicity. **Breastfeeding** [Product name] is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Contraindications). Studies in rats have shown mycophenolate to be excreted in milk. It is not known whether this medicine is excreted in human milk. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** General disorders and administration site conditions: (uncommon) de novo purine synthesis inhibitors-associated acute inflammatory syndrome <u>General disorders and administration site conditions</u> De novo purine synthesis inhibitors-associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product. **Post-marketing experience:** **Congenital Disorders** Congenital malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy (see Use in Pregnancy). **Pregnancy, Puerperium and Perinatal Conditions** Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported (see Use in Pregnancy). **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **SIDE EFFECTS** Tell your doctor or pharmacist if you notice any of the following: fever, joint pain and muscle pain. **References**: **Directive No. 6, 2016.** ***BPFK/PPP/07/25 (37)*** *Direktif Untuk Semua Produk Yang Mengandungi*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Mycophenolate (Mycophenolate Mofetil dan Mycophenolic Acid): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Teratogenik **Directive No. 19, 2021**. ***NPRA.600-1/9/13(29)*** *Direktif Untuk Semua Produk Yang Mengandungi Mycophenolate (Mycophenolate Mofetil dan Mycophenolic Acid): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko De Novo Purine Synthesis Inhibitors-Associated Acute Inflammatory Syndrome*
155.	**NEVIRAPINE** The following statement shall be included in the package insert of products containing Nevirapine: Addition of this statement at approved Indication: "Avoid usage of Nevirapine in patient with CD4+cell count greater than 250cells/mm3". **Reference:** ***Bil. (43) dlm. BPFK/02/5/1.3*** *Pendaftaran Produk Yang Mengandungi Nevirapine*
156.	**NIFEDIPINE** The following statement shall be included in the package inserts of "short acting" Nifedipine products: **WARNINGS AND PRECAUTIONS** Several well documented studies have described profound hypotension, myocardial infarction and death when immediate release nifedipine capsules are used sublingually for acute reduction of blood pressure. **DOSAGE** • Lower doses may be required in elderly patients as a result of reduced drug clearance. • For hypertension, the dose used should not exceed 60mg daily.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
157.	**NITRATES** The following statements shall be included in the package inserts of all "**NITRATES FOR STABLE ANGINA PECTORIS**": • An appropriate statement concerning the development of tolerance (under **precaution** section). A suggested statement would be as follows: 'Development of tolerance may occur with all forms of nitrate therapy particularly with the long acting preparations that maintain continuously high plasma nitrate concentration'. • An appropriate recommendation on dosage regimens. The recommended dosage regimens should be one that is able to provide a low-nitrate period or a nitrate-free period of 8-12 hours every 24 hours to prevent the development of tolerance and thus maintain the antianginal effects.
158.	**NORADRENALINE** The following statements shall be included in the package insert of products containing noradrenaline; **Package Insert** **a) Adverse Effects/Undesirable Effects:** Cardiac disorders Frequency 'not known': stress cardiomyopathy **Reference: Directive No. 5, 2019.** ***BPFK/PPP/07/25 (5) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Noradrenaline: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Stress Cardiomyopathy*
159.	**NORFLOXACIN** The following statement shall be included in the package inserts of products containing Norfloxacin: **PRECAUTION** i. Should not be used in children or pregnant women ii. Phototoxicity may occur

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
160.	**NORMAL GLOBULIN** **INTRAMUSCULAR (IM)** The following statement shall be included in the package inserts of Normal globulin IM preparations: **WARNINGS AND PRECAUTIONS** Do not administer this preparation intravenously because of potential for serious hypersensitivity reactions.
161.	**NOSCAPINE** 1. The following **contraindication** shall be included on the labels of products containing Noscapine: **Contraindicated in Women of Child-bearing Potential** 2. The following statement shall be included in the package inserts of products containing Noscapine: **WARNINGS AND PRECAUTIONS** Experimental data now suggests that noscapine may exhibit a mutagenic effect in vitro. Because of the possible consequent risk to the developing foetus, the products containing noscapine is contraindicated in women of child bearing potential, therefore pregnancy should be excluded before treatment, and effective contraception maintained throughout treatment with such products. **PRECAUTION** In view of potential mutagenicity shown in vitro, potential risks should be balanced against anticipated benefits when treating children and neonates.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
162.	**NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)** The following statement shall be included in the package insert of products containing NSAID including COX-2 Inhibitors: **WARNINGS AND PRECAUTIONS** Risk of GI Ulceration, Bleeding and Perforation with NSAID Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.
163.	**OFLOXACIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing ofloxacin for systemic use (oral and injection dosage forms): **Package Insert** **a) Warnings & Precautions:** Psychiatric reactions Psychiatric reactions may occur even after the first administration of fluoroquinolones, including [Product name]. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, [Product name] should be discontinued and appropriate measures instituted. Caution is recommended if [Product name] is to be used in psychotic patients or in patients with a history of psychiatric disease. **b) Adverse Effects/ Undesirable Effects:** Psychiatric disorders Rare: Psychotic disorder (for e.g.hallucination)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Very Rare: Psychotic behaviour Frequency not known (cannot be estimated from the available data): Psychotic disorders and depression with self-endangering behavior including suicidal ideation or suicide attempt **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) While you are using it:** You may experience mental health problems even when taking/ using fluoroquinolone antibiotics, including [Product name] for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts. If you develop such reactions, stop taking/ using [Product name] and inform your doctor immediately. **b) Side effects:** Rare: Psychotic reactions with a risk of having suicidal thoughts or actions, hallucination, depression Very rare: Psychotic behaviour Not known (frequency cannot be estimated from the available data): Psychotic reactions with a risk of having suicidal thoughts or actions **Reference: Directive No. 8, 2024.** *<u>NPRA.600-1/9/13 (39)Jld.1</u> Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour*
164.	**OLANZAPINE** The following statements shall be <u>included in the package insert and RiMUP</u> of products containing Olanzapine: **<u>Package Insert</u>** **a) Warnings and Precautions**: <u>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)</u> Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	DRESS is suspected. **b) Adverse Effects/ Undesirable Effects**: **Skin and subcutaneous tissue disorders** Very rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects**: Very rare: Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia). **Reference: Directive No. 19, 2016.** ***BPFK/PPP/07/25 (5) Jld.1*** *Direktif Bagi Semua Produk Yang Mengandungi Olanzapine Dengan Maklumat Keselamatan Berkaitan Kesan Advers Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)*
165.	**OLMESARTAN (INCLUDING COMBINATION PRODUCTS)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing olmesartan (including combination products): **<u>Package Insert</u>** **a) Adverse Effects/ Undesirable Effects:** <u>Hepatobiliary disorders</u> Frequency 'not known': Autoimmune hepatitis* *Cases of autoimmune hepatitis with a latency of few months to years have been reported post-marketing, that were reversible after the withdrawal of olmesartan. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side effects:** Frequency not known: • If you experience yellowing of the whites of the eyes, dark urine, itching of the skin, even if you started therapy with [product name] longer time ago, contact your doctor immediately who will evaluate your symptoms and decide on how to continue your blood pressure medication.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 11, 2024. ***NPRA.600-1/9/13 (42)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Olmesartan (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hepatitis Autoimun (Autoimmune Hepatitis)*
166.	**ONDANSETRON** The following statements shall be included in the package inserts and Consumer Medication Information Leaflet (RiMUP) for products containing Ondansetron; **Package Insert** **a) Dosage And Administration:** **CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV AND RINV)** **CINV and RINV in Adults** …. IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes. …. **CINV and RINV in Elderly** Ondansetron is well tolerated by patients over 65 years of age. In patients 65 years of age or older, all IV doses should be diluted and infused over 15 minutes and, if repeated, given no less than 4 hours apart. In patients 65 to 74 years of age, the initial IV dose of ondansetron 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart. In patients 75 years of age or older, the initial IV dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart. *Reference: Zofran™ Injection package insert (June 2014 version)*

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	b) Pregnancy and Lactation: Pregnancy The use of ondansetron in pregnancy is not recommended. In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformations, the epidemiological studies showed conflicting results. Three epidemiological studies in the US assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in offspring born to mothers exposed to ondansetron during the first trimester of pregnancy. • One cohort study with 88,467 pregnancies exposed to ondansetron showed an increased risk of oral clefts (3 additional cases per 10,000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03-1.48)) without an apparent increase in risk of cardiac malformations. A separately published subgroup analysis of 23,877 pregnancies exposed to intravenous ondansetron did not find an increased risk of either oral clefts or cardiac malformations. • One case-control study using population-based birth defect registries with 23,200 cases across two datasets showed an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study. • The second cohort study with 3,733 pregnancies exposed to ondansetron found an increased risk of ventricular septal defect, adjusted RR 1.7 (95%CI 1.0-2.9), but no statistically significant increase in risk of cardiac malformations. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus. Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with [product name]. Females of reproductive potential should be advised that it is possible that [product name] can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using [product name] during the treatment and for two days after stopping treatment with [product name]. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** [Product name] is not recommended for use during pregnancy.

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	• Tell your doctor if you are pregnant or planning to become pregnant. [Product name] may harm your unborn baby. • If you do become pregnant during treatment with [product name], tell your doctor. If you are a woman of childbearing age, your doctor will check if you are pregnant and perform a pregnancy test if necessary before starting treatment with [product name]. If you may become pregnant, you should use effective birth control during treatment and for at least 2 days after stopping [product name]. Ask your doctor about options of effective birth control. **Reference: Directive No. 5, 2021.** ***NPRA.600-1/9/13(15)*** *Direktif Untuk Semua Produk Yang Mengandungi Ondansetron: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Kecacatan Kelahiran (Birth Defects) Susulan Penggunaan Ketika Hamil*
167.	**OPIOID** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing opioid: **Package Insert** **a) Warnings and Precautions:** 1. Risks from Concomitant Use with Benzodiazepines Profound sedation, respiratory depression, coma, and death may result from the concomitant use of [product name] with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use. If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

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	Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when [product name] is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See Drug Interactions). 2. <u>Serotonin Syndrome with Concomitant Use of Serotonergic Drugs</u> Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of [product name] with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue [product name] if serotonin syndrome is suspected. 3. <u>Adrenal Insufficiency</u> Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency. 4. <u>Sexual Function/Reproduction</u> Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Postmarketing Experience) **b) Adverse Effects/ Undesirable Effects:** <u>Postmarketing Experience:</u>

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Serotonin syndrome (See Warnings and Precautions)

Adrenal insufficiency (See Warnings and Precautions)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

c) Interactions:

1. Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

2. Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue [product name] if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor

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	antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions). **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) While you are using it:** Things to be careful of: - Serotonin syndrome: [Product name] may cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. If you have some or all of these symptoms: feeling confused, feeling restless, sweating, shaking, shivering, hallucinations, sudden jerks in your muscles or a fast heartbeat, seek medical attention immediately. - Adrenal insufficiency: Long-term use of [product name] may cause adrenal insufficiency, a potentially life-threatening condition that may present with non-specific symptoms and signs such as nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. Seek medical attention if you experience a constellation of these symptoms. - Infertility: Long-term use of [product name] may cause reduced fertility. It is not known whether these effects on fertility are reversible. **b) Taking other medicines:** Taking [product name] with a benzodiazepine (medicine used as sedatives or to treat anxiety) can depress your central nervous system. Inform your doctor if you are currently taking any benzodiazepine. Seek medical attention immediately if you or the person taking this medication experience(s) symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness. **References:** **Directive No. 23, 2017.** ***<u>BPFK/PPP/07/25 (28) Jld. 1</u>*** *Direktif Untuk Semua Produk Yang Mengandungi Opioid dan Benzodiazepin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat* **Directive No. 27, 2017.** ***<u>BPFK/PPP/07/25 (32) Jld. 1</u>*** *Direktif Untuk Semua Produk Yang Mengandungi Opioid: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Serotonin Syndrome Kesan Daripada Interaksi Dengan Serotonergic Drugs dan Risiko Kesan Advers Adrenal Insufficiency dan Androgen Deficiency Akibat Penggunaan Jangka Panjang*

