APPENDIX 9: LABELLING REQUIREMENTS

This appendix comprises of two (2) parts:

a) General Labelling Requirements for:

i) Section D : Label (Mock-Up) for Immediate Container and Outer Carton

ii) Section D : Proposed Package Insert (PI)

iii) Section E8/ F8 : Consumer Medication Information Leaflet (RiMUP)

b) Specific Labelling Requirements

9.1 GENERAL LABELLING REQUIREMENTS

The following information in **Table 1** shall present on the label of a product at outer carton, immediate container or blister/ strips:

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
1.	Product Name	✓	✓	✓
2.	Dosage Form	✓	✓*	NA
3.	Name of Active Substance(s)	✓	✓	✓**
4.	Strength of Active Substance(s)	✓	✓	✓**
5.	Batch Number	✓	✓	✓
6.	Manufacturing Date	✓	✓*	NA
7.	Expiry Date	✓	✓	✓
8.	Route of Administration	✓	✓	NA
9.	Storage Condition	✓	✓*	NA
10.	Country's Registration Number	✓	✓*	NA
11.	Name & Address of Product Registration Holder (PRH)	✓	✓*	Name/ Logo of Manufacturer/ Product Owner
12.	Name & Address of Manufacturer	✓ At least name of town/ city and country of manufacturer	✓* At least name of town/ city and country of manufacturer	NA
13.	Warnings and/or Specific Labelling (if applicable)	✓	✓*	NA
14.	Pack Sizes (unit/ volume)	✓	✓	NA

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
15.	Name & content of preservative(s) where present	✓	✓	NA
16.	Name & content of alcohol, where present	✓	✓	NA
17.	To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine.	✓	✓	NA
18.	To declare the source of capsule shell (if applicable)	✓	✓	NA
19.	Recommended daily allowance (RDA) for vitamins/ multivitamins/ mineral preparations used as dietary supplements (optional)	✓	✓	NA
20.	The words “Keep medicine out of reach of children” or words bearing similar meaning in both *Bahasa Malaysia* & English	✓	✓*	NA
21.	Other country specific labelling requirements (if applicable)	✓	✓*	NA
22.	The words “Controlled Medicine/ *Ubat Terkawal*” **(For scheduled poison only)**	✓	✓*	NA
23.	Security Label (Hologram)	✓ #	-	NA

NA : Not Applicable

* Exempted for small labels (i.e. 5ml and less) used for ampoules/ cartridge, vials, eye drops, ear drops, and nose drops.

** For multi-vitamins and minerals preparations it is suggested to label as multi-vitamins and minerals.

i. In case of a product without an outer carton, the security label shall be applied onto the immediate label. The security label shall however not be applied onto the outer shrink wrap of the product.

ii. Exemption will be for small labels (i.e. volume of 5ml and less) such as for ampoules/ cartridge/vials.

No. 15, 20, 22 & 23 of the above are country specific requirements for Malaysia.

- Declaration of nutrition information per serving (for example energy, carbohydrate, protein and fat) is not permitted in a health supplement product label.

ADDITIONAL INFORMATION:

a) All labels and package inserts must be in *Bahasa Malaysia* or English. In additional to this, translation to another language will be allowed.

b) If the product is without an outer carton, the inner label shall bear all the information that is required.

c) Official website of the company or website for any purpose of product promotion from the PRH/ product owner/ manufacturer is not allowed to be printed on the product label (applicable to all categories of products inclusive of imported products). However, the email address of the company is permissible on the label.

d) The colours of labels shall be differentiated between strengths of products as well as between products containing different active ingredients which belong to the same holder.

e) Only a single label artwork is permitted for all pack sizes of a registered product.

f) No stick-on label is permitted. Any usage of stick-on label shall have prior approval by the Authority. The Authority will only consider the following situations:

i) Stick-on label of such information and printing of registration number for label redressing of a registered product is permitted:

Words with "Controlled Medicine/ *Ubat Terkawal", "Keep out of reach of children/ Jauhkan daripada capaian kanak-kanak"*, information of Product Registration Holder, and Malaysia Specific Labelling Requirements (if any) shall be printed in a single label.

ii) The label shall be made from good quality material and not easy to be torn out.

iii) Registration number shall be printed permanently on the product (ink-jet) and it is not allowed to be printed on the stick-on label.

g) Use of QR code is permitted only for the purpose of monitoring inventory of the product, such as batch number, expiry date and manufacturing date, BUT NOT for linkage to any website. The addition of QR code on registered product labels without variation approval from NPRA can be considered only if that is the only proposed change to the currently approved labels.

h) The label of a registered product containing any Scheduled Poison shall not have colourful atrwork or graphics that can be misleading or will adversely influence caregivers'/patients'/children's perceptions of the appropriateness of the medication.

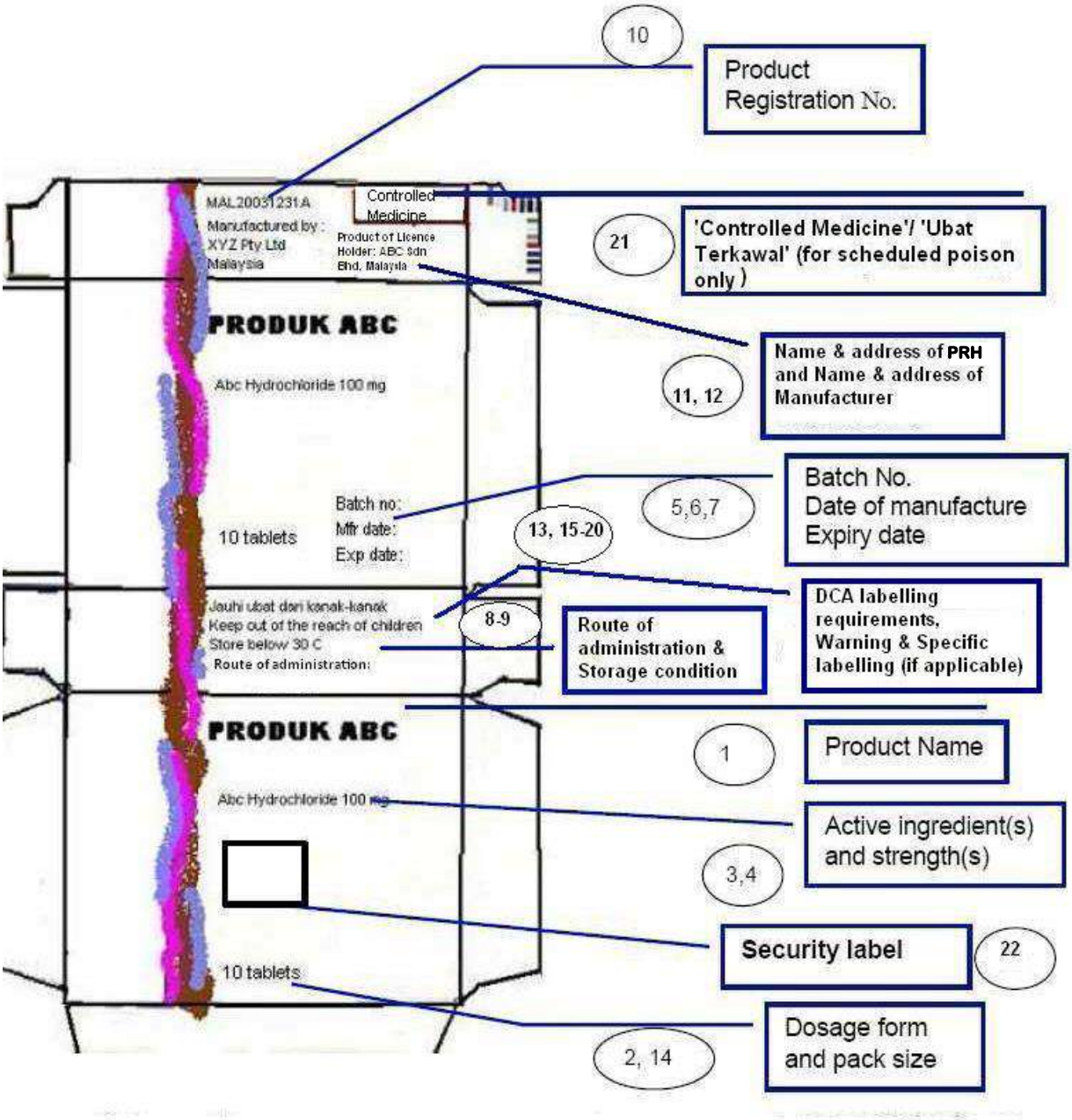
i) Font size of the product name on the label, including alphabets and numbers, should be equal in size.

j) For a product containing 2 or more active ingredients, font size of each active ingredient that is highlighted on the inner/ outer carton must be of equal size and equal prominence (Note: this is not referring to the product name, but the statement made on the label).Justification for highlighting certain ingredients only on the product name / label must be provided and subject to approval by the Evaluation Committee.

9.1.1 LABEL (MOCK-UP) FOR IMMEDIATE CONTAINER AND OUTER CARTON

Please refer to **Figure 1** as an example of a product label which in accordance to the labelling requirements.

Figure 1:



Note:

Numerical notations shown in the above figure are in line with the numbering for the parameters, shown in Table 1 above, to be included in the product label (as identified and adopted by the ACCSQ-PPWG).

9.1.2 PROPOSED PACKAGE INSERT

Package insert (PI) is required for products containing scheduled poison and for injectable OTC products. PI may also be submitted for other OTC products. The draft copy of the PI shall be submitted for evaluation.

Sharing of PI is only allowed for products having the same active ingredient(s) but with different strengths.

The following information is required to be included in the PI:

a) Brand or Product Name
b) Name and Strength of Active Substance(s)
c) Product Description
d) Pharmacodynamics/ Pharmacokinetics
e) Indication
f) Recommended Dosage
g) Route of Administration
h) Contraindications
i) Warnings and Precautions
j) Interactions with Other Medicaments
k) Statement on usage during pregnancy and lactation
l) Adverse Effects/ Undesirable Effects
m) Overdose and Treatment
n) Incompatibilities (For injections only)
o) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
p) Dosage forms and packaging available
q) Name and address of manufacturer/ product registration holder
r) Date of revision of PI

9.1.3 CONSUMER MEDICATION INFORMATION LEAFLET (RiMUP)

Consumer Medication Information Leaflet or in *Bahasa Malaysia* known as *Risalah Maklumat Ubat untuk Pengguna (RiMUP),* is compulsory for products which are self-administered by patients, including:

a) Scheduled poisons (Category A);
b) Over-the-Counter, OTC products (Category X);
c) Herbal products; and health supplements with high claims (disease risk reduction).

For details, please refer to:

i) *Direktif Penguatkuasaan Keperluan Mengemukakan Risalah Maklumat Ubat untuk Pengguna (RiMUP) Bil. 5 Year 2011* Bil (15) dlm BPFK/PPP/01/03 Jld 1
ii) *Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna (RiMUP)*

The draft copy of the RiMUP in both English and *Bahasa Malaysia* shall be submitted for evaluation.

Note:

RiMUP is not compulsory to be distributed with the product. All approved RiMUP will be uploaded onto NPRA website as reference for consumers. Healthcare professionals can access the RiMUP and disseminate to patients if necessary.

For OTC Products, if the product is intended to be sold without a PI or RiMUP, the information required to be included in the PI or RiMUP shall be printed on the unit outer-carton of the product. However, submission of the RiMUP softcopy is compulsory as mentioned above.

9.1.4 PRODUCT NAME

Product name is defined as a name given to a product which may either be a proprietary name (an invented name); or a generic name (common name) or scientific name, together with a trade mark or the name of the manufacturer.

- Product name shall consist of dosage form and strength (for single active ingredient product). (e.g. X Brand Paracetamol Tablet 500mg)
- The generic name cannot be used alone as product name but in combination with another name, other than the generic name.
  - The generic name means the international non-proprietary name recommended by WHO (rINN), or if one does not exist, the usual approved name.
- The invented name shall not be liable to confusion with the common name.
- Font size of the product name on the label, including alphabets and numbers, should be equal in size.
- If a product name is found similar in terms of spelling and pronunciation to another registered product or any other name which deemed inappropriate by the Authority, NPRA reserves the rights to request for the change of the product name.

Product names which are not permitted to be registered are as specified in **Table 2** below:

No.	Non-Permissible Product Names	Example
1.	**20 disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983)**	**Example :** Diabetes, Asthma, Cancer
2.	**Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika**	**Example :** Tongkat Ali Capsule ---- But product contains tongkat ali, ginseng, ect.

No.	Non-Permissible Product Names	Example
3.	**Use of Superlatives - Names which indicates superiority in efficacy**	**Example :** Power/ Kuasa, Superior, Pure, Mustajab, Safe, Healthy/ Sihat, Penawar/ Shifa, VIP, Good, Heal/ Sembuh, Premium, Mustajab, Men/ Women/ Children Complete, Men/ Women/ Children Enriched, Paradise/ Syurga, Menawan, Booster
4.	**Use of spelling of words which may cause confusion** **Words which involve names of/part thereof:** iv) 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) v) Diseases without scientific evidence of efficacy/ prescription medication to treat diseases/ parameters that indicate certain diseases (e.g. insulin, glucose) vi) Prohibited indication (e.g. to detoxify body)	**Example :** a) Go Out = GOUT b) UTix = Urinary Tract Infection c) Diabecine = Diabetes d) Metformon = Metformin e) Insuprem = Insulin f) Glucosey = Glucose g) DetoxB = Detox body
5.	**Use of names which may cause ambiguity** Ambiguous product name	**Example:** B For Energy?
6.	**Use of names which may be offensive or indecent**	**Example:** SENXBIG=SEnXBIG(label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire*(Dezire),Sensual (Xenxual),Asmara,Syok*

No.	Non-Permissible Product Names	Example
7.	**Use of product names which are incoherent with the approved indication** Name containing a product claim whereas product is indicated for more than the approved indication	**Example:** Cough Syrup X= Approved indication for cough, dizziness, flu and itch
8.	**Use of product names which has elements of ludicrous belief** Statements referring to ancient believe/ negative spirits/ supernatural power	**Example:** Words such as miracle, magic, magical, miraculous, saintly, heavenly
9.	**Use of product names similar to the existing approved product names** Product names similar to the spelling and pronunciation of words of the existing product names	**Example:** Tenormin vs Tenormine vs Tenormy Re-Liv vs Re-Lif
10.	**Use of product names which may cause ambiguity in the nature of product (drug/ food/ beverage)** Product names similar to a food/ beverage product	**Example:** Juice, Health drink, Beverage, Kooky
11.	**Use of product names which represents professional advice or opinion or referring to the profession**	**Example:** Dr Sunny, Dr Noortier Rooibose Tea, Professor, Herbalist, Doctor
12.	**Use of product names which represent weight loss/ slimming properties/ names that can be associated with weight loss/ slim**	**Example:** Slim, Langsing, Trim, Trimnfit, *Sleen, Kurus, Susut perut,Xlim, Weight watcher*
13.	**Use of product names referring to any religious content**	**Example:** Maksum, Mahmudah, Arifbillah
14.	**Use of product names referring to internal organs**	**Example:** Leever, Brainey, Kidnee, etc.

No.	Non-Permissible Product Names	Example
15.	**Use of abbreviation as a product name unless it carries no meaning**	**Example:** TB, UTI, HB, etc.
16.	**Use of product name which carries 'traditional' and/ or 'non-professional' image for Pharmaceutical products**	**Example:** Cap Ikan Emas, Brand Ayam Jati, Tablet Kuat Badan
17.	**Other prohibited product names**	**Example:** Minda, IQ, Smart, Genius, Ultra Mega, Detox

Note:

1. *This list is not meant to be exhaustive and will be reviewed from time to time*
2. *The Authority reserves the right to disallow any other words or phrases for product names which in its opinion is misleading, improper or not factual.*

9.1.5 PROHIBITED VISUAL/ GRAPHICS/ STATEMENTS ON LABEL

The lists are as shown in **Table 3** below:

No.	Issue	Example	Note
1.	Marketing strategy	**Example:** "Money back guarantee" "Buy 1 free 1" "Backed by RM5 million product Liability Insurance"	-
2.	Usage guide which promotes use of other product(s)	**Example:** "After consumption of this product (Product A), for better results, it is recommended to take Product B"	-

No.	Issue	Example	Note
3.	Consumer testimonial	-	-
4.	Clinical Trial results or any information on clinical trial done on product	Example : “Clinically Tested” “Randomized Double Blind Placebo Control Clinical Study”	-
5.	Reference to Hadith/ Al-Quran/ Bible/ Religious books	-	-
6.	Opinion of prominent figure(s) on product or its active ingredient/ content	**Example:** Opinion of product/formulation inventor	-
7.	Label design (graphic and color) similar to labels from another company	-	-
8.	Statement on active ingredient origin	**Example:** Source from the Mountains of Alps	Allowed if proven true
9.	Introduction of founder/ Manufacturer	-	-

No.	Issue	Example	Note
10.	Logo with certification	**Example:** SIRIM/ ISO / GMP/ HACCP	Prohibited on product label because certification renewal is on a yearly basis
11.	Name/ Statement/ Logo/ registered trademark which does not satisfy the specifications	**Example:** “Dr.ABC’s Formula” “Nothing like it”	-
12.	Patency claim/ Patency number/ Special technique used/ superiority in ingredients (Example: capsule coat)	**Example:** Patented technique	Allowed if proven true
13.	Nutritional claims with analysis certificate attached	**Example:** Calorie, Fat, Protein and others	-
14.	Graphics or picture of internal organs	**Example:** Kidney, Heart, Nerves.	-
15.	Gender symbol (male or female)	(♀ and/or ♂)	-
16.	Indecent photographs/ pornography/ graphics/ images	-	-

No.	Issue	Example	Note
17.	Graphics which are incoherent with the indication	**Example:** - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose.	-
18.	Highlighting unnecessary body parts	**Example:** Indication is for general health but graphics on label highlights male and female sexual organ parts	-
19.	Graphics of plants or animal which may cause confusion	**Example:** Radix Ginseng which is improvised as a male sexual part	-
20.	Negative Statements/ Visual	**Example:** - This product is GMO/ LMO free - This product is free from animal origin - Free from Preservative	-
21.	Other statements deemed relevant to be prohibited by the authority	**Example:** - This product is blended with premium quality	-

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual*

9.2 SPECIFIC LABELLING REQUIREMENTS

Please refer Table 4: List of Substances Which Requires Specific Labelling Requirements and Table 5: Details of Specific Labelling Requirements.