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168.	**OSELTAMIVIR** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Oseltamivir; **Package Insert** **a) Adverse Effects/Undesirable Effects:** Blood and lymphatic system disorders Frequency 'Rare' : Thrombocytopenia **Consumer Medication Information Leaflet (RiMUP)** **a) Side effects**: Rare side effects: - thrombocytopenia (low platelet count) **Reference: Directive No. 6, 2021.** ***NPRA.600-1/9/13 (16)*** *Direktif Untuk Semua Produk Yang Mengandungi Oseltamivir: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Thrombocytopenia*
169.	**PALBOCICLIB** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing palbociclib; **Package Insert** **a) Warnings & Precautions:** Venous thromboembolism Venous thromboembolic events were reported in patients treated with [Product name] [see Adverse Effects/Undesirable Effects]. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate. **b) Adverse Effects/ Undesirable Effects:** Other Clinical Trials Experience The following adverse reaction has been reported following administration of [Product name]: Venous thromboembolism **Consumer Medication Information Leaflet (RiMUP)**

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	a) Side effects: - signs of blood clots in the vein (venous thromboembolism) such as pain or stiffness, swelling and redness in the affected leg (or arm), chest pain, shortness of breath, light-headedness, rapid breathing or rapid heart rate **Reference: Directive No. 2, 2026.** ***NPRA.600-1/9/13 (73)Jld.1*** *Direktif untuk semua produk yang mengandungi palbociclib: Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko venous thromboembolism (VTE)*
170.	**PALIPERIDONE** The following statement shall be included in the package inserts of products containing Paliperidone: **Warnings and Precautions** **Intraoperative Floppy Iris Syndrome** Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone. IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy. **Adverse Effects / Undesirable Effects** **Postmarketing Data** Eye Disorders Frequency: Not known – Floppy iris syndrome (intraoperative) **Reference:** ***Bil. (17) dlm.BPFK/PPP/01/03 Jld.3*** *Pekeliling Untuk Mengemaskini Sisip Bungkusan Semula Produk Yang Mengandungi Risperidone Atau Paliperidone Dengan Amaran Berkaitan Risiko Intraoperative Floppy Iris Syndrome (IFIS) Pada Pesakit Yang Menjalani Pembedahan Katarak*
171.	**PARACETAMOL** The following statement shall be included on the labels, package inserts and RiMUP of ALL products containing Paracetamol: **WARNING** This preparation contains PARACETAMOL. Do not take any other paracetamol containing medicines at the same time.

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	• **Allergy alert:** Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash. These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away. **Package Insert** **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** • Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported. **Reference: Directive No. 5, 2015.** ***Bil. (29) dlm.BPFK/PPP/07/25*** *Direktif Untuk Produk Yang Mengandungi Paracetamol, Termasuk Produk Kombinasi: Pengemaskinian Label, Sisip Bungkusan, dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Kesan Advers Serius Pada Kulit*
172.	**PARACETAMOL WITH CAFFEINE IN COMBINATION** The following statement shall be included on the labels and in the package inserts and RiMUP of products containing Paracetamol with Caffeine in combination: **WARNING** • Avoid other caffeine containing products. Too much caffeine may cause rapid heart rate, nervousness or sleeplessness. • Ask a doctor or pharmacist before use if you have high blood pressure, glaucoma, or overactive bladder syndrome. • **DO NOT exceed 8 tablets in 24 hours**. • **DO NOT** take more than the recommended dose unless advised by your doctor. Use the smallest effective dose. Taking more than the maximum daily dose may cause **severe or possibly fatal liver damage.** • **DO NOT** use with other drugs containing **paracetamol.** • **NOT recommended for children under 12 years** **Package Insert** **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** • Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported. **Reference: Directive No. 5, 2015.** ***Bil. (29) dlm.BPFK/PPP/07/25*** *Direktif Untuk Produk Yang Mengandungi Paracetamol, Termasuk Produk Kombinasi: Pengemaskinian Label, Sisip Bungkusan, dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Kesan Advers Serius Pada*

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	Kulit
173.	**PARENTERAL NUTRITION CONTAINING AMINO ACIDS AND/OR LIPIDS (INDICATED FOR USE IN PEDIATRIC POPULATION AGED UNDER 2 YEARS)** The following statements shall be included in the package insert of parenteral nutrition products containing amino acids and/or lipids (indicated for use in pediatric population aged under 2 years); **Package Insert** **a) Dosage and Administration:** When used in neonates and children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (See Section **Warnings and Precautions**). **b) Warnings and Precautions:** Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, <product name> should be protected from ambient light until administration is completed (See Section **Dosage and Administration**). **Reference: Directive No. 15, 2020.** ***NPRA.600-1/9/13 (6)*** *Direktif Untuk Semua Produk Parenteral Nutrition Yang Mengandungi Asid Amino Dan/Atau Lipid (Yang Indikasinya Termasuk Untuk Kegunaan Dalam Kalangan Golongan Pediatrik Di Bawah Usia Dua Tahun): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Kesan Advers (Adverse Outcomes) Akibat Pendedahan Produk Kepada Cahaya Semasa Administrasi*
174.	**PEGFILGRASTIM** The following statement shall be included in the package inserts of ALL biosimilar products containing PEGFILGRASTIM **WARNINGS AND PRECAUTIONS** Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care. Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally

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	resolved after withdrawal of G-CSF. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** Clinical Trials **In Cancer Patients** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥1/1000 to < 1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony stimulating factors. **In Normal Donors undergoing peripheral blood progenitor cell mobilization** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony stimulating factors. Post Marketing **Vascular disorders** Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. Frequency "rare": Aortitis **References:** **Directive No. 13, 2014.** ***Bil. (20) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim dan Pegfilgrastim: Amaran Berkaitan Risiko Capillary Leak Syndrome (CLS) Bagi Pesakit Kanser dan Healthy Donor (Filgrastim) dan Bagi Pesakit Kanser (Pegfilgrastim)* **Directive No. 30, 2018.** ***Bil. (30) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim, Pegfilgrastim dan Lenograstim: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Aortitis*
175.	***PELARGONIUM SIDOIDES*** The following warning shall be included on the labels and in the package inserts of products containing *Pelargonium Sidoides*: **WARNING** In very rare cases, *pelargonium sidoides* may cause hypersensitivity reactions.

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176.	**PEMETREXED** The following statements shall be <u>included in the package insert</u> for products containing pemetrexed: **a) Warnings and Precautions:** Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with pemetrexed alone or with other chemotherapeutic agents. Most of these events resolved after pemetrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia). **b) Adverse Effects/Undesirable Effects:** Nephrogenic diabetes insipidus and renal tubular necrosis have been reported in post marketing setting with an unknown frequency. **Reference: Directive No. 29, 2018.** ***BPFK/PPP/07/25 (29) Jld.2*** *Direktif Untuk Semua Produk Yang Yang Mengandungi Pemetrexed: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Nephrogenic Diabetes Insipidus dan Renal Tubular Necrosis*
177.	**PENICILLIN** The following <u>statement</u> shall be <u>included on the labels</u> of products containing penicillin: ‘**Not to be used in patients with known hypersensitivity to Penicillin**’
178.	**PHENIRAMINE** The following <u>statement</u> shall be <u>included on the label and in the package inserts</u> of liquid oral products containing Pheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor’s/ pharmacist’s advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

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179.	**PHENYLEPHRINE** The following statement shall be included on the labels and in the package insert of liquid oral products containing Phenylephrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
180.	**PIPERACILLIN (INCLUDING COMBINATION PRODUCTS)** The following statements shall be included in the package insert for products containing piperacillin (including combination products); **Package Insert** **a) Warnings and Precautions:** Haemophagocytic lymphohistiocytosis (HLH) Rare cases of haemophagocytic lymphohistiocytosis (HLH) have been observed following therapy (>10 days) with [active ingredient], often as a complication of DRESS. HLH is a pathologic immune activation which leads to excessive systemic inflammation and can be life-threatening and early diagnosis and rapid initiation of immunosuppressive therapy is essential. Characteristic signs and symptoms include fever, hepatosplenomegaly, cytopenias, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, and haemophagocytosis. If [active ingredient] is suspected as possible trigger, treatment should be discontinued. **Reference: Directive No. 13, 2022.** ***NPRA.600-1/9/13 (13)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Piperacillin (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Haemophagocytic Lymphohistiocytosis*

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181.	**PIROXICAM (SYSTEMIC)** The following additional information shall be included in the package inserts of products containing Piroxicam (systemic): **WARNINGS AND PRECAUTIONS** • Treatment should always be initiated by a physician experienced in the treatment of rheumatic diseases. • Use the lowest dose (no more than 20mg per day) and for the shortest duration possible. Treatment should be reviewed after 14 days. • Always consider prescribing a gastro-protective agent. **CONTRAINDICATIONS** • Piroxicam should not be prescribed to patient who is more likely to develop side effects, such as those with a history of gastro-intestinal disorders associated with bleeding, or those who have had skin reactions to other medicines. • Piroxicam should not be prescribed in association with any other NSAID or an anticoagulant. **Reference:** ***Bil. (80) dlm. BPFK/02/5/1.3*** *Menghadkan Indikasi bagi Produk untuk Kegunaan 'Systemic' yang Mengandungi Piroxicam kepada 'For the symptomatic relief of pain and inflammation in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis' dan Tambahan Amaran Dan Kontraindikasi Terkini Pada Sisip Bungkusan*
182.	**PRAVASTATIN** The following additional information shall be included in the package insert of products containing Pravastatin. **DOSAGE AND ADMINISTRATION** Dosage in Patients Taking Cyclosporine In patients taking cyclosporine, with or without other immunosuppressive drugs, concomitantly with [Product Name], therapy should be initiated with 10mg/day and titration to higher doses should be performed with caution. Most patients treated with this combination received a maximum pravastatin dose of 20mg/day. **WARNINGS AND PRECAUTIONS** Skeletal Muscle Effects The use of fibrates alone may occasionally be associated with myopathy. The benefit of further alterations in lipid levels by the combined use of [Product Name] with fibrates should be carefully weighed against the potential risks of this combination.