Table 4: List of Substances Which Requires Specific Labelling Requirements:

NO.	SUBSTANCES
1.	5-ALPHA REDUCTASE INHIBITOR (5-ARI)
2.	ACE INHIBITORS
3.	ACETAZOLAMIDE
4.	ACETYLCYSTEINE
5.	ACETYLSALICYLIC ACID (ASPIRIN)
6.	ACTIVATED CHARCOAL/ ATTAPULGITE
7.	ALBENDAZOLE & BENZIMIDAZOLE ANTIHELMINTICS
8.	ALFALFA (*MEDICAGO SATIVA*)
9.	ALLOPURINOL
10.	ALPHA DIHYDROERGOCRYPTINE
11.	ALPRAZOLAM
12.	AMIODARONE
13.	AMOXICILLIN
14.	ANTIDEPRESSANTS
15.	ANTIEPILEPTICS
16.	ANTIPSYCHOTIC AGENTS
17.	APOMORPHINE
18.	ARGININE
19.	ARIPIPRAZOLE

20.	ARTESUNATE
21.	ASPARTAME
22.	ATORVASTATIN
23.	AZITHROMYCIN
24.	BEE POLLEN
25.	BENZODIAZEPINE
26.	BENZOYL PEROXIDE
27.	BENZYL ALCOHOL
28.	BERBERINE ALKALOIDS – NATURAL OCCURING BERBERINE E.G. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA ETC.
29.	BLACK COHOSH (*CIMICIFUGA RACEMOSA*)
30.	BOSWELLIA SPP.
31.	BROMAZEPAM
32.	BROMOCRIPTINE
33.	BROMPHENIRAMINE
34.	CABERGOLINE
35.	CAMPHOR
36.	CARBAMAZEPINE
37.	CARBIMAZOLE
38.	CARBOCISTEINE
39.	CEFTRIAXONE
40.	CETIRIZINE
41.	*CHELIDONIUM MAJUS*
42.	CHITOSAN

43.	CHLORHEXIDINE
44.	CHLORPHENIRAMINE
45.	CHORIONIC GONADOTROPHIN
46.	CLEMASTINE
47.	CLINDAMYCIN
48.	CLOBAZAM
49.	CLOPIDOGREL
50.	CLOZAPINE
51.	COBICISTAT
52.	CODEINE
53.	COLCHICINE
54.	CORTICOSTEROID
55.	COX-2 INHIBITORS
56.	CYPROTERONE ACETATE
57.	CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION
58.	CYTOTOXIC AGENT
59.	DEXBROMPHENIRAMINE
60.	DEXTROMETHORPHAN
61.	DIAZEPAM
62.	DICLOFENAC SODIUM
63.	DICYCLOMINE
64.	DIPHENHYDRAMINE
65.	DIPHENOXYLATE
66.	DOMPERIDONE

67.	DOPAMINERGIC INGREDIENT
68.	DOXYCYCLINE
69.	EFAVIRENZ
70.	EPHEDRINE
71.	ERYTHROMYCIN
72.	ETHINYLESTRADIOL
73.	ETORICOXIB
74.	FAMOTIDINE
75.	FIBRATES
76.	FILGRASTIM
77.	FLUCLOXACILLIN
78.	FLUCONAZOLE
79.	FLUORIDE
80.	FLUOROQUINOLONES
81.	FLURAZEPAM HYDROCHLORIDE
82.	GABAPENTIN
83.	GADOBENIC ACID
84.	GADOBUTROL
85.	GADODIAMIDE
86.	GADOLINIUM OXIDE
87.	GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
88.	GADOTERIC ACID
89.	GADOVERSETAMIDE
90.	GADOXETIC ACID

91.	GAMAT/ STICHOPUS spp.
92.	GENTAMICIN TOPICAL PREPARATIONS
93.	GINKGO BILOBA/ GINKGO EXTRACT
94.	GINSENG
95.	GLUCOSAMINE
96.	HIV PROTEASE INHIBITORS
97.	HYDROQUINONE
98.	HYOSCINE
99.	IMMUNOSUPPRESANTS
100.	INSULIN
101.	INGREDIENTS DERIVED FROM SEAFOOD
102.	INTERFERON ALPHA
103.	INTERFERON BETA
104.	KAOLIN, PECTIN, KAOLIN-PECTIN
105.	KETOCONAZOLE
106.	KETOROLAC TROMETHAMOL (KETOROLAC TROMETHAMINE)
107.	LEVETIRACETAM
108.	LEVODOPA
109.	LEVONORGESTREL
110.	LINCOMYCIN
111.	LISURIDE
112.	LIQUID PARAFFIN
113.	LOPERAMIDE
114.	LORAZEPAM

115.	LOVASTATIN
116.	MEFLOQUINE
117.	MELALEUCA LEUCADENDRA
118.	MESALAZINE
119.	METFORMIN
120.	METHYL SALICYLATE
121.	METHYLPHENIDATE HCL
122.	METOCLOPRAMIDE
123.	METRONIDAZOLE
124.	MICONAZOLE
125.	MIDAZOLAM
126.	MINOCYCLINE
127.	MINOXIDIL
128.	MOMORDICA CHARANTIA
129.	MONTELUKAST
130.	MUCOLYTIC AGENT
131.	NEVIRAPINE
132.	NIFEDIPINE
133.	NITRATES
134.	NITRAZEPAM
135.	NORFLOXACIN
136.	NORMAL GLOBULIN
137.	NOSCAPINE
138.	NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)

139.	OLANZAPINE
140.	ONDANSETRON
141.	OPIOID
142.	PALIPERIDONE
143.	PARACETAMOL
144.	PARACETAMOL WITH CAFFEINE IN COMBINATION
145.	PEGFILGRASTIM
146.	*PELARGONIUM SIDOIDES*
147.	PENICILLIN
148.	PHENIRAMINE
149.	PHENYLEPHRINE
150.	PIRIBEDIL
151.	PIROXICAM
152.	PRAMIPEXOLE
153.	PRAVASTATIN
154.	PREDNISONE AND PREDNISOLONE
155.	PROMETHAZINE HCL
156.	PROPAFENONE
157.	PROPOFOL
158.	PROPOLIS (ORAL)
159.	PROPOLIS (TOPICAL)
160.	PROPYLTHIOURACIL
161.	PSEUDOEPHEDRINE
162.	PROTON PUMP INHIBITORS (PPI)

163.	PSYCHOTROPIC PRODUCTS
164.	PSYLLIUM/ PLANTAGO (SEED/ HUSK)
165.	QUETIAPINE
166.	QUINAGOLIDE
167.	RISPERIDONE
168.	RED YEAST RICE (MONASCUS PURPUREUS)
169.	ROPINIROLE
170.	ROSIGLITAZONE
171.	ROSUVASTATIN
172.	ROYAL JELLY
173.	SALBUTAMOL
174.	SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)
175.	SEDATIVE – HYPNOTIC PRODUCTS
176.	SELENIUM SULPHIDE
177.	SENNA (CASSIA SPP.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part
178.	SIMVASTATIN
179.	SODIUM METABISULPHITE (EXCIPIENT)
180.	SODIUM VALPROATE
181.	ST. JOHN'S WORT *(Hypericum perforatum)*
182.	STATINS
183.	STRONTIUM RANELATE
184.	SULPHONAMIDES/ TRIMETHOPRIM
185.	SYNTHETIC SALMON CALCITONIN

186.	TABEBUIA SPP. (PAU D'ARCO)
187.	TEMOZOLAMIDE
188.	TERBUTALINE
189.	TESTOSTERONE
190.	TETRACYCLINE SYRUP
191.	THIOMERSAL
192.	THROMBOLYTIC AGENTS
193.	TIAPROFENIC ACID
194.	TOPIRAMATE
195.	TRAMADOL
196.	TRETINOIN (TOPICAL)
197.	TRIAZOLAM
198.	TRIMETAZIDINE
199.	TRIPROLIDINE
200.	VARENICLINE
201.	VITAMIN K
202.	WARFARIN
203.	ZIPRASIDONE
204.	ZOLPIDEM TARTRATE
205.	ZOPICLONE

Table 5: Details of Specific Labelling Requirements

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: **1.1 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 EVENTS: POST MARKETING EXPERIENCE** Male breast cancer **1.2 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	[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 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 EVENTS: POST MARKETING EXPERIENCE** Male breast cancer **1.3 <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.

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	Reference: ***a) Circular Bil (19) dlm BPFK/PPP/01/03 Jld 1:*** *Direktif untuk Memuatkan Kenyataan Amaran Berkaitan dengan Risiko High-Grade Prostate Cancer dalam Sisip Bungkusan Semua Produk 5-Ari* ***b) Circular Bil (64) dlm BPFK/PPP/01/03 Jld 1:*** *Direktif untuk Memuatkan Kenyataan Amaran Berkaitan dengan Risiko Kanser Payudara Di Kalangan Pesakit Lelaki dalam Sisip Bungkusan Semua Produk Yang Mengandungi Finasteride*
2.	**ACE INHIBITORS** The following statement shall be <u>included in the package inserts</u> of products containing ACE inhibitors: **WARNING** • 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:*** *Produk yang Mengandungi 'ACE Inhibitors'*
3.	**ACETAZOLAMIDE** The following statements shall be <u>included in the package insert</u> and <u>Consumer Medication Information Leaflet (RiMUP)</u> for products containing Acetazolamide; **<u>Package Insert</u>** **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:**

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	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:** [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 Year 2018. Ref. 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)
4.	**ACETYLCYSTEINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing acetylcysteine; **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

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	severe hypersensitivity reaction occurs, immediately stop the infusion of acetylcysteine and initiate appropriate treatment. 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. All other products (not indicated for treatment of paracetamol overdose)** **<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).

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	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 with Other Medicaments:** 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 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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 14 Year 2018. Ref. 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* (SCAR)
5.	**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.

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6.	**ACTIVATED CHARCOAL/ ATTAPULGITE** 4.1 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** 4.2 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** **WARNING** Activated charcoal/ attapulgite may interfere with the absorption of other drugs, including antibiotics, when administered concurrently. **PRECAUTION** 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.
7.	**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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
8.	**ALFALFA (*MEDICAGO SATIVA*)** The following boxed warning shall be included on the labels of products containing Alfalfa (*Medico sativa*): This product contains **Alfalfa** (*Medico sativa*). Individual with a predisposition to **systemic lupus erythematosus** should consult their physician before consuming this product.
9.	**ALLOPURINOL** The following statement shall be included in the package inserts of products containing Allopurinol: **WARNING** 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.
10.	**ALPHA DIHYDROERGOCRYPTINE** Please refer to DOPAMINERGIC INGREDIENT
11.	**ALPRAZOLAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE

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12.	**AMIODARONE** The following boxed warning shall be included on the package inserts of products containing Amiodarone: **This product is to be used only by a registered medical practitioner with experience in cardiology.**
13.	**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) Warnings and Precautions:** Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. **b) 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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference : Directive No. 8 Year 2018. Ref. 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
14.	**ANTIDEPRESSANTS** The following statement shall be included in the package inserts of products used as antidepressants: **WARNING** 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 stated / included. ***Reference: Circular 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'*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
15.	**ANTIEPILEPTICS** The following statement shall be included in the package inserts of products used as antiepileptics: **WARNING AND PRECAUTION** Potential for an increase in risk of suicidal thoughts or behaviors. ***Reference: Circular Bil (43) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berkaitan Dengan "Potential for an Increase in Risk of Suicidal Thoughts or Behaviours" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Antiepileptik*
16.	**ANTIPSYCHOTIC AGENTS** **13.1 ALL ANTIPSYCHOTIC AGENTS** The following statement shall be included in the package inserts of products containing antipsychotic: **PREGNANCY AND LACTATION** Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are 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: Circular Bil (16) dlm BPFK/PPP/01/03 Jld 1:*** *Directive 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* **13.2 ATYPICAL ANTIPSYCHOTIC AGENTS** The following statement shall be included in the package inserts of products containing atypical antipsychotic agents: a. Clozapine

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	b. Olanzepine c. Risperidone d. Quetiapine e. Ziprasidone f. Aripiprazole **WARNING** <u>Hyperglycemia and Diabetes Mellitus</u> Hyperglycemia 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 hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-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, 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 hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. ***Reference: Circular Bil (31)dlm BPFK/02/5/1.3:*** *Tambahan Amaran Berkaitan Dengan Hyperglycemia Bagi Keluaran 'Atypical Antipsychotic Agents'*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
17.	**APOMORPHINE** Please refer to DOPAMINERGIC INGREDIENT
18.	**ARGININE** The following statement shall be included on the labels and in the package inserts of oral preparations containing Arginine for **health supplement products**: **WARNING** Arginine is not recommended for patients following a heart attack. ***Reference: Circular Bil (64) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran Produk Mengandungi 'Arginine'*
19.	**ARIPIPRAZOLE** (Please also refer to ANTIPSYCHOTIC AGENTS) 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

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	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. **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 Year 2017. Ref.** 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*
20.	**ARTESUNATE** Please refer to MEFLOQUINE for products containing Mefloquine in combination with other active ingredients (mefloquine/artesunate)

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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 – 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**

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	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: Circular Bil (17) dlm BPFK/PPP/07/25. Directive Bil 10 Year 2014.*** **DIREKTIF UNTUK SEMUA PRODUK ATORVASTATIN: MENGEHADKAN DOS PENGGUNAAN ATORVASTATIN UNTUK MENGURANGKAN RISIKO KECEDERAAN OTOT**
23.	**AZITHROMYCIN** 1. The following statement shall be included in the package insert of product that contains Azithromycin: **Special Warnings and Precautions for Use** **Hypersensitivity** As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, the drug should be discontinued and

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	appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued. **<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 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 **Adverse Drug Reactions** **Post-marketing experience:** <u>Cardiac Disorders</u>: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see **Special Warnings and Precautions for Use)**. <u>Skin and Subcutaneous Tissue Disorders</u>: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, SJS, TEN and DRESS have been reported. **Reference:** <u>Circular Bil (34) dlm BPFK/PPP/07/25</u>**. Directive Bil 3 Year** 2016. 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)* 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);

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Package Insert **a) Warnings and Precautions:** 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: 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 Year 2017. Ref.** 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)*
24.	**BEE POLLEN** The following statement shall be included on the labels and in the package inserts of product 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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
25.	**BENZODIAZEPINE** The following statements shall be <u>included in the package insert and RiMUP</u> of pharmaceutical products containing benzodiazepine such as alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate potassium, diazepam, lorazepam, midazolam, nitrazepam and triazolam; **<u>Package Insert</u>** **c) Warnings and Precautions:** <u>Risks from Concomitant Use with Opioids</u> 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 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Interactions). **d) Drug Interactions:** <u>Opioids</u> 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. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **b) 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 Year 2017. Ref.** 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)
26.	**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.
27.	**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.**
28.	**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 the 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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference : *Circular: Bil.(22)dlm.BPFK/PPP/06/12 Jld.26. Kawalan produk mengandungi bahan aktif yang mempunyai berberine secara semulajadi.*
29.	**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: Circular Bil (61) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran Produk Mengandungi 'Black Cohosh'*
30.	**BOSWELLIA SPP.** The following statement shall be included on label and package inserts for 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 Year 2018. Ref. BPFK/PPP/07/25(10)Jld2.** Direktif Penambahan Kenyataan Amaran Bagi Semua Produk Yang Mengandungi *Boswellia Spp.*
31.	**BROMAZEPAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE
32.	**BROMOCRIPTINE** Please refer to DOPAMINERGIC INGREDIENT

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
33.	**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: Circular 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)*
34.	**CAMPHOR** 1. The following boxed warning shall be included on the labels 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 warning and precaution shall be included in the package insert of products containing Camphor: **WARNING** This product is contraindicated in **children** below 2 years of age. Caution must be exercised when older children are treated. **PRECAUTION:** It is dangerous to place any camphor containing product into the nostril of children. A small amount applied this way may cause immediate collapse.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
35.	**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. Potential for an increase in risk of suicidal thoughts or behaviours.
36.	**CARBIMAZOLE** The following statement shall be included in the package inserts of products containing Carbimazole: **WARNING** 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.
37.	**CABERGOLINE** Please refer to DOPAMINERGIC INGREDIENT
38.	**CARBOCISTEINE** The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) for products containing carbocisteine; **Label**