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	Cases of myopathy, including rhabdomyolysis, have been reported with pravastatin co-administered with colchicine, and caution should be exercised when prescribing pravastatin with colchicine. Pravastatin must not be co-administered with systemic fusidic acid. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Pravastatin therapy may be re-introduced seven days after the last dose of fusidic acid. **INTERACTIONS** Concomitant Therapy with Other Lipid Metabolism Regulators: Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. Therefore, combined drug therapy should be approached with caution. Gemfibrozil and nicotinic acid: Gemfibrozil and nicotinic acid do not statistically significantly affect the bioavailability of pravastatin. However, in a limited size clinical trial, a trend toward CK elevations and musculoskeletal symptoms was seen in patients treated concurrently with pravastatin and gemfibrozil. Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency. Cyclosporine: In a multicentre study, the AUC values of pravastatin were shown to be five-fold higher in the presence of cyclosporine. There was no accumulation of pravastatin after multiple doses Clarithromycin, colchicine: The risk of myopathy/rhabdomyolysis is increased with concomitant administration of clarithromycin or colchicine with pravastatin. Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of pravastatin with systemic fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. **Reference: Directive No. 8, 2014.** ***Bil. (15) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Pravastatin: Mengehadkan Dos Penggunaan Pravastatin Untuk Mengurangkan Risiko Kecederaan Otot*
183.	**PREDNISONE AND PREDNISOLONE (EXCEPT TOPICAL PREPARATIONS)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Prednisone dan Prednisolone (except topical preparations); **Package Insert** **a) Warnings and Precautions:** Scleroderma renal crisis Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you start to use it:** Talk to your doctor before taking [product name], if you have: Systemic sclerosis (an autoimmune disorder). Taking daily doses of 15 mg or more may increase the risk of a serious complication called scleroderma renal crisis which may cause your blood pressure to increase and reduce urination. **Reference: Directive No. 17, 2018.** ***BPFK/PPP/07/25 (17) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Prednisone dan Prednisolone (Kecuali Persediaan Topikal) : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Schleroderma Renal Crisis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
184.	**PROMETHAZINE HCL** The following additional information shall be included on the label and in the package insert of liquid oral products containing Promethazine HCl: **WARNING** When used for treatment of cough and cold (a) "It (brand or generic names) should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression". (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
185.	**PROPAFENONE** The following warning shall be included in the package insert of products containing propafenone: **Propafenone is not recommended for treatment of less severe arrhythmias such as nonsustained ventricular tachycardias or frequent premature ventricular contractions even if the patients are symptomatic, because of recent evidence in the US of increase mortality in patients with non-lifethreatening arrhythmias who were treated with encainide and flecainide.**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
186.	**PROPOFOL** The following statement shall be included in the package inserts of products containing Propofol: **a) WARNINGS AND PRECAUTIONS** Propofol is not recommended for paediatric general anaesthesia and sedation because its safety and effectiveness in these patients have not been established. There have been recent reports of adverse cardiac events and deaths associated with its use in paediatric intensive care. Although there is no evidence of a causal link of death with propofol in these cases, the drug could not be ruled out as a contributing factor. Until further data establishing its safety and delineating its appropriate dose range are available, propofol should not be used in paediatric intensive care. There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction orbemergence from anaesthesia induced by propofol. **b) INTERACTIONS:** A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered. **c) ADVERSE EFFECTS/UNDESIRABLE EFFECTS:** Reproductive system and breast disorders: Frequency "not known": Priapism **References:** **Directive No. 7, 2018**. ***BPFK/PPP/07/25(7) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Propofol dan Sodium Valproate : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat* **Directive No. 16, 2020**. ***NPRA.600-1/9/13(7)*** *Direktif Untuk Semua Produk Yang Mengandungi Propofol: Pengemaskinian Sisip Bungkusan Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Priapism*
187.	**PROPOLIS (ORAL)** For products containing Propolis (for oral use), please state: - **"This product contains propolis and may cause severe allergic reactions including fatal anaphylactic reaction in susceptible individuals."** - **"Asthma and allergy sufferers may be at a greater risk."**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
188.	**PROPOLIS (TOPICAL)** The following information shall be included on the labels and/ or package inserts of products containing Propolis (for topical use): **WARNINGS** Propolis may cause allergic skin reaction. **References:** ***Bil. (48) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk)* ***Bil. (56) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk yang Mengandungi Propolis (topikal) dan Royal Jelly (Semua Bentuk)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
189.	**PROPYLTHIOURACIL** The following statement shall be included in the package inserts of products containing propylthiouracil: **[1]WARNINGS AND PRECAUTIONS** Potential risk of serious hepatoxicity or liver injury including liver failure and death. Patients who are initiated with propylthiourasil should be closely monitored for signs and symptoms of liver injury (e.g. fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising or yellowing of the eyes or skin) especially during the first six months. If liver injury is suspected, promptly discontinue propylthiouracil therapy. Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of the alternatives available. **[2]**The following boxed warning shall be included in the package inserts of products containing propylthiouracil: ***BOXED WARNING*** *Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.* *Propylthiouracil should be reserved to patients who cannot tolerate carbimazole/ methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for management of hyperthyroidism.* *Because of the risk of fetal abnormalities associated with carbimazole/ methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (See Warnings and Precautions).* **References:** ***Circular [1]Bil (41) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berkaitan Dengan "Potential for an Increase in Risk of Hepatotoxicity" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Propylthiouracil* ***Circular [2]Bil (55) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berbentuk "Boxed Warning" Yang Wajib Dimuatkan Pada Sisip Bungkusan Produk Propylthiouracil Dengan "Severe Liver Injury"*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
190.	**PROTON PUMP INHIBITORS (PPI)** The following statements shall be <u>included in the package insert and RiMUP</u> of pharmaceutical products containing Proton Pump Inhitors (PPI): **<u>Package Insert</u>** **1. Warnings and Precautions:** <u>Regular Surveillance</u> Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance. <u>Subacute Cutaneous Lupus Erythematosus (SCLE)</u> Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping {product name}. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors. <u>Hypomagnesaemia</u> Severe hypomagnesaemia has been reported in patients treated with PPI like {product name} for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment. <u>Fracture</u> Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Clostridium Difficile Diarrhea Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Vitamin B12 Deficiency Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed. **2. Adverse Effects/ Undesirable Effects:** Gastrointestinal disorders Microscopic colitis: Frequency 'not known' Subacute Cutaneous Lupus Erythematosus (SCLE) Skin and subcutaneous tissue disorders Frequency 'not known': Subacute cutaneous lupus erythematosus Interstitial Nephritis Renal and urinary disorders: Interstitial nephritis Hypomagnesaemia Metabolism and nutritional disorders Frequency "not known": hypomagnesaemia. Fracture Musculoskeletal disorders Frequency "uncommon": Fracture of the hip, wrist or spine. Clostridium Difficile Diarrhea Infections & infestations: Clostridium difficile associated diarrhea. Fundic Gland Polyps (Benign) Gastrointestinal disorders Frequency "common": Fundic gland polyps (benign) Vitamin B12 Deficiency Metabolic/Nutritional: Vitamin B12 deficiency

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

3. Warnings and Precautions - Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, [product name] treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

4. Pharmacodynamic

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Consumer Medication Information Leaflet (RiMUP)

i. Side Effects:

When you are taking this medicine, your doctor will want to monitor you (especially if you are taking it for long term). Hence, you should report any new and exceptional symptoms and circumstances whenever you see your doctor. Please tell your doctor promptly if you get any of the symptoms below:

- Rash (especially in areas exposed to the sun), possibly with pain in the joints (Subacute Cutaneous Lupus Erythematosus, SCLE)
- Fever, extreme tiredness, pus/blood in urine.
- Involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate
- Fracture in the hip, wrist or spine.
- Watery stool, stomach pain and fever that do not go away
- Anemic (pale skin, weakness, tiredness or lightheadedness), shortness of breath, a smooth tongue, nerver problems (numbness or tingling, muscle weakness and problems walking), vision loss and mental problems (depression, memory loss or behavioral changes).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

a) Subacute Cutaneous Lupus Erythematosus (SCLE)
Frequency "not known"

b) Interstitial Nephritis
Kidney problems (interstitial nephritis)

c) Hypomagnesaemia
Frequency "not known": Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood.

d) Fracture
Frequency "uncommon": Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can ncrease the risk of osteoporosis).

e) Clostridium Difficile Diarrhea
Severe diarrhoea which may be caused by an infection (Clostridium difficile) in your intestines.

f) Fundic Gland Polyps (Benign)
Frequency "Common": Benign polyps in the stomach

g) Vitamin B12 Deficiency
Proton pump inhibitors may cause vitamin B12 deficiency.

h) Inflammation in the large bowel
Frequency 'not known': Inflammation in the large bowel, that causes persistent watery diarrhea

ii. Before you start to use it

Tell your doctor before taking this medicine, if you are due to have a specific blood test (Chromogranin A).

References:

Directive No. 16, 2017. ***BPFK/PPP/07/25 (21) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Proton Pump Inhibitors (PPI): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Akibat Penggunaan Jangka Panjang (no. 1, 2, i)*

Directive No. 15, 2017. ***BPFK/PPP/07/25 (20) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Proton Pump Inhibitors (PPI): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Elevated Circulating Levels of Chromogranin A (CgA) (no. 3, 4, ii)*

Directive No. 7, 2020. ***BPFK/PPP/07/25 (7) Jld. 4*** *Direktif Untuk Semua Produk Yang Mengandungi Proton Pump Inhibitors (PPI) Termasuk Produk Kombinasi: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Microscopic Colitis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
191.	**PSEUDOEPHEDRINE** The following statement shall be included on the labels and in the package inserts of liquid oral products containing Pseudoephedrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
192.	**PSYCHOTROPIC PRODUCTS** The following statement shall be included conspicuously on the labels of all psychotropic products: **CAUTION:** This preparation may be habit forming on prolonged use.
193.	**PSYLLIUM/ PLANTAGO (SEED/ HUSK)** For products containing Psyllium/ Plantago (Seed/ Husk), please state: - **"If the constipation does not resolve within 3 days or if abdominal pain occurs or in case of any irregularity of faeces, the use of psyllium should be discontinued and medical advice must be sought."** **"Please consume a large amount of fluid/ water when taking this product."**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
194.	**RED YEAST RICE *(Monascus purpureus)*** "This product contains naturally occurring lovastatin. Please consult your doctor/ pharmacist before using this product." "Do not take this product if you are already on statin products (lovastatin, atorvastatin, fluvastatin, prasvastatin, simvastatin, rosuvastatin, etc). "If you experience any allergic reactions or side effects such as lethargy, body and muscle aches, please stop using this product" "Concurrent use of fibrates may cause severe myositis and myoglobinuria."
195.	**RETINOID (ORAL)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> of products containing retinoid (oral); **<u>Package Insert</u>** **a) Warnings and Precautions:** <u>Psychiatric symptoms</u> Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration. *An additional statement should also be included in the package insert of oral isotretinoin: Suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** Talk to your doctor before taking [product name] If you have ever had any kind of mental health problems. This includes depression, aggressive tendencies or mood changes.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	*An additional statement should also be included in the RiMUP of oral isotretinoin: It also includes suicidal thoughts. Mental health problems Your mood may be affected while taking [product name]. You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that you are taking this medicine. They may notice these changes and help you quickly identify any problems that you need to talk to your doctor about. **Reference: Directive No. 6, 2019.** ***BPFK/PPP/07/25 (6) Jld. 3*** *Direktif Untuk Semua Produk Yang Mengandungi Retinoid (Oral): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Neuropsychiatric Disorders*
196.	**RETINOIDS (ORAL) INDICATED FOR TREATMENT OF SKIN DISEASES** The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) of products containing oral retinoids indicated for treatment of skin diseases: **Label** A boxed warning should be added to the outer packaging as follows: **WARNING** CAN SERIOUSLY HARM AN UNBORN BABY Women must use effective contraception Do not use if you are pregnant or you think you may be pregnant **Package Insert** **a) Contraindications:** • Pregnant women • Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (See Section Warnings and Precautions)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

b) Warnings and Precautions:

Teratogenic effects
[Product name] is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.

[Product name] is strictly contraindicated in:
- Pregnant women
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

Pregnancy Prevention Programme

[Product name] is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- [approved indications] (See Section Indications)
- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk.
- She understands the need for frequent follow-up (e.g. on a monthly basis).
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month* [*3 years for acitretin] after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.
- Even if she has amenorrhea she must follow all the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment [for acitretin this statement should be - She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment].
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of [product name].

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	The prescriber must ensure that: • The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding. • The patient has acknowledged the aforementioned conditions. • The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month* [*3 years for acitretin] after cessation of treatment. • Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented. for acitretin this last bullet point should be] • Negative pregnancy test results have been obtained before, during and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. The dates and results of pregnancy tests should be documented. If pregnancy occurs in a woman treated with [product name], treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the fetus. This risk persists until the product has been completely eliminated, which is within one month* following the end of treatment [*3 years for acitretin]. **Contraception** Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional. As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month* [*3 years for acitretin] after stopping treatment with [product name], even in patients with amenorrhea. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Pregnancy testing Prior to starting therapy At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with [product name]. Follow-up visits Follow-up visits should be arranged at regular intervals, ideally monthly. Follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber. End of treatment 1 month after stopping treatment, women should undergo a final pregnancy test. [for acitretin this last paragraph should be] Women should undergo pregnancy test periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. **Prescribing and dispensing restrictions** For women of childbearing potential, the prescription duration of [product name] ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of [product name] should occur on the same day. This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication. **Male patients** The available data suggest that the level of maternal exposure from the semen of the patients receiving [product name] is not of a sufficient magnitude to be associated with the teratogenic effects of [product name]. Male patients should be reminded that they must not share their medication with anyone, particularly not females. **Additional precautions** Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment. Patients should not donate blood during therapy and for 1 month* [*3 years for acitretin] following discontinuation of [product name] because of the potential risk to

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

the foetus of a pregnant transfusion recipient.

Educational material

In order to assist healthcare professionals and patients in avoiding fetal exposure to [product name] the Product Registration Holder will provide educational material to reinforce the warnings about the teratogenicity of [product name], to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

*Please also refer to **Appendix 22: Educational Materials***

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

WARNING

CAN SERIOUSLY HARM AN UNBORN BABY

Women must use effective contraception

Do not use if you are pregnant or you think you may be pregnant

When you must not use it:

- If you are pregnant or breast-feeding
- If there is any chance you could become pregnant

Women must use effective contraception before, during and after taking [product name]:

- You must agree to use at least one very reliable method of contraception (for example an intra uterine device or contraceptive implant) or, two effective methods that work in different ways (for example a hormonal contraceptive pill and a condom). Discuss with your doctor which methods would be suitable for you.
- You must use contraception for a month before taking [product name], during treatment and for a month* afterwards [*for acitretin should be 3 years].
- You must use contraception even if you do not have periods or you are not sexually active (unless your doctor decides this is not necessary).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Women must agree to pregnancy testing before, during and after taking [product name]: • You must agree to regular follow-up visits, ideally every month. • You must agree to have regular pregnancy tests, ideally every month during treatment and, because some medicine may still be left in your body, 1 month after stopping [product name] (unless your doctor decides this is not necessary in your case). {for acitretin: 'every 1 to 3 months for 3 years after stopping [product name]'}. • You must agree to extra pregnancy tests if your doctor asks you. • You must not get pregnant during treatment or for a month afterwards because some medicine may still be left in your body. for acitretin this last bullet point should be: • You must not get pregnant during treatment or for 3 years afterwards because some medicine may still be left in your body. If you get pregnant while taking [product name], stop taking the medicine straight away, and contact your doctor. Also, if you become pregnant within one month* [3* years for acitretin] after you stop taking [product name], you should contact your doctor. **Advice for men** The levels of oral retinoid in the semen of men taking [product name] are too low to harm their partners' unborn baby. However, you must never share your medication with anyone, especially females. **Additional precautions** You should never give this medicinal product to another person. Please take any unused capsules to your pharmacist at the end of treatment. You should not donate blood during treatment with this medicine and for 1 month* [*3 years for acitretin] after stopping [product name] because an unborn baby could be harmed if a pregnant patient receives your blood. **Reference: Directive No. 16, 2019**. ***BPFK/PPP/07/25 (16) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Oral Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
197.	**RETINOIDS (TOPICAL)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of topical products containing retinoids: **Package Insert** **a) Contraindications:** • Pregnancy (see Section Pregnancy and Lactation) • Women planning a pregnancy **b) Pregnancy and Lactation [replacing specific labeling requirements – Tretinoin Topical]:** Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure. [Product name] is contraindicated (see Section Contraindications) in pregnancy, or in women planning a pregnancy. If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Do not use [product name] if you are pregnant or thinking of becoming pregnant. Your doctor can give you more information. **Reference: Directive No. 16, 2019.** ***BPFK/PPP/07/25 (16) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Oral Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
198.	**RHUBARB (e.g. *Radix et Rhizoma Rhei / Rheum Palmatum / Rheum Officinalis*) – root part** The following statement shall be included on the label and in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Rhubarb (e.g. *Radix et Rhizoma Rhei / Rheum Palmatum / Rheum Officinalis*) – root part (for oral use only): • Do not use when abdominal pain, nausea or vomiting is present. • Frequent or prolonged use of this preparation may result in dependence towards the product and 'imbalanced electrolytes'. • Please consult a health care practitioner for use beyond 7 days.
199.	**RISPERIDONE** The following statement shall be included in the package inserts of products containing Risperidone: **Warnings and Precautions** **Intraoperative Floppy Iris Syndrome** Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone. IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy. **Adverse Effects / Undesirable Effects** **Postmarketing Data** Eye Disorders Frequency: Not known – Floppy iris syndrome (intraoperative) **Reference:** ***Bil. (17) dlm.BPFK/PPP/01/03 Jld.3*** *Pekeliling Untuk Mengemaskini Sisip Bungkusan Semua Produk Yang Mengandungi Risperidone Atau Paliperidone Dengan Amaran Berkaitan Risiko Intraoperative Floppy Iris Syndrome (IFIS) Pada Pesakit Yang Menjalani Pembedahan Katarak*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
200.	**RITUXIMAB (INJECTION ONLY)** The following statements shall be <u>included in the package insert</u> for products containing rituximab (injection only); **<u>Package Insert</u>** **a) Warnings & Precautions:** <u>Infections</u> Cases of enteroviral meningoencephalitis including fatalities have been reported following use of rituximab. <u>False negative serologic testing of infections</u> Due to the risk of false negative serologic testing of infections, alternative diagnostic tools should be considered in case of patients presenting with symptoms indicative of rare infectious disease e.g. West Nile virus and neuroborreliosis. **b) Adverse Effects/ Undesirable Effects:** <u>Infections and infestations</u> Frequency 'not known': Enteroviral meningoencephalitis* *observed during post-marketing surveillance **Reference: Directive No. 8, 2025.** ***NPRA.600-1/9/13 (55)Jld.1*** *Direktif untuk semua produk yang mengandungi rituximab (sediaan injeksi sahaja): Pengemaskinian sisip bungkusan dengan maklumat keselamatan berkaitan risiko enteroviral meningoencephalitis dan false negative serologic testing of infections*
201.	**RIVASTIGMINE** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing rivastigmine; **<u>Package Insert</u>** **a) Warnings & Precautions:** <u>QT Prolongation and torsade de pointes</u> Electrocardiogram QT prolongation may occur in patients treated with certain cholinesterase inhibitor products including rivastigmine. Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, hypokalemia or hypomagnesemia, personal or family history of QT prolongation, or concomitant use with medicinal products known to induce QT prolongation

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	and/or torsade de pointes. Clinical monitoring may also be required. **b) Interactions:** Medicinal products known to prolong the QT interval Caution is advised when rivastigmine is used in combination with other medicinal products known to prolong the QT interval (including but not limited to quinidine, amiodarone, pimozide, halofantrine, cisapride, citalopram, mizolastin, moxifloxacin, erythromycin). Clinical monitoring may also be required. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you start to use [product name]:** Tell the doctor if you have, or have ever had heart conditions such as irregular or slow heartbeat, QTc prolongation, a family history of QTc prolongation, torsade de pointes, or have low potassium or magnesium. Your doctor may need to monitor you more closely while you are on this medicine. **b) Taking other medicines:** Caution when [product name] is taken together with medicinal product know to prolong the heart's electrical system (QT interval) [including but not limited to quinidine (medicine used to treat irregular heartbeat), amiodarone (medicine used to treat serious /fatal irregular heartbeat), pimozide (medicine works on central nervous system), halofantrine (antimalaria medicine), cisapride (medicine used to treat symptoms of night-time heartburn), citalopram (medicine used to treat depression), mizolastin (antihistamine medicine), medicine used to treat bacterial infection such as moxifloxacin, erythromycin]. Your doctor may also monitor your clinical condition as needed. **Reference: Directive No. 3, 2024.** *NPRA.600-1/9/13 (34)Jld.1 Direktif Untuk Semua Produk Yang Mengandungi Rivastigmine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko QT Prolongation dan Torsade de Pointes (TdP)*
202.	**ROCURONIUM** The following statements shall be included in the package insert for products containing Rocuronium; **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Cardiac disorders Frequency 'not known': Kounis Syndrome

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 11, 2021. ***NPRA.600-1/9/13(21)*** *Direktif Untuk Semua Produk Yang Mengandungi Rocuronium: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kounis Syndrome*
203.	**ROSIGLITAZONE** 1. The following **black box warning** shall be included in the first part of package inserts of products containing Rosiglitazone as single ingredient or in combination with other active ingredients: • Rosiglitazone is contraindicated in patients with established NYHA Class I to IV heart failure and in patients with known ischaemic heart disease, particularly in those taking nitrates. • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Patients on rosiglitazone should be monitored carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered. 2. The following information shall be included in the package inserts of products containing Rosiglitazone as single ingredient or in combination with other active ingredients: **CONTRAINDICATIONS** Rosiglitazone is contraindicated in patients with NYHA Class I to IV heart failure or history of cardiac failure, patients with known ischaemic heart disease and patients with Acute Coronary Syndrome (unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction. **WARNINGS AND PRECAUTIONS** Rosiglitazone has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short term clinical studies compared to combined active/placebo control (2.00% versus 1.53%). Death from myocardial ischaemic events occurred in 0.15% on rosiglitazone – containing regimens and 0.12% on comparator regimen. **Reference: Directive No. 10, 2010.** ***Bil. (6) dlm. BPFK/PPP/01/03 Jilid 1*** *Direktif Memperketatkan Penggunaan Rosiglitazone dan Memperkukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Kardiovaskular Pada Sisip Bungkusan Semua Produk Rosiglitazone Termasuk Produk Kombinasi*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
204.	**ROSUVASTATIN** The following information shall be included on the labels and/or package inserts of products containing Rosuvastatin: **DOSAGE AND ADMINISTRATION** Dosage in patients with pre-disposing factors to myopathy The recommended start dose is 5 mg in patients with pre-disposing factors to myopathy Concomitant Therapy Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir). Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing [Product Name] therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered. **CONTRAINDICATIONS** [Product Name] is contraindicated in patients receiving concomitant cyclosporine. **WARNINGS AND PRECAUTIONS** Skeletal Muscle Effects Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. All generic products containing Rosuvastatin should update their package inserts respectively according to the innovator's information such as parts for Interactions, Pharmacokinetics and other parts deemed relevant. **Reference: Directive No. 9, 2014**. ***Bil. (16) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Rosuvastatin: Mengehadkan Dos Penggunaan Rosuvastatin Untuk Mengurangkan Risiko Kecederaan Otot*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
205.	**ROXITHROMYCIN** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> of products containing Roxithromycin; **<u>Package Insert</u>** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/Undesirable Effects:** <u>Skin and Subcutaneous Tissue Disorders</u> Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 22, 2018.** ***<u>Bil. (22) dlm. BPFK/PPP/07/25 Jld.2</u>*** *Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin dan Roxithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
206.	**ROYAL JELLY** The following information shall be included on the labels and/or package inserts of products containing Royal jelly: **WARNINGS** This product contains royal jelly and may cause severe allergic reactions including fatal anaphylactic reactions in susceptible individuals. Asthma and allergy sufferers may be at the greater risk. **References:** ***Bil. (48) dlm. BPFK/02/5/1.3*** *Pernyatan Amaran Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk)* ***Bil. (56) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran pada Label dan Sisip Bungkusan Produk yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk)* ***Bil. (12) dlm. BPFK/PPP/01/03*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Royal Jelly (Produk Kosmetik)*
207.	**SACCHAROMYCES BOULARDII** The following statements shall be included in the package insert, Consumer Medication Information Leaflet (RiMUP) and label of products containing *Saccharomyces boulardii*; **Package Insert** **a) Contraindications:** • Patients having a central venous catheter • Critically ill patients or immunocompromised patients due to a risk of fungaemia (See Section Warnings & Precautions) **b) Warnings and Precautions:** There have been very rare cases of fungaemia reported mostly in patients with central venous catheter, critically ill or immuno-compromised patients, most often resulting in pyrexia. In most cases, the outcome has been satisfactory after cessation of treatment by *Saccharomyces boulardii*, administration of antifungal treatment and removal of the catheter when necessary. However, the outcome was fatal in some critically ill patients (see Section Contraindications & Section Adverse Effects/Undesirable Effects).