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 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>** **a) 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. **<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: • 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 Year 2018. Ref. 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* (SCAR)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
39.	**CEFTRIAXONE** The following statement shall be included in the package inserts of products containing Ceftriaxone: **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. **WARNING** • 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: Circular Bil (48) dlm. BPFK/PPP/01/03:*** *Pindaan Pada Kenyataan Amaran Berkaitan Dengan "Potential Risk Associated With Concomitant Use Of Ceftriaxone With Calcium - Containing Intravenous Solutions" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Ceftriaxone*
40.	**CETIRIZINE** The following statement shall be included in the package insert of products containing Cetirizine: **PRECAUTION** 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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
41.	***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: Circular (bil 17) dlm bpfk02/5/1.3:*** *Label Amaran Tentang Penggunaan Bahan Chelidonium majus*
42.	**CHITOSAN** The following statement shall be included on the labels and package inserts of products containing chitosan. **"DERIVED FROM SEAFOOD"** ***Reference: Circular Bil (52) dlm BPFK/02/5/1.3:*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Daripada Sumber Laut'*
43.	**CHLORHEXIDINE** The following statements shall be included in the package insert, label and RiMUP of pharmaceutical products containing Chlorhexidine: **Package Insert** **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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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) Undesirable Effects/Side Effects:** Immune system disorders Frequency not known: Hypersensitivity including anaphylactic shock **Label and Consumer Medication Information Leaflet (RiMUP)** [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. **Reference : Directive No. 8 Year 2017. Ref.** 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
44.	**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: Circular 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)*
45.	**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**
46.	**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: Circular 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)
47.	**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. • 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.
48.	**CLOBAZAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
49.	**CLOPIDOGREL** The following statement shall be included in the package inserts of products containing Clopidogrel: **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE** Pharmacogenetics: Based on literature data, patients with genetically reduced CYP22C19 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 WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF 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: Circular 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*
50.	**CLOZAPINE** Please refer to ANTIPSYCHOTIC AGENT
51.	**COBICISTAT** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Cobicistat; **Package Insert** **a) Interactions with Other Medicaments:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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.*

<u>Consumer Medication Information Leaflet (RiMUP)</u>

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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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. **Reference : Directive No. 2 Year 2018. Ref. 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
52.	**CODEINE** (Please also refer to OPIOID) The following safety information/ statements shall be included in the package inserts of products containing Codeine: **Therapeutic 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). Pada bahagian **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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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.

Special Warnings and Precautions for use

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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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. 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 Year 2016. Rujukan BPFK/PPP/07/25 (2) Jld 1.** DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI CODEINE DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO KESAN ADVERS RESPIRATORY DEPRESSION
53.	**COLCHICINE** The following statement shall be included in the package inserts of products containing Colchicines: **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:** Potential risk of severe drug interactions, including death, in certain patients treated with colchicine and concomitant P-glycoprotein or strong

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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: Circular 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*
54.	**CORTICOSTEROID** 1. The following statements shall be <u>included in the package insert and RiMUP</u> of inhaled corticosteriod used for treatment of Chronic Obstructive Pulmonary Disease (COPD) such as **budesonide** and **fluticasone** (product containing single active ingredient and in combination) and **beclomethasone** (only for combination product): **<u>Package Insert</u>** **a) Special Warnings and Precautions for Use:** <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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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) Undesirable Effects:

"Pneumonia (in COPD patients)" to be listed as "Common" adverse drug reaction in the "Infections and Infestations" SOC.

Consumer Medication Information Leaflet (RiMUP)

a) Possible Side Effects

Pneumonia (infection of the lung) in COPD patients (common side effect)

- 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 included in the package insert and RiMUP of products containing corticosteroid (except products for external use):

(i) Products containing Beclomethasone:

Package Insert

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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **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:** **Package Insert** **a) Interactions with Other Medicaments:** 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. **Consumer Medication Information Leaflet (RiMUP)** **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). **Reference:** 1. **Directive No. 9 Year 2017. Ref.** 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* 2. **Directive No. 2 Year 2018. Ref.** 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
55.	**COX-2 INHIBITORS** The following statement shall be included in the package insert for COX-2 Inhibitors products containing Celecoxib and Etoricoxib:

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• 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, 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: Circular Bil (46) dlm BPFK/02/5/1.3:*** *Keputusan Mesyuarat PBKD - Tindakan-tindakan regulatori terhadap Cox-2 Inhibitors: Celecocib dan Etoricoxib*
56.	**CYPROTERONE ACETATE** The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Cyproterone acetate: **WARNING** 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.
57.	**<u>CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION</u>** **CYPROTERONE ACETATE 2MG AND ETHINYLESTRADIOL 0.035MG**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	The following statement shall be included in the package inserts of products containing Cyproterone acetate 2mg and Ethinylestradiol 0.035mg **INDICATION:** - 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) **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.** **UNDESIRABLE EFFECTS:** - Vascular Disorders - Rare: Thromboembolism
58.	**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.*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
59.	**DEXBROMPHENIRAMINE** The following statement shall be included on the labels and package inserts 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: Circular 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)*
60.	**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: Circular 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)*
61.	**DIAZEPAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
62.	**DICLOFENAC SODIUM** The following statement shall be included in the package inserts of products containing Diclofenac sodium: **PRECAUTION** 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. **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** 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**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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 DRUG REACTIONS** **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** **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). ***Circular :*** *(30)dlm.bpfk/ppp/07/25 ; Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	7 Year 2015 : Direktif Untuk Semua Produk Yang Mengandungi Diclofenac (Formulasi sistemik) : Pengemaskinian Sisip Bungkusan Dengan MaklumatKeselamatan Berkaitan Kesan Advers Kardiovaskular
63.	**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
64.	**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: Circular 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)*
65.	**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.**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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.** **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.
66.	**DOMPERIDONE** The following statement shall be included on the package inserts of products containing Domperidone: **THERAPEUTIC 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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Adults and adolescents ≥ 12 years and weighing ≥35 kg and children 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 reevaluated and the need for continued treatment reassessed.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Film-coated tablets (10 mg/tablet)	1 tablet three to four times per day	40 mg (4×10 mg tablet)
Oral suspension (1 mg/ml)	10 mL three to four times per day	40 mg (40 mL of 1 mg/mL oral suspension)

Neonates, Infants and children < 12 years of age and weighing < 35 kg, and adults and adolescents 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). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life, the risk of neurological side effects is higher in young children. Overdosing may cause nervous system disorders in children. The dose should be determined accurately based on body weight and not exceed the recommended maximum individual and daily dose in neonates, infants, toddlers and children.

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. Film-coated tablets and orodispersible tablets are unsuitable for use in children, adults and adolescents weighing less than 35 kg. Suppositories are unsuitable for use in children.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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)

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).
- 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).
- 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).

WARNINGS AND PRECAUTIONS

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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. 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 REACTIONS** {information to be included} **Postmarketing:** **Cardiac Disorders** Frequency: Very rare Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, Sudden cardiac death (see Warnings and Precautions) **Reference Directive : (28)dlm.bpfk/ppp/07/25 ;** **ARAHAN PENGARAH KANAN PERKHIDMATAN FARMASI BILANGAN 4 YEAR 2015 :**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	DIREKTIF UNTUK SEMUA PRODUK DOMPERIDONE UNTUK MENGEHADKAN PENGGUNAAN BERIKUTAN RISIKO KESAN ADVERS JANTUNG
67.	**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: a. alpha-dihydroergocryptine b. apomorphine c. bromocriptine d. cabergoline e. levodopa f. lisuride g. piribedil h. pramipexole i. quinagolide j. ropinirole **SPECIAL WARNING & SPECIAL PRECAUTIONS FOR USE** ……. 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 special warnings and special precautions for use). **UNDESIRABLE EFFECTS** ……. is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Circular (bil 14) dlm bpfk02/5/1.3: *Keluaran yang mengandungi bahan aktif dopaminergik- tanda amaran berkaitan dengan ' sudden sleep onset'*
68.	**DOXYCYCLINE** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Doxycycline; **<u>Package Insert</u>** **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:** <u>Immune system disorders</u> Frequency not known: Jarisch-Herxheimer reaction (see Section Warnings and Precautions) **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **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. **Reference: Directive No. 19 Year 2018. Ref. <u>BPFK/PPP/07/25 (19) Jld 2.</u>** Direktif Untuk Semua Produk Yang Mengandungi Doxycycline : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Jarisch-Herxheimer Reaction*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
69.	**EFAVIRENZ** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Efavirenz; **<u>Package Insert</u>** **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. **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 with Other Medicaments:** 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	and Precautions). Consider alternatives to [Product name] when coadministered with a drug with a known risk of Torsade de Pointes. **<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. **Reference: Directive No. 18 Year 2018. Ref. 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*
70.	**EPHEDRINE** The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> 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: Circular 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)
71.	**ERYTHROMYCIN** The following statement shall be <u>included in the package insert and RiMUP</u> of products containing erythromycin (except topical/ external and ophtalmic preparations); **<u>Package Insert</u>** **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:** <u>Postmarketing Experience:</u> Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **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 Year 2017. Ref.** <u>BPFK/PPP/07/25 (33) Jld 1.</u> 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)
72.	**ETHINYLESTRADIOL** Please refer to CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION for products containing cyproterone acetate 2mg with ethinylestradiol 0.035mg in combination. The following statements shall be <u>included in the package insert</u> and <u>Consumer Medication Information Leaflet (RiMUP)</u> for 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 with Other Medicaments:** 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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 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 Year 2018. Ref. 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
73.	**ETORICOXIB** (Please also refer to COX-2 INHIBITORS) 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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Ankylosing spondylitis 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. **Consumer Medication Information Leaflet (RiMUP)** **Recommended Dose/How Much to Use** Rheumatoid arthritis The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. Ankylosing spondylitis The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. **Reference : Directive No. 13 Year 2017. Ref. 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
74.	**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. **PRECAUTION** As elderly patients are more likely to have decreased clearance of famotidine,

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	care should be taken in dose selection and it may be useful to monitor renal function.
75.	**FIBRATES** The following statement shall be included in the package inserts of products containing Fibrates: a. Clofibrate, b. Bezafibrate c. Ciprofibrate, Etofibrate d. Fenofibrate e. Simfibrate f. etc. **DRUG INTERACTION** Concurrent use of fibrates with HMG-CoA reductase inhibitors may cause severe myositis and myoglobinuria.
76.	**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. **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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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. **Reference: Circular Bil (20) dlm. BPFK/PPP/07/25. Directive No. 13 Year 2014. 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)**
77.	**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)
78.	**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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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.