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	c) Adverse Effects/Undesirable Effects: Infections and Infestations Very rare: Fungaemia in patients with a central venous catheter and in critically ill or immunocompromised patients (see Section Warnings and Precautions). **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** When you must not take it Do not take this product if you are immunocompromised (altered/weakened immune system) or have central venous catheter. **b) Side Effects:** Very rare side effects: Penetration of yeast into blood (fungaemia) **Label** Please consult your doctor/pharmacist before using this product. Do not take this product if you are immunocompromised (altered/ weakened immune system) or have central venous catheter. **Reference: Directive No. 23, 2018.** ***Bil. (23) BPFK/PPP/07/25 Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Saccharomyces Boulardii: Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Fungaemia*
208.	**SALBUTAMOL** 1. The following information shall be included in the package inserts of products containing Salbutamol in **injection** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	a physician experienced in cardiology. • Cautious use of salbutamol injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractibility. During IV infusion of salbutamol, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. 2. The following information shall be included in the package inserts and product literature of products containing Salbutamol in **oral tablet/ capsule** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. 3. The following warning statement shall be included in the package inserts of products containing Salbutamol in **injection and oral** dosage form under section of **Warning and Precautions**: **Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.** **References:** ***Bil. (6) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Mengenai Insiden* 'Myocardial Ischaemia' *Pada Wanita Mengandung Yang Menerima Rawatan* 'Beta Agonist' *Bagi Rawatan Melambatkan Kelahiran Pramatang Pada Sisip Bungkusan Kumpulan Produk Ini* **Directive No. 8, 2011.** ***Bil. (18) dlm. BPFK/PPP/01/03 Jld.1*** *Direktif Untuk Memperkukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Serius Pada Jantung Termasuk Kematian Dengan Penggunaan Produk Suntikan dan Oral Beta Agonis Dalam Rawatan Kelahiran Pra-Matang*
209.	**SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)** Please state: "Individual allergic to aspirin/ other NSAID should avoid this product."

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210.	**SEDATIVE – HYPNOTIC PRODUCTS** The following statement shall be included in the package inserts of sedative-hypnotic products: **WARNINGS AND PRECAUTIONS** • Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken • Complex sleep – related behaviors which may include sleep driving, making phone calls, preparing and eating food while asleep **Reference:** ***Bil. (75) dlm. BPFK/02/5/1.3*** *Keputusan Mesyuarat PBKD - Pernyataan Amaran Pada Sisip Bungkusan Semua Produk Sedatif-Hipnotik Oral Berkaitan dengan Risiko Complex Sleep - Related Behaviors Which May Include Sleep Driving, Making Phone Calls, Preparing and Eating Food (While Asleep)*
211.	**SELENIUM SULPHIDE** The following statement shall be included on the labels of products containing Selenium sulphide: **WARNING** Do not use on broken skin or inflamed. Avoid contact with eyes. (***AMARAN:*** *Selenium sulphide tidak boleh digunakan pada kulit yang pecah dan radang. Elakkan daripada terkena mata.*)
212.	**SENNA (CASSIA SPP.) – fruit/ pod/ semen / leaf** The following statement shall be included on the label and in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Senna (Cassia spp.) – fruit / pod / semen / leaf (for oral use only): • Do not use when abdominal pain, nausea or vomiting is present. • Frequent or prolonged use of this preparation may result in dependence towards the product and 'imbalanced electrolytes'. • Please consult a health care practitioner for use beyond 7 days.

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213.	**SERTRALINE** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing sertraline; **<u>Package Insert</u>** **a) Adverse Effects/ Undesirable Effects:** <u>Gastrointestinal disorders</u> Microscopic colitis/ Colitis microscopic* *ADR identified post-marketing **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects:** Inflammation of the colon (causing diarrhoea) **Reference: Directive No. 14, 2022.** ***NPRA.600-1/9/13 (14)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Sertraline: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Microscopic Colitis*
214.	**SIMVASTATIN** The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Simvastatin: **1. Dosage and Administration** The 80mg dose is only recommended in patients at high risk for cardiovascular complications who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. <u>Concomitant Therapy</u> In patients taking fibrates (other than gemfibrozil and fenofibrate) concomitantly with [Product Name], the dose of [Product Name] should not exceed 10mg/day. In patients taking amiodarone, verapamil or diltiazem concomitantly with [Product Name], the dose of [Product Name] should not exceed 20mg/day. In patients taking amlodipine or lipid-lowering dose of niacin (≥1g/day) concomitantly with [Product Name], the dose of [Product Name] should not exceed 40mg/day.

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	2. Contraindications • Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone). • Concomitant administration of gemfibrozil, cyclosporine, or danazol. **3. Interactions** <u>Contraindicated Drugs</u> Potent inhibitors of CYP3A4: Concomitant use with medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g.: itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir or nefazodone) is contraindicated. If treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with simvastatin is contraindicated. <u>Other Drugs</u> • Other fibrates: The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil or fenofibrate. When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small short-term clinical studies with careful monitoring. • Amiodarone: In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone. • Calcium channel blockers: - Verapamil or diltiazem: In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem. - Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine. - Niacin (≥1g/day): The dose of simvastatin should not exceed 40mg daily in

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	patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin. **Reference:** ***Bil. (18) dlm.BPFK/PPP/01/03 Jld.3*** *Pekeliling Untuk Mengemaskini Sisip Bungkusan Semua Produk Yang Mengandungi Simvastatin Dengan Memuatkan Kontraindikasi dan Had Dos Yang Baru*
215.	**SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS** The following statements shall be included in the Consumer Medication Information Leaflet (RiMUP) of products containing Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: **Consumer Medication Information Leaflet (RiMUP)** 'Seek immediate medical attention when symptoms such as nausea, vomiting, decreased appetite, abdominal pain, excessive thirst, difficulty in breathing, confusion, unusual fatigue or sleepiness, frequent urination and fruity-smelling breath occur'.
216.	**SODIUM METABISULPHITE (EXCIPIENT)** The following statement shall be included in the package inserts of products containing Sodium metabisulphite: **WARNINGS AND PRECAUTIONS** This preparation contains Sodium metabisulphite that may cause serious allergic type reactions in certain susceptible patients. Do not use if known to be hypersensitive to bisulphites.
217.	**SODIUM VALPROATE** The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) of products containing sodium valproate and related substances, including valproic acid: **Label** *A boxed warning should be added to the outer packaging as follows:* ***WARNING FOR WOMEN AND GIRLS***

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This medicine can seriously harm an unborn baby

Always use effective contraception during treatment with sodium valproate

If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.

You must CONTINUE taking sodium valproate unless your doctor tells you to stop

Package Insert

PANCREATITIS:
CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.

a) Posology and Method of administration:

Female children and women of childbearing potential
Sodium valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, Warnings and precautions and Fertility, pregnancy and lactation sections). The benefit and risk should be carefully reconsidered at regular treatment reviews. Sodium valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses.

b) Contraindications:

Sodium valproate is contraindicated in the following situations:

- In epilepsy
  - sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
  - sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Warnings and precautions and Fertility, pregnancy and lactation sections)

- In bipolar disorder

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- sodium valproate is contraindicated in pregnancy
- sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section)

c) Warnings and Precautions:

Female children, Women of childbearing potential, and pregnant women:
Sodium valproate has a high teratogenic potential and children exposed in utero to sodium valproate have a high risk for congenital malformations and neurodevelopmental disorders.

Sodium valproate is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment for epilepsy indication.
- In pregnancy for bipolar disorder indication.
- In women of childbearing potential unless below conditions are fulfilled.

<u>Conditions of Pregnancy Prevention Programme:</u>
The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see Fertility, Pregnancy and Lactation).

Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a physician experienced in the management of epilepsy.

- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with sodium valproate.

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- The patient understands the need for regular (at least annual) review of treatment by a prescriber experienced in the management of epilepsy.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with sodium valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

<u>Female children</u>
The prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the doctor once the female child using sodium valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.

In patients who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the prescriber to switch female children to alternative treatment before they reach adulthood.

<u>Pregnancy test</u>
Pregnancy must be excluded before start of treatment with sodium valproate. Treatment with sodium valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

<u>Contraception</u>

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	Women of childbearing potential who are prescribed sodium valproate must use effective contraception without interruption during the entire duration of treatment with sodium valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception. <u>Annual treatment reviews by the prescriber</u> The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review and ensure that the patient has understood its content. <u>Pregnancy planning</u> If a woman is planning to become pregnant, a prescriber experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning. <u>In case of pregnancy</u> If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment with sodium valproate and consider alternative treatment options. The patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. <u>Pharmacists must ensure that:</u> • The Patient Card is provided with every sodium valproate dispensation and that patients understand its content. • Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy. **<u>Educational materials</u>** In order to assist healthcare professionals and patients in avoiding exposure to sodium valproate during pregnancy, the Marketing Authorisation Holder has

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

provided educational materials to reinforce the warnings, provide guidance regarding use of sodium valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using sodium valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber. at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant

Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a doctor experienced in the management of epilepsy.

*Please also refer to **Appendix 22: Educational Materials***

d) Fertility, Pregnancy and Lactation:

- Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Sodium valproate is contraindicated as treatment for bipolar disorder during pregnancy.
- Sodium valproate is contraindicated for use in women of childbearing potential unless the above mentioned conditions of Pregnancy Prevention Programme are fulfilled (see Contraindications and Warnings and precautions sections)

Pregnancy Exposure Risk related to sodium valproate
Both sodium valproate monotherapy and sodium valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a greater risk of congenital malformations than sodium valproate monotherapy.

Teratogenicity and developmental effects

Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to sodium valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.
Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial

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	dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. **Developmental disorders** Data have shown that exposure to sodium valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to sodium valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of sodium valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to sodium valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes. Available data show that children exposed to sodium valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to sodium valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). Female children and woman of childbearing potential (see **Contraindications and Warnings and precautions sections**) **If a Woman plans a Pregnancy** If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning. **Pregnant women** Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless

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	there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy. It is recommended to: - Use the lowest effective dose and divide the daily dose sodium valproate into several small doses to be taken throughout the day. - The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations. All patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to sodium valproate exposure. **e) Warnings & Precautions:** <u>Use in male patients of reproductive potential</u> A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam (see Pregnancy). Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk. The prescribers should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment. The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known. The male patient should be advised: - not to donate sperm during treatment and for 3 months after stopping the treatment, - of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception,

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	- that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception. The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use (Annual Risk Acknowledgement Form). Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to all men of reproductive potential using valproate **f) Reproduction:** <u>Teratogenicity and developmental effects from female and male exposure</u> Risk to children of fathers treated with valproate A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam. The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07). Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see Warnings/Precautions) <u>Fertility</u> Valproate administration may also impair fertility in men (see Section Adverse Reactions). In the few cases in which valproate was switched/discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed.

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g) Adverse Effects/ Undesirable Effects:

Reproductive system and breast disorders:
Rare: male infertility

h) Nonclinical Safety Data:

Reproductive and developmental toxicity

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits.

In published literature, behavioural abnormalities have been reported in first generation offspring of mice and rats after in utero exposure to clinically relevant doses/exposures of valproate. In mice, behavioural changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute in utero exposure of the first generation. The relevance of these findings for humans is unknown.

Impairment of fertility

In sub-chronic/ chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs. In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Relevance of the testicular findings to pediatric population is unknown.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

WARNING FOR WOMEN AND GIRLS

This medicine can seriously harm an unborn baby

Always use effective contraception during treatment with sodium valproate

If you are thinking about becoming pregnant, or if you are pregnant, contact your

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doctor urgently.

You must CONTINUE taking sodium valproate unless your doctor tells you to stop

Before you start to use it:

- Tell your healthcare professionals if you are pregnant.
- If you are a woman able to have a baby you must not take sodium valproate unless you use an effective method of birth control (contraception) at all times during your treatment with sodium valproate.

b) While you are using it:

Things you must do:

- Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.
- If you are a parent or a caregiver of a female child treated with sodium valproate, you should contact their doctor once your child experiences their first period (menarche).

Things you must not do:

- Continue taking sodium valproate or using your birth control (contraception) until you have discussed your pregnancy or your plan to get pregnant with your doctor.

Things to be careful of:

- Sodium valproate can seriously harm an unborn baby when taken during pregnancy.
- The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take sodium valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because sodium valproate has been used for many years it is known that in women who take sodium valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.

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	- It is estimated that up to 30-40% of preschool children whose mothers took sodium valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory. - Autistic spectrum disorders are more often diagnosed in children exposed to sodium valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD). **c) Taking other medicines:** Some medicines and sodium valproate may interfere with each other, these include propofol (a medicine used before and during general anaesthesia). Tell your doctor that you are taking [product name] if you are going for an operation. **d) While you are using it:** **Important advice for male patients able to father a child** Potential risk related to taking valproate in the 3 months prior to conception A study suggests that if you take valproate in the 3 months prior to conception, your child may have a higher risk for impaired mental and/or motor development compared to children born to fathers who used lamotrigine or levetiracetam, other medicines that can be used to treat your disease. In this study, around 5 children in 100 had such disorders when born from fathers treated with valproate, and around 3 children in 100 when born from fathers treated with the other medicines. There are no data on this potential risk to children fathered more than 3 months after stopping valproate treatment (the time needed for new sperm to be formed). As a precautionary measure, your doctor will discuss with you - The potential risk when fathering a child if you are treated with valproate, - The need to use effective contraception (birth control) for you and your female partner during the treatment and for 3 months after stopping valproate - The need to consult your doctor to discuss alternative treatment options, as soon as you are planning to father a child and before discontinuing contraception (birth control), - To not donate sperm during treatment and for 3 months after stopping treatment. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse. If your female partner becomes

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	pregnant while you used valproate in the 3 months prior to conception, both of you should contact the doctor for counselling You should get regular (at least annual) appointments with your doctor. During this visit your doctor will make sure you acknowledge the risk and precautions associated with valproate use. Make sure you read the patient guide that you will receive from your doctor. **e) Side effects:** - male infertility (may be reversible after dose reduction or discontinuation) **References:** **Directive No. 17, 2016.** ***BPFK/PPP/07/25 (3) Jld.1*** *Direktif Bagi Semua Produk Yang Mengandungi Sodium Valproate Bagi Memperkukuhkan Amaran Berkaitan Risiko Abnormal Pregnancy Outcomes* **Directive No. 7, 2018.** ***BPFK/PPP/07/25 (7) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Propofol dan Sodium Valproate: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat* **Directive No. 21, 2019.** ***BPFK/PPP/07/25 (21) Jld. 3*** *Direktif Untuk Semua Produk Yang Mengandungi Sodium Valproate: Pengukuhan Maklumat Keselamatan Pada Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Berkaitan Risiko Kecacatan Kongenital dan Masalah Perkembangan Dalam Kalangan Bayi dan Kanak-Kanak Yang Terdedah Kepada Penggunaan Sodium Valproate Semasa Dalam Kandungan Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Sodium Valproate* **Directive No. 15, 2025.** ***NPRA.600-1/9/13 (62)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Valproate Termasuk Terbitannya (Sodium Valproate, Valproic Acid)*
218.	**ST. JOHN'S WORT *(Hypericum perforatum)*** The following boxed statement shall be included on the labels of products containing St. John's Wort: Please consult your physician/ pharmacist before using this product if you are on any prescription medicines as there is possibility that interactions may occur with certain drugs. *(Sila dapatkan nasihat doktor/ ahli farmasi sebelum menggunakan produk ini, kerana kemungkinan berlakunya interaksi dengan penggunaan ubat preskripsi).*
219.	**STATINS** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of ALL products containing statins (single active or in combination):

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Package Insert

a) INTERACTION:

Concurrent use of fibrates may cause severe myositis and myoglobinuria.

b) ADVERSE EFFECTS / UNDESIRABLE EFFECTS:

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

Musculoskeletal disorders
Frequency not known: Immune-mediated necrotizing myopathy

Nervous system disorders
Frequency 'not known': myasthenia gravis

Eye disorders
Frequency 'not known': ocular myasthenia

c) WARNINGS AND PRECAUTIONS:

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

Myasthenia Gravis/ Ocular Myasthenia
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. [Product name] should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you start to use it:** Talk to your doctor or pharmacist before taking [product name]: • If you have or have had myasthenia (a disease with general muscle weakness including in some cases muscles used when breathing), or ocular myasthenia (a disease causing eye muscle weakness) as statins may sometimes aggravate the condition. **b) Side effects:** *If you have muscle problems that do not go away even after your doctor has told you to stop taking {product name}, please refer to your doctor. Your doctor may do further tests to diagnose the cause of your muscle problems.* Unknown frequency: • Myasthenia gravis (a disease causing general muscle weakness including in some cases muscles used when breathing). • Ocular myasthenia (a disease causing eye muscle weakness). Talk to your doctor if you experience weakness in your arms or legs that worsens after periods of activity, double vision or drooping of your eyelids, difficulty swallowing, or shortness of breath. **References:** **Directive No. 7, 2014.** ***Bil. (14) dlm.BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Statin: Memperkukuhkan Amaran Berkaitan Risiko Kesan Advers Kognitif dan Peningkatan HBA1C Serta Fasting Blood Glucose (FBG)* **Directive No. 29, 2017.** ***BPFK/PPP/07/25 (34) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Statin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Immune-Mediated Necrotizing Myopathy (IMNM)* **Directive No. 6, 2025.** ***NPRA.600-1/9/13 (53)Jld.1*** *Direktif untuk semua produk yang mengandungi statin (termasuk produk kombinasi): Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko myasthenia gravis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

220. **STRONTIUM RANELATE**

1. The following **<u>black boxed warning</u>** shall be <u>included in the first part of package inserts</u> of products containing Strontium Ranelate:

> *[Brand Name]* should only be used for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.
> *[Brand Name]* is contraindicated in patients with:
> - established, current or past history of ischaemic heart disease; peripheral arterial disease and/or cerebrovascular disease;
> - uncontrolled hypertension;
> - current or previous venous thromboembolic events (VTE);
> - temporary or permanent immobilisation.

2. The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Strontium Ranelate:

<u>Indications</u>

- Treatment of severe/established osteoporosis in postmenopausal women at high risk of fracture to reduce the risk of vertebral and hip fractures
- Treatment of severe/established osteoporosis in men at increased risk of fracture

  [Brand Name] should only be used for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.

<u>Contraindications</u>

- Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease
- Uncontrolled hypertension

<u>Warnings and precautions</u>

<u>Cardiac ischaemic events</u>

In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in strontium ranelate treated patients compared to placebo.

Before starting treatment, patients should be evaluated with respect to cardiovascular risk.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration. During [BRAND NAME] treatment, these cardiovascular risks should be monitored on a regular basis generally every 6 to 12 months. Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled. **Adverse Effects/ Undesirable Effects:** SOC Cardiac disorders: - Common: Myocardial infarction **Myocardial infarction** In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in strontium ranelate treated patients as compared to placebo (1.7% versus 1.1%), with a relative risk of 1.6 (95% CI = [1.07; 2.38]). **Reference:** ***Bil. (16) dlm.BPFK/PPP/01/03 Jld.3*** *Pekeliling Tentang Langkah-langkah Pengurangan Risiko Bagi Produk Yang Mengandungi Strontium Ranelate Susulan Risiko Kesan Advers Kardiovaskular*
221.	**SUCCINYLATED GELATIN (MODIFIED FLUID GELATIN)** The following statements shall be included in the package insert of products containing Succinylated Gelatin (Modified Fluid Gelatin); **Warnings and Precautions:** Due to possible cross-reactions involving the allergen galactose-alpha-1,3-galactose (alpha-Gal), the risk of sensitization and consequent anaphylactic reaction to gelatin-containing solutions could be highly increased in patients with history of allergy to red meat (mammal meat) and offal and/or tested positive for anti-alpha-Gal IgE antibodies. In these patients, [Product name] should be administered only after a careful assessment of benefit/risk, including alternative treatments, and only under close supervision of well trained personnel with resuscitation equipment ready. **Reference: Directive No. 28, 2018.** ***BPFK/PPP/07/25 (28) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Succinylated Gelatin (Modified Fluid Gelatin): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Cross-Reaction Yang Melibatkan Alergen Galactose-Alpha-1,3-Galactose (Alpha-Gal)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
222.	**SULFASALAZINE** The following statements shall be <u>included in the Package Insert and Consumer Medication Information Leaflet (RiMUP)</u> of products containing sulfasalazine: **<u>Package Insert</u>** **a) Warnings and Precautions:** Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use nicotinamide adenine dinucleotide [NAD(H)] or nicotinamide adenine dinucleotide phosphate [NADP(H)]. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine (see Section Interactions). **b) Interactions:** Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), ammonia, thyroxine, or glucose. Consult with the testing laboratory regarding the methodology used. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings (see Section Warnings and Precautions). **c) Adverse Effects/Undesirable Effects:** <u>Renal and urinary disorders</u> Frequency 'not known' : Nephrolithiasis* * Adverse effects identified post-marketing. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [Product Name]:** <u>Before you start to use it</u> Tell your doctor if you are taking or have recently taken [product name], or any other sulfasalazine containing products, because they may affect results of blood and urine tests.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Side effects: - kidney stones and associated pain **References:** **Directive No. 20, 2019.** ***BPFK/PPP/07/25 (20) Jld. 3*** *Direktif Untuk Semua Produk Yang Mengandungi Sulfasalazine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Gangguan Terhadap Ujian Makmal Yang Menggunakan Reaksi Dihydronicotinamide-Adenine Dinucleotide/ Dihydronicotinamide-Adenine Dinucleotide Phosphate (NADH/NADPH)* **Directive No. 1, 2021.** ***NPRA.600-1/9/13 (11)*** *Direktif Untuk Semua Produk Yang Mengandungi Mesalazine dan Sulfasalazine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Nephrolithiasis*
223.	**SULPHONAMIDES/ TRIMETHOPRIM** 1. The following statement shall be included on the labels of products containing Sulphonamides and Trimethoprim as single ingredient or in combination of both ingredients: Discontinue treatment with this drug immediately if skin rash or any sign of adverse reaction occurs. 2. The following statement shall be included in the package inserts of products containing Sulphonamides and Trimethoprim as single ingredient or in combination of both ingredients: Fatalities associated with the administration of sulphonamides and trimethoprim, either alone or in combination, have occurred due to severe reactions, including Steven-Johnson syndrome, toxic epidermal necrolysis and other reactions. The drug should be discontinued at the first appearance of skin rash or any sign of adverse reaction.