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)

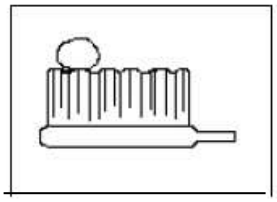
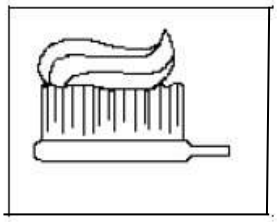
a) Before you use <product name>

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 Year 2017. Ref. 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)
79.	**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)
80.	**FLUOROQUINOLONES** The following statement shall be included in the package inserts of products containing fluoroquinolones: **WARNING AND PRECAUTION** Exacerbation of myasthenia gravis 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 REACTIONS/SIDE EFFECTS** Exacerbation of myasthenia gravis Post Marketing Experience ***Reference: Circular Bil (20) dlm BPFK/PPP/01/03 Jld 1:*** *Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Exacerbation of Myasthenia Gravis dalam Sisip Bungkusan Semua Produk Antibiotik dalam Kumpulan Fluoroquinolones*
81.	**FLURAZEPAM HYDROCHLORIDE** Please refer to SEDATIVE – HYPNOTIC PRODUCTS
82.	**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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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 **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) While You Are Using It:** <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. **Reference : Directive No. 9 Year 2018. Ref. 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*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
83.	**GADOBENIC ACID** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING **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.
84.	**GADOBUTROL** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
85.	**GADODIAMIDE** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
86.	**GADOLINIUM OXIDE** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
87.	**GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING** The following <u>boxed warning and warning</u> shall be <u>included in the package inserts</u> of products containing:

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

a. Gadobenate Dimeglumine
b. Gadobenic acid
c. Gadobutrol
d. Gadodiamide
e. Gadolinium oxide
f. Gadoteric acid
g. Gadoversetamide
h. Gadoxetic acid

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/1.73m²), 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.

WARNING

- Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• 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 single and multiple administrations of GBCAs. ***Reference: Circular Bil (2) dlm. BPFK/PPP/01/03 Jld. 1:*** *PENAMBAHAN AMARAN BERKOTAK DAN AMARAN TERKINI KE DALAM SISIP BUNGKUSAN SEMUA AGEN "CONTRAST MEDIUM" YANG BERASASKAN GADOLINIUM (GADOLINIUM BASED) UNTUK TUJUAN 'MAGNETIC RESONANCE IMAGING' "*
88.	**GADOTERIC ACID** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
89.	**GADOVERSETAMIDE** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
90.	**GADOXETIC ACID** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
91.	**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."**
92.	**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
93.	**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: Circular Bil (47) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran Pada Label Dan Sisip Bungkusan Produk Yang Mengandungi Ginkgo Biloba / Ginkgo Ekstrak*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
94.	**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.
95.	**GLUCOSAMINE** 71.1 The following statement shall be included on the labels and package inserts of products containing Glucosamine (derived from seafood); **"DERIVED FROM SEAFOOD"** 71.2 The following statement shall be included in the package inserts of products containing Glucosamine: **SIDE EFFECT** • 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. ***Reference:*** *a)* ***Circular Bil (52) dlm BPFK/02/5/1.3:*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Daripada Sumber Laut'* *b)* ***Circular Bil (72) dlm BPFK/02/5/1.3:*** *Mengemaskini dan menyelaraskan maklumat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	mengenai kesan sampingan pada label & sisip bungkusan produk yang mengandungi glucosamine
96.	**HIV PROTEASE INHIBITORS** The following statement shall be included in the package inserts of products containing HIV Protease inhibitors: **ADVERSE REACTION** 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.
97.	**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: Circular (bil 26) dlm bpfkweb.bpkp.3.2000:*** *Amaran bagi Produk Mengandungi Hydroquinone*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
98.	**HYOSCINE (FOR INJECTION ONLY)** The following statements shall be <u>included in the package insert</u> for products containing Hyoscine: **<u>Package Insert</u>** **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:** <u>Immune system disorders</u> Not known: anaphylactic shock including cases with fatal outcome, anaphylactic reactions. <u>Cardiac disorders</u> Common: tachycardia **Reference : Directive No. 17 Year 2017. Ref.** 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
99.	**IMMUNOSUPPRESANTS** The following information shall be included in the package inserts of products containing the following immunosuppressants: a) Sirolimus b) Cyclosporin c) Mycophenolate mofetil d) Mycophenolic acid e) Tacrolimus **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: Circular 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*
100.	**INSULIN** The label of the product shall state clearly the source of insulin.
101.	**INGREDIENTS DERIVED FROM SEAFOOD** The following statement shall be included on the labels and package inserts of products. **"DERIVED FROM SEAFOOD"** ***Reference: Circular Bil (52) dlm BPFK/02/5/1.3:*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Daripada Sumber Laut'*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
102.	**INTERFERON ALPHA** The following statements shall be <u>included in the package insert and RiMUP</u> of products containing Interferon Alpha: **<u>Package Insert</u>** **a) Adverse Drug Reactions:** **<u>Respiratory, thoracic and mediastinal disorders:</u>** 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. **<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 Year 2017. Ref. <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)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
103.	**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 Drug Reactions:** **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 Year 2017. Ref. <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)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
104.	**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.
105.	**KETOCONAZOLE** a) 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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.

Reference: ***Directive (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*

b) 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 & 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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. **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. **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 & PRECAUTIONS). ***Reference: Directive Bil (22) dlm BPFK/PPP/01/03 Jld 1:*** *Direktif memperkukuhkan amaran berkaitan dengan risiko hepatoksisiti yang teruk dalam sisip bungkusan semua produk oral ketoconazole*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
106.	**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
107.	**LEVETIRACETAM** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Levetiracetam;

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Package Insert **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) 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. 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. **Consumer Medication Information Leaflet (RiMUP)** **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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 3 Year 2018. Ref. 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*
108.	**LEVODOPA** Please refer to DOPAMINERGIC INGREDIENT
109.	**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. **b) Interaction of Other Medicaments:** 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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)

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 Year 2017. Ref. BPFK/PPP/07/25 (16) Jld 1. Direktif Untuk

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Semua Produk Kontraseptif Kecemasan Yang Mengandungi Levonorgestrel Dengan Maklumat Berkaitan Interaksi Antara Ubat-Ubatan Yang Dikelaskan Sebagai *Hepatic Enzyme Inducer* Dan Keberkesanan Kontrasepsi
110.	**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.
111.	**LISURIDE** Please refer to DOPAMINERGIC INGREDIENT
112.	**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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

113. **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 in individuals with opioid addiction (see Overdose).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

d) Adverse Reactions

Post-marketing Experience

Cardiac Disorders: QT/QTc interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death (see Warning and Precautions)>

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.

3. The following statement shall be included in the RiMUP of products containing Loperamide:

a) 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
- weak breathing

Reference : Directive No. 14 Year 2017. Ref. 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
114.	**LORAZEPAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE
115.	**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 Strong inhibitors of CYP3A4: Concomitant use with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole,

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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.
116.	**MEFLOQUINE** The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Mefloquine as single ingredient or in combination with other active ingredients: **1. SPECIAL WARNINGS AND PRECAUTIONS FOR USE** 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,

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

[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)**.

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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Eye disorders	
Common	Visual impairment
Not known	Vision blurred, cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment

References: Circular (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*

117. **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:-

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.

References: Directive No. 13, Year 2016 Ref. (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

118. **MESALAZINE**
The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing mesalazine;

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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. **b) Adverse Effects/ Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency "rare": Photosensitivity **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Photosensitivity: Itchy eruption and exaggerated sunburn on patches of sun-exposed skin **Reference: Directive No. 12 Year 2018. Ref. BPFK/PPP/07/25 (12) Jld 2.** Direktif Untuk Semua Produk Yang Mengandungi Mesalazine : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers *Photosensitivity*
119.	**METFORMIN** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Metformin: **Package Insert** **1. Recommended Dosage:** a) Products containing Metformin as a single active ingredient: **Renal impairment** A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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.

GFR mL/min	Total maximum daily dose (to be divided into 2-3 daily doses)*	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	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.
30-44	1000 mg	
<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) <u>Combination products containing Metformin:</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.

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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

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].