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224.	**SYNTHETIC SALMON CALCITONIN** 1. Indication and duration of use for products containing synthetic salmon calcitonin (according to the stated dosage forms) are restricted as follows, and the package insert of the product shall be amended accordingly: a) For dosage form: Injection *Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures.* ***The duration of treatment should not be more than 4 weeks.*** *For the treatment of Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment.* ***The duration of treatment is limited to 3 months.*** *Treatment of hypercalcaemia of malignancy.* b) For dosage form: Nasal spray *Prevention of osteoporosis: In acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures. Miacalcic should be supplemented with adequate doses of calcium and Vit D, as needed by the individual patient, to prevent further bone loss.* ***The maximum duration of treatment is 3 months.*** *Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable.* ***The duration of treatment is normally 3 months.*** *Algodystrophy or Sudeck's Disease (Neurodystrophic disorders) due to various causes and predisposing factors such as posttraumatic painful osteoporosis, reflex dystrophy, shoulder arm syndrome, causalgia and drug-induced neurotrophic disorders.* ***The duration of treatment is up to 6 weeks.*** 2. Under "Dosage" in the package insert of products containing synthetic salmon calcitonin (injection and nasal spray), the following statement shall be stated: *The treatment duration in all indications should be limited to the shortest period of time possible and using the lowest effective dose.* **Reference: Directive No. 4, 2014.** ***Bil. (10) dlm.BPFK/PPP/07/25*** *Direktif Untuk Mengehadkan Indikasi dan Tempoh Penggunaan Produk Yang Mengandungi Calcitonin Salmon Sintetik Dalam Bentuk Injeksi dan Intranasal 'Nasal Spray' Berikutan Risiko Kanser*

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225.	**TABEBUIA SPP. (PAU D'ARCO)** The following warning statement shall be included on the labels of products containing Tabebuia spp. (Pau d'arco): "As the use of Tabebuia spp. (Pau d'arco) may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicine and before you undergo any surgical/ dental procedure." (Memandangkan pengambilan Tabebuia spp. (Pau d'arco) boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau akan menggunakan ubat lain dan sebelum prosedur pembedahan/ dental dijalankan)
226.	**TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 (EXCIPIENT)*** The following statements shall be included in the package inserts and Consumer Medication Information Leaflet (RiMUP) of products containing TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 / Aluminic Lake: **Package Insert / Product label**** **a) Warnings and Precautions** This preparation contains Tartrazine / FD & C Yellow No.5 / MA Yellow A-2 / Aluminic Lake that may cause allergic reactions in certain susceptible patients. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use (product name)** Before you start to use it (Product name) contains TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 / Aluminic Lake. This is a colouring agent, which may cause allergic reactions. *This is not applicable to external use product **In cases where a package insert and RiMUP are not available. For example; natural products, health supplements, or over-the-counter (OTC) products evaluated via abridge evaluation. **Reference: Directive No. 13, 2025.** *NPRA.600-1/9/13 (60)Jld.1 Direktif berkenaan penetapan had harian dan pengemaskinian maklumat keselamatan bagi tartrazine*

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227.	**TEMOZOLOMIDE** The following statement shall be included in the package inserts of products containing Temozolomide: **WARNINGS AND PRECAUTIONS** Hepatic injury, including fatal hepatic failure has been reported in patients receiving temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/ risks prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 days treatment cycle, liver function test should be repeated midway during this cycle. For all patients, liver function test should be checked after treatment cycle. For patient with significant liver function abnormalities, physicians should assess the benefit/ risks of continuing treatment. Liver toxicity may occur several weeks or more after the last reatment of temozolomide. **Reference: Directive No. 11, 2014.** ***Bil. (18) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Temozolomide: Maklumat Keselamatan Baru Berkaitan Dengan Risiko Kecederaan Hati*
228.	**TERBUTALINE** 1. The following statement shall be included in the package inserts of products containing Terbutaline in **injection** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. • Cautious use of terbutaline injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference

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	with uterine contractibility. During IV infusion of terbutaline, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. 2. The following information shall be included in the package insert and product literature of products containing Terbutaline in **oral tablet/ capsule** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. 3. The following warning statement shall be included in the package inserts of products containing terbutaline in **injection and oral** dosage form under section of **Warning and Precautions**: • **Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.** **References:** ***Bil. (6) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Mengenai Insiden* 'Myocardial Ischaemia' *pada Wanita Mengandung yang Menerima Rawatan* 'Beta Agonist' *Bagi Rawatan Melambatkan Kelahiran Pramatang Pada Sisip Bungkusan Kumpulan Produk Ini* **Directive No. 8, 2011.** ***Bil. (18) dlm. BPFK/PPP/01/03 Jilid 1*** *Direktif Untuk Memperkukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Serius Pada Jantung Termasuk Kematian Dengan Penggunaan Produk Suntikan dan Oral Beta Agonis dalam Rawatan Kelahiran Pra-Matang*

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229.	**TESTOSTERONE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Testosterone; **Package Insert** **a) Warnings and Precautions:** Drug Abuse and Dependence Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids (AAS). Abuse of testosterone and other AAS are seen in adults and adolescents, including athletes and body builders. Testosterone and AAS abuse can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Section Adverse Effects/Undesirable Effects). If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and AAS. Conversely, consider the possibility of testosterone and AAS abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events. Continued abuse of testosterone and other AAS may result in dependence and withdrawal symptoms. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism. Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented. **b) Overdose:** Chronic Overdose Caused by Abuse Chronic overdose caused by abuse of testosterone and other anabolic androgenic steroids (AAS) can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Sections Warnings and Precautions and Adverse Effects/ Undesirable Effects). **c) Adverse Effects/Undesirable Effects:** Abuse-Related Adverse Reactions Serious adverse reactions have been reported in individuals who abuse testosterone and anabolic androgenic steroids (AAS) and include cardiac arrest,

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	myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression. The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidaemias, testicular atrophy, subfertility, and infertility. The following additional adverse reactions have been reported in women: hirsutism, virilisation, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities. The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty. Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) How to use [product name]:** If you use too much (overdose): If you have taken more than the recommended dose of [product name], contact your doctor immediately or go to the Emergency Department of your nearest hospital. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention. Taking more than the recommended dose of [product name] for a long period of time can cause serious health problems including effects on the heart, liver, and reproductive functions, as well as serious psychiatric problems. **b) While you are using it:** Things you must not do: Do not take more than the recommended dose of [product name]. Individuals who have taken more than the recommended dose for a long period of time may experience withdrawal symptoms lasting for weeks or months after abrupt discontinuation or a significant dose reduction of [product name]. These include: changes in mood and appetite, fatigue, insomnia, decreased sex drive as well as loss of function of the testes and ovaries. **Reference: Directive No. 19, 2017.** ***BPFK/PPP/07/25 (24) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Testosteron: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Susulan Penyalahgunaan*

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	dan Kebergantungan Ubat
230.	**TETRACYCLINE SYRUP** The following boxed warning shall be included on the label and in the package inserts of products containing Tetracycline (syrup) **NOT TO BE GIVEN TO CHILDREN UNDER 12 YEARS OF AGE**
231.	**THIOMERSAL** ***Note:*** Thiomersal is not allowed in ophthalmic preparations as preservative**.** The following statement shall be included on the label and package inserts of products containing thiomersal for preparations other than ophthalmic preparation: **WARNING** **'RISK OF SENSITIZATION IN RELATION TO THIOMERSAL AND OTHER PRESERVATIVES'** **Reference:** ***Bil. (34) dlm. BPFK/02/5/1.3*** *Penggunaan Thiomersal Dalam Persediaan Vaksin*
232.	**THROMBOLYTIC AGENTS** The following caution shall be disclosed prominently in the package inserts of products containing "systemic thrombolytic agent" in particular "the tissue plasminogen activators": **WARNINGS AND PRECAUTIONS** Severe bleeding such as intracranial haemorrhage may occur following administration of the drug, particularly in the elderly patients. The risk must be balanced against the potential benefit of thrombolysis. The following precautions need to be observed: Patients should be carefully observed for clinical signs during and following administration of the drug for early detection of bleeding. Frequent haematological tests such as blood coagulation tests are mandatory. To prevent bleeding at the site of centesis or other regions, caution must be exercised concerning procedures and management of arterial/ venus puncture. The use of heparin in conjunction with the thrombolytic agent for the purpose of

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	prevention of reocclusion may increase the risk of intracranial haemorrhage. Close monitoring of patients is strongly recommended.
233.	**TIAPROFENIC ACID** The following statement shall be included in the package inserts of products containing Tiaprofenic acid: **WARNINGS AND PRECAUTIONS** Urinary symptoms (bladder pain, dysuria, and frequency), haematuria or cystitis may occur. In certain exceptional cases, the symptoms have become severe on continued treatment. Should urinary symptoms occur, treatment with tiaprofenic acid must be stopped.
234.	**TOPIRAMATE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing topiramate: **Package Insert** **a) Special Warnings and Precautions for Use** **Visual field defects** Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible following topiramate discontinuation, however some cases were not. In a large proportion of postmarketing case reports reversibility was unknown, but in cases where an outcome was reported, the majority were reversible. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug. **b) Warnings and Precautions:** Chronic, untreated metabolic acidosis may increase the risk of nephrocalcinosis Women of childbearing potential [Product name] may cause fetal harm when administered to a pregnant woman. Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed and a highly effective contraceptive method used. The patient should be fully informed of the risks

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	related to the use of topiramate during pregnancy. [Product name] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **c) Adverse Effects/Undesirable Effects:** <u>Renal and urinary disorders</u> Very rare: Nephrocalcinosis Postmarketing data: <u>Eye disorders</u> Frequency "not known": Uveitis **d) Contraindication:** *For product indicated for migraine prophylaxis, to state: Migraine prophylaxis: in pregnancy and in women of childbearing potential if not using a highly effective method of contraception. **e) Pregnancy** [Product name] can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems) and neurodevelopmental disorders (e.g., autism spectrum disorders and intellectual disability). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen. In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of antiepileptic drugs in combination therapy. The risk has been observed in all doses and effects were reported to be dose-dependent. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects:** - There is a potential significant risk for metabolic acidosis that may have no symptoms and if left untreated may be associated with adverse effects on kidneys (e.g. kidney stone/ nephrocalcinosis). - Sudden changes in your eyesight (e.g. blurred vision)

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	- Eye pain - Red eye **b) Before you use [product name]:** <u>When you must not use it</u> *For product indicated for migraine prophylaxis, to state: For migraine prevention: if you are pregnant or if you are a woman of childbearing potential unless you are using effective contraception. You should talk to your doctor about the best kind of contraception to use while you are taking [Product name]. If you are not sure if the above applies to you, talk to your doctor or pharmacist before using [Product name]. *For all products containing topiramate, to state: As with other anti-epileptic medicines, there is a risk of harm to the unborn child if [Product name] is used during pregnancy. Make sure you are very clear about the risks and the benefits of using [Product name] during pregnancy: • If you take [Product name] during pregnancy, your baby has a higher risk for birth defects, particularly, cleft lip (split in the top lip) and cleft palate (split in the roof of the mouth). Newborn boys may also have a malformation of the penis (hypospadias). These defects can develop early in pregnancy, even before you know you are pregnant. • Your child is also at risk for developing autism and other intellectual disabilities. • There may be other medicines to treat your condition that have a lower risk of birth defects. • Tell your doctor straight away if you become pregnant or planning to get pregnant while taking [Product name]. You and your doctor should decide if you will continue to take [Product name] while you are pregnant. • It is important that you do not stop taking your medicine without first consulting your doctor. • You should talk to your doctor about the best kind of birth control to use while you are taking [Product name]. You should use effective contraception. Before the start of treatment with [Product name], a pregnancy test should be performed. Talk to your doctor if you wish to become pregnant. **References:** **Directive No. 15, 2014.** ***Bil. (22) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Amaran Berkaitan Risiko Gangguan Penglihatan* **Directive No. 13, 2019.** ***BPFK/PPP/07/25 (13) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk*

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	Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Nephrocalcinosis **Directive No. 14, 2020.** ***NPRA.600-1/9/13(5)*** *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Uveitis* **Directive No. 11, 2023.** ***NPRA.600-1/9/13 (29) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan:* *i. Risiko gangguan neurodevelopmental dalam kalangan kanak-kanak yang terdedah kepada topiramate semasa kehamilan ibu* *ii. Penyelarasan maklumat keselamatan berkenaan risiko kecacatan kongenital (congenital malformation)*
235.	**TRAMADOL** The following statements shall be <u>included in the package insert and RiMUP</u> of products containing Tramadol: **<u>Package Insert</u>** **a) Recommended Dosage:** <u>Adults and adolescents (12 years and older)</u> [Product name] is not approved for use in patients below 12 years old. <u>Paediatric population</u> The safety and efficacy of [product name] has not been studied in the paediatric population. Therefore, use of [product name] is not recommended in patients under 12 years of age. **b) Contraindications:** - Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids. - Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems. **c) Warnings and Precautions:** <u>Paediatric population</u> The safety and efficacy of [product name] has not been studied in the paediatric population. Therefore, use of [product name] is not recommended in patients under 12 years of age. <u>Respiratory depression</u> Administer [product name] cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients,

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	even therapeutic doses of [product name] may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures. Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism Some individuals may be CYP2D6 ultra-rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. **d) Pregnancy and Lactation:** Pregnancy Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. [Product name] is not recommended for pregnant women. Lactation Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol. **e) Adverse Effects/Undesirable Effects:** Respiratory depression (rare) **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]** When you must not use it: - you are less than 12 years old. - you have slow or shallow breathing, or other breathing problems. - you are pregnant. - you are breastfeeding.

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	b) While you are using it: Things to be careful of: - Tramadol is not to be used during breast-feeding. Small amounts of tramadol is excreted into breast milk. On a single dose it is usually not necessary to interrupt breast-feeding. If you have taken [product name] when you are breastfeeding, seek immediate medical attention if you notice your baby has any changes in their breathing (such as weak, difficult or fast breathing). **Reference: Directive No. 20, 2017.** ***BPFK/PPP/07/25 (25) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Tramadol Dengan Maklumat Bagi Mengehadkan Penggunaan Tramadol Dalam Kalangan Kanak-Kanak dan Amaran Berkaitan Penggunaan Dalam Kalangan Ibu Mengandung dan Ibu Menyusu*
236.	**TRIMETAZIDINE** 1. Indication of products containing Trimetazidine shall be amended as follows: a) Indication of Trimetazidine for treatment of pectoris angina is limited to second-line add on therapy; and the indication in otology and ophthalmology field shall be removed. b) Permitted indication is ***trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.*** 2. The following warning statement shall be included in the package inserts of products containing Trimetazidine: a) **Dosage and method of administration:** For products containing Trimetazidine 20mg: *The dose is one tablet of 20mg of trimetazidine three times a day during meals.* *The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.* *Special populations* *Patients with renal impairment:* *In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals.* *Elderly patients:* *Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is*

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	1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals. Dose titration in elderly patients should be exercised with caution. <u>For products containing Trimetazidine 35mg:</u> *The dose is one tablet of 35mg of trimetazidine twice daily during meals.* *The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.* <u>*Special populations*</u> *Patients with renal impairment:* *In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast.* *Elderly patients:* *Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast. Dose titration in elderly patients should be exercised with caution.* b) **Contraindications:** - *Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders* - *Severe renal impairment (creatinine clearance < 30ml/min).* c) **Warnings and precautions:** *Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.* *The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.* *These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.* *Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment.*

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	Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected: - *moderate renal impairment,* - *elderly patients older than 75 years old.* d) **Adverse Effects/ Undesirable Effects:** *Nervous system disorders:* *Frequency not known:* — *Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation.* **Reference: Directive No. 5, 2013.** ***Bil. (4) dlm.BPFK/PPP/07/25*** *Direktif Untuk Menghadkan Penggunaan Produk Mengandungi Trimetazidine dan Mengukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Simptom Parkinson Pada Sisip Bungkusan Semua Produk Trimetazidine*
237.	**TRIPROLIDINE** The following statement shall be included on the label and in the package inserts of liquid oral products containing Triprolidine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
238.	**VALACICLOVIR** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing valaciclovir; **Package Insert** **a) Warnings & Precautions:** Immune: Drug reaction with eosinophilia and systemic symptoms (DRESS),

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	which can be life-threatening or fatal, has been reported in association with valaciclovir treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of DRESS appear, valaciclovir should be withdrawn immediately and an alternative treatment considered (as appropriate). If a patient has developed DRESS with the use of valaciclovir, treatment with valaciclovir must not be restarted in this patient at any time. **b) Adverse Effects/ Undesirable Effects:** Immune system disorders Drug reaction with eosinophilia and systemic symptoms (DRESS). **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect one or more organs): fever, severe rash, peeling skin, swelling of the face, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinating less often, less urine. **Reference: Directive No. 6, 2023.** ***NPRA.600-1/9/13 (24)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Valaciclovir: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)*

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239.	**VARENICLINE** The following statement shall be included in the package inserts of products containing Varenicline: **WARNINGS AND PRECAUTIONS** Effect of smoking cessation: Smoking cessation, with or without pharmacotherapy has been associated with the exacerbation of underlying psychiatric illness (eg. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly. Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt. **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** Post marketing cases of MI, depression and suicidal ideation have been reported in patients taking varenicline. **Reference:** ***Bil. (83) dlm. BPFK/17/FV/28*** *Maklumat Dari European Medicines Agency (EMEA) Berkaitan Penggunaan Produk Champix (Varenicline) Untuk Rawatan Berhenti Merokok (Smoking Cessation)*
240.	**Vascular Endothelial Growth Factor (VEGF) Inhibitors** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing VEGF inhibitors for systemic use (except application on eyes); **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Vascular disorders Frequency "not known": aneurysms and artery dissections **Consumer Medication Information Leaflet (RiMUP)** **a) Side effects:** Frequency 'not known': An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections). **Reference: Directive No. 10, 2021**. ***NPRA.600-1/9/13(20)*** *Direktif Untuk Semua Produk Yang Mengandungi Vascular Endothelial Growth Factor (VEGF) Inhibitors Untuk Kegunaan Sistemik (Kecuali Kegunaan Pada Mata): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Artery Dissections dan Aneurysms*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
241.	**VITAMIN K** 1. The following statement shall be included in the label and package insert of health supplement products containing Vitamin K as combined ingredients with other vitamins and minerals in oral preparation: **'Consult a healthcare practitioner if you are on anticoagulant/ blood thinner products.** 2. The following statement shall be included in the package inserts of products containing Vitamin K1 (phytomenadione) as single ingredient used intravenously: **WARNINGS AND PRECAUTIONS** Severe reactions, including fatalities, have occurred during and immediately after intravenous injection of Vitamin K1. Restrict intravenous use to emergency case. When intravenous administration is necessary, the rate of injection should not exceed 1mg per minute. **ADMINISTRATION**: In severe bleeding, or situations where other routes are not feasible, Vitamin K1 may be given by very slow intravenous injection, at a rate not exceeding 1mg per minute.
242.	**WARFARIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Warfarin: **Package Insert** **Caution** Topical preparations containing methyl salicylate should be used with care in patients on **Warfarin** and excessive usage is to be avoided as potentially dangerous drug interaction can occur. **Contraindications** Co-administration with miconazole oral gel (see Interactions).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Warnings and Precautions: • Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphatemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin. • Co-administration with topical miconazole (see Interactions). • <u>Anticoagulant-related nephropathy</u> In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and hematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with a supratherapeutic INR and hematuria (including microscopic). **Interactions** The following drugs have been reported to potentiate the warfarin effect (increase INR): • Miconazole **Adverse Effects/ Undesirable Effects**: Skin and subcutaneous tissue disorders Frequency 'not known': Calciphylaxis <u>Renal and urinary disorders</u> Frequency 'not known': Anticoagulant-related nephropathy **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **Side Effects**: Frequency 'not known': Impairment of renal function occurring with excessive anticoagulation and presence of blood in urine (anticoagulant-related nephropathy).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Tell your doctor straight away if you have any of the following side effects : [...] A painful skin rash. On rare occasions warfarin can cause serious skin conditions, including one called calciphylaxis that can start with a painful skin rash but can lead to other serious complications. This adverse reaction occurs more frequently in patients with chronic kidney disease. **Before You Use [Product Name]** *When you must not use it* Do not take [product name] together with miconazole oral gel *Before you start to use it* Some commonly used medicines and products that may interfere with [product name] include: • Miconazole **References:** **Directive No. 15, 2016.** ***BPFK/PPP/07/25 (1) Jld.1*** *Direktif Bagi Semua Produk Yang Mengandungi Warfarin Dengan Risiko Kesan Advers Calciphylaxis* **Directive No. 12, 2017.** ***BPFK/PPP/07/25 (17) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Warfarin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat* **Directive No. 4, 2022.** ***NPRA.600-1/9/13 (4)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Warfarin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Anticoagulant-Related Nephropathy (ARN)*