Consumer Medication Information Leaflet (RiMUP)

a) Before you use <product name>:

Do not take <product name>:

- If you have severely reduced kidney function.
- If you have lactic acidosis [too much lactic acid in the blood (see

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

"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).

b) 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 <product 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 function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Reference : Directive No. 25 Year 2017. Ref. BPFK/PPP/07/25 (30) Jld 1. Direktif Untuk

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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*
120.	**METHYL SALICYLATE** The following statements shall be included in the package inserts and product literature of topical preparations containing methyl salicylate ≥5%: **CAUTION** 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.
121.	**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 immediate medical attention. ***Reference:* *Circular (19) dlm.BPFK/PPP/07/25* Directive No. 12 Year 2014**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Direktif Untuk Semua Produk Yang Mengandungi Methylphenidate: Amaran Berkaitan Risiko *Priapism* (Kesan Ereksi Yang Berpanjangan) Di Kalangan Lelaki
122.	**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. **WARNING** • 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 the directive (24)dlm.BPFK/PPP/07/25. As below: **1) PARENTERAL ROUTE** • **Indication** • **Dose and Administration** • **Contraindication** • **Special Warnings and Precautions For Use** **2) ORAL ROUTE (Tablet/ Syrup)** • **Indication** • **Dose and Administration** • **Contraindication** • **Special Warnings and Precautions For Use** **3) RECTAL ROUTE (Suppository)** • **Indication** • **Dose and Administration** • **Contraindication** • **Special Warnings and Precautions For Use**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference Circular : (24)dlm.BPFK/PPP/07/25. Directive No. 17 Year 2014. **Direktif Untuk Semua Produk Metoclopramide: Memperketatkan Indikasi Dan Mengehadkan Dos Penggunaan Berikutan Risiko Kesan Advers Neurologik**
123.	**METRONIDAZOLE (ALL PRODUCTS EXCEPT FOR EXTERNAL USE)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for 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)** **b) 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

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	urine, light or clay-coloured stools or itching. **Reference : Directive No. 18 Year 2017. Ref.** 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 *Cockyne Syndrome*
124.	**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:** Circular (bil 45) dlm bpfkweb.bpkp.2.2001: 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**

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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)

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 included in the package insert and RiMUP of preparations (other than oral gel) containing Miconazole:

Package Insert

a) Warnings and Special 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 Special Precautions).

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	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 Year 2017. Ref.** BPFK/PPP/07/25 (15) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi Miconazole : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat
125.	**MIDAZOLAM** (Please also refer to BENZODIAZEPINE) The following statements shall be included in the package inserts of IV preparations containing Midazolam: **WARNING** 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. Please refer to SEDATIVE – HYPNOTIC products for additional information.

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126.	**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. **b) Adverse Effects/ Undesirable Effects:** Skin and subcutaneous tissue disorders: 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. 6 Year 2018. Ref. BPFK/PPP/07/25 (6) Jld 2.** Direktif Untuk

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	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)
127.	**MINOXIDIL** The label and the package insert shall include the following statement: **To be supplied only on the prescription of a registered medical practitioner.** ***Note:*** The statement is exempted for external use preparation containing not more than 5% of Minoxidil; its salts; its derivatives *(Please refer latest Poison List: Preparations for external use containing not more than 5% of Minoxidil; its salts; its derivatives, which is under Group C)*
128.	**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."**
129.	**MONTELUKAST** The following statement shall be included in the package insert of product that contains Montelukast: Addition of this statement at **ADVERSE EFFECTS:** Postmarketing Experience Blood and lymphatic system disorders : thrombocytopenia ***Reference Directive : (31)dlm.bpfk/ppp/07/25 ;*** *Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 6 Year 2015 :* *Direktif Untuk Semua Produk Yang Mengandungi Montelukast : Pengemaskinian Sisip Bungkusan Dengan Maklumat Kesan Advers Berkaitan Thrombocytopenia*

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130.	**MUCOLYTIC AGENT** 1. The following warning shall be included in the package inserts of products containing: a) Acetylcysteine b) Carbocysteine c) Methylcarbocysteine (Mecysteine) **CONTRAINDICATIONS** Contraindicated in children below two (2) years of age. 2. The following warning shall be included in the package insert, label and Consumer Medication Information Leaflet (RiMUP) of products containing: a) Ambroxol b) Bromhexine **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

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	Johnson syndrome, Toxic epidermal necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized 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: 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:** 1. **Circular <u>Bil (7) dlm BPFK/PPP/01/03 Jld 1:</u>** 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.* **Directive No. 1 Year 2018. Ref. <u>BPFK/PPP/07/25 (1) Jld 2.</u>** 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)
131.	**NEVIRAPINE** The following statement shall be included in the <u>package insert</u> of product that contains Nevirapine: Addition of this statement at approved Indication: "Avoid usage of Nevirapine in patient with CD4+cell count greater than 250cells/mm3". ***Reference: Circular <u>Bil (43) dlm BPFK/02/5/1.3:</u>*** *Pendaftaran Produk Yang Mengandungi Nevirapine*

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132.	**NIFEDIPINE** The following statement shall be included in the package inserts of "short acting" Nifedipine products: **WARNING/ PRECAUTION** 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.
133.	**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.
134.	**NITRAZEPAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE

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135.	**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
136.	**NORMAL GLOBULIN** **INTRAMUSCULAR (IM)** The following statement shall be included in the package inserts of Normal globulin IM preparations: **WARNING** Do not administer this preparation intravenously because of potential for serious hypersensitivity reactions.
137.	**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: **WARNING** 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.

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138.	**NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)** The following statement shall be included in the package insert of products containing NSAID including COX-2 Inhibitors: **WARNING** 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.
139.	**OLANZAPINE** (Please also refer to ANTIPSYCHOTIC AGENT) The following statements shall be included in the package insert and RiMUP of products containing Olanzapine: **Package Insert** **a) Special Warnings and Precautions for Use**: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) 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 DRESS is suspected.

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	b) Adverse Drug Reactions: **Skin and subcutaneous tissue disorders** Very rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). **Consumer Medication Information Leaflet (RiMUP)** **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. 17 Year 2016. Ref. 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)
140.	**ONDANSETRON** The following statements shall be included in the package inserts of injection products containing Ondansetron: **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**

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	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)
141.	**OPIOID** The following statements shall be <u>included in the package insert and RiMUP</u> of pharmaceutical products containing opioid such as alfenanil, buprenorphine, codeine, dihydrocodeine, fentanyl, methadone, morphine, nalbuphine, oxycodone, pentazocine, pethidine, remifentanil, tapentadol and tramadol; **<u>Package Insert</u>** **a) Warnings and Precautions:** 1. <u>Risks from Concomitant Use with Benzodiazepines</u> 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.

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	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 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

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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. Sexual Function/Reproduction
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:

Postmarketing Experience:

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) Drug 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

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	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. <u>Serotonergic Drugs</u> 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 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 <product name>:** 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

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	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. **Reference :** **1. Directive No. 23 Year 2017. Ref.** 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 **2. Directive No. 27 Year 2017. Ref.** BPFK/PPP/07/25 (32) Jld 1. 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
142.	**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

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	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. **Undesirable Effects** **Postmarketing Data** Eye Disorders Frequency: Not known – Floppy iris syndrome (intraoperative) **References:** **Circular (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

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143.	**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. • **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. **ADVERSE EFFECT/UNDESIRABLE EFFECT** **(For product with package insert)** • Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported. Reference Directive : (29)dlm.bpfk/ppp/07/25 ; Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 5 Year 2015 : 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

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144.	**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** • **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. **ADVERSE EFFECT/UNDESIRABLE EFFECT** **(For product with package insert)** • Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported. Reference Directive : (29)dlm.bpfk/ppp/07/25 ; Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 5 Year 2015 : 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
145.	**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. **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. **Reference: Circular Bil (20) dlm. BPFK/PPP/07/25. Directive No. 13 Year 2014. 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)**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
146.	***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.
147.	**PENICILLIN** The following statement shall be included on the labels of products containing penicillin: '**Not to be used in patients with known hypersensitivity to Penicillin**'
148.	**PHENIRAMINE** The following statement shall be included on the label and in the package inserts 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:*** ***Circular 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)
149.	**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:*** ***Circular 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)*
150.	**PIRIBEDIL** Please refer to DOPAMINERGIC INGREDIENT

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
151.	**PIROXICAM** The following additional information shall be included in the package inserts of products containing Piroxicam: **WARNING AND PRECAUTION** • 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. **CONTRAINDICATION** • 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:*** ***Circular 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*
152.	**PRAMIPEXOLE** Please refer to DOPAMINERGIC INGREDIENT

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
153.	**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. 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-

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	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 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: Circular Bil (15) dlm. BPFK/PPP/07/25. Directive No. 8 Year 2014 Direktif Untuk Semua Produk Pravastatin: Mengehadkan Dos Penggunaan Pravastatin Untuk Mengurangkan Risiko Kecederaan Otot**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
154.	**PREDNISONE AND PREDNISOLONE (EXCEPT TOPICAL PREPARATIONS)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Prednisone dan Prednisolone (except topical preparations); **<u>Package Insert</u>** **a) Warnings and Precautions:** <u>Scleroderma renal crisis</u> 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. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **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 Year 2018. Ref. <u>BPFK/PPP/07/25 (17) Jld 2.</u>** 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)
155.	**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:*** ***Circular 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)*
156.	**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)
157.	**PROPOFOL** The following statement shall be included in the package inserts of products containing Propofol: **a) WARNING** 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. **Reference: (b) Directive No. 7 Year 2018. Ref. 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
158.	**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."**
159.	**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. ***Reference:*** *a) **Circular 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)* *b) **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)
160.	**PROPYLTHIOURACIL** The following statement shall be included in the package inserts of products containing propylthiouracil: **[1]WARNING AND PRECAUTION** 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 & Precautions).*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: ***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"*
161.	**PROTON PUMP INHIBITORS (PPI)** **(Products containing Pantoprazole, Omeprazole, Lansoprazole, Esomeprazole, Rabeprazole, Dexlansoprazole)** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Proton Pump Inhitors (PPI): **Package Insert** **1. Warnings and Precautions:** Regular Surveillance Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance. Subacute Cutaneous Lupus Erythematosus (SCLE) 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. Hypomagnesaemia 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),

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	health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment. Fracture 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. 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. Undesirable Effects/Side Effects:** 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.

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	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 **3. Warnings & 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

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(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).

a) <u>Subacute Cutaneous Lupus Erythematosus (SCLE)</u>
Frequency “not known”

b) <u>Interstitial Nephritis</u>
Kidney problems (interstitial nephritis)

c) <u>Hypomagnesaemia</u>
Frequency “not known”: Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood.

d) <u>Fracture</u>
Frequency “uncommon”: Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can ncrease the risk of osteoporosis).

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

f) <u>Fundic Gland Polyps (Benign)</u>
Frequency “Common”: Benign polyps in the stomach

g) <u>Vitamin B12 Deficiency</u>
Proton pump inhibitors may cause vitamin B12 deficiency.

ii. Before you start to use it

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	Tell your doctor before taking this medicine, if you are due to have a specific blood test (Chromogranin A). **Reference :** 1. **Directive No. 16 Year 2017. Ref.** 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) 2. **Directive No. 15 Year 2017. Ref.** 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)
162.	**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:*** ***Circular 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)*
163.	**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.

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164.	**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."**
165.	**QUETIAPINE** Please refer to ANTIPSYCHOTIC AGENT
166.	**QUINAGOLIDE** Please refer to DOPAMINERGIC INGREDIENT
167.	**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."

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
168.	**RISPERIDONE** Please refer to ANTIPSYCHOTIC AGENT The following statement shall be <u>included in the package inserts</u> of products containing Risperidone: **<u>Warnings and Precautions</u>** **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. **<u>Undesirable Effects</u>** **Postmarketing Data** Eye Disorders Frequency: Not known – Floppy iris syndrome (intraoperative) ***References:*** **Circular (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*
169.	**ROPINIROLE** Please refer to DOPAMINERGIC INGREDIENT
170.	**ROSIGLITAZONE** 1. The following **<u>black box warning</u>** shall be <u>included in the first part of package inserts</u> of products containing Rosiglitazone as single ingredient or in combination with other active ingredients :

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

- 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 <u>included in the package inserts</u> 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.

WARNING & 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: ***Circular Bil (6) dlm BPFK/PPP/01/03 Jld 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)
171.	**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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Circular (16)dlm. BPFK/PPP/07/25 Directive No. 9 Year 2014. Direktif Untuk Semua Produk Rosuvastatin: Mengehadkan Dos Penggunaan Rosuvastatin Untuk Mengurangkan Risiko Kecederaan Otot
172.	**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. ***Reference:*** *a)* ***Circular 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)* *b)* ***Circular 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)* *c)* ***Circular Bil (12) dlm. BPFK/PPP/01/03:*** *Pernyataan amaran pada label dan sisip bungkusan produk yang mengandungi royal jelly (produk kosmetik)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
173.	**SALBUTAMOL** 1. The following information shall be included in the <u>package inserts</u> of products containing Salbutamol in **<u>injection</u>** 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 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 <u>package inserts and product literature</u> of products containing Salbutamol in **<u>oral tablet/ capsule</u>** 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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 & 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.** **Reference:** *a)* ***Circular 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* *b)* ***Circular 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*
174.	**SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)** Please state: “Individual allergic to aspirin/ other NSAID should avoid this product.”

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
175.	**SEDATIVE – HYPNOTIC PRODUCTS** The following statement shall be included in the package inserts under section on 'Warning' and 'Precaution' of products containing: a. Alprazolam b. Bromazepam c. Clobazam d. Diazepam e. Flurazepam hydrochloride f. Lorazepam g. Midazolam h. Nitrazepam i. Triazolam j. Zolpidem tartrate k. Zopiclone **WARNING/ PRECAUTION** • 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:*** ***Circular Bil (75) dlm BPFK/02/5/1.3:*** *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)***
176.	**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.*)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
177.	**SENNA (CASSIA SPP.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part** The following statement shall be included on the labels of products containing senna (*cassia spp.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part:* • 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.
178.	**SIMVASTATIN** The following statement shall be included in the package inserts 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. Concomitant Therapy 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. **2. Contraindications** • Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and

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	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

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	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 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. ***References:*** **Circular (18)dlm.BPFK/PPP/01/03 Jld.3:** *Pekeliling untuk mengemaskini sisip bungkusan semula produk yang mengandungi Simvastatin dengan memuatkan kontraindikasi dan had dos yang baru*
179.	**SODIUM METABISULPHITE (EXCIPIENT)** The following statement shall be included in the package inserts of products containing Sodium metabisulphite: **WARNING** 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.
180.	**SODIUM VALPROATE** 1. The following boxed warning shall be included in the package insert of products containing Sodium valproate: **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 d ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE g SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.

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	Package Insert **a) Posology and Method of Administration:** Female children, female adolescents, women of childbearing potential and pregnant women [Product Name] should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably [Product Name] should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses. **b) Special Warnings and Precautions for Use:** Female children/Female adolescents/ Women of childbearing potential/Pregnancy [Product Name] should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with [Product Name] plans a pregnancy or if she becomes pregnant. Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of [Product Name] during pregnancy (see Fertility, Pregnancy and Lactation). The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks. In particular the prescriber must ensure the patient understands: • The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders. • The need to use effective contraception.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• The need for regular review of treatment. • The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible: Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. **c) Fertility, Pregnancy and Lactation:** [Product Name] should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible. <u>Pregnancy Exposure Risk related to valproate</u> Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. <u>Congenital malformations</u> Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to 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 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. <u>Developmental disorders</u> Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The

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	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 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 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 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 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 valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). <u>Female children, female adolescents and woman of childbearing potential (see above and Special Warnings and Precautions for use)</u> If a Woman wants to plan a Pregnancy • 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. • In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed • In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible. Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a

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	physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to: - Use the lowest effective dose and divide the daily dose 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 in order to avoid high peak plasma concentrations. - Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure. - To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations. **d) Interactions:** Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered. **Consumer Medication Information Leaflet (RiMUP)** **a) 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. **Reference :** 1. **Directive No. 17 Year 2016. Rujukan BPFK/PPP/07/25 (3) Jld 1.** Direktif Bagi Semua Produk Yang Mengandungi Sodium Valproate Bagi Memperkukuhkan Amaran Berkaitan Risiko Abnormal Pregnancy Outcomes 2. **Directive No. 7 Year 2018. Ref. 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

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
181.	**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).*

182. **STATINS**

The following statement shall be included in the package inserts and RiMUP of ALL products containing statins (single active or in combination):

a. Atorvastatin
b. Fluvastatin
c. Lovastatin
d. Pravastatin
e. Rosuvastatin
f. Simvastatin
g. etc.

Package Insert

a) DRUG INTERACTION:

Concurrent use of fibrates may cause severe myositis and myoglobinuria.

b) 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

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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.

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.

d) Adverse Effects/Undesirable Effects:

Musculoskeletal disorders:
Frequency not known: Immune-mediated necrotizing myopathy

<u>Consumer Medication Information Leaflet (RiMUP)</u>

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.

References:

1. Circular (14) dlm.BPFK/PPP/07/25**. Directive No. 7 Year 2014.** Direktif Untuk Semua Produk Statin: Memperkukuhkan Amaran Berkaitan Risiko Kesan Advers Kognitif Dan Peningkatan HBA1C Serta *Fasting Blood Glucose (FBG)*
2. **Directive No. 29 Year 2017. Ref.** 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)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

183. **STRONTIUM RANELATE**

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

Indication

- 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.

Contraindications

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

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	Special warnings and precautions for use: **Cardiac ischaemic events** **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.** **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.** **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]).** ***References:*** *Circular (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*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
184.	**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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
185.	**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 (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*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
186.	**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)
187.	**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 day 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: Circular Bil (18) dlm BPFK/PPP/07/25. Directive No. 11 Year 2014.*** **DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI TEMOZOLOMIDE: MAKLUMAT KESELAMATAN BARU BERKAITAN DENGAN RISIKO KECEDERAAN HATI**

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188.	**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 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

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	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 & 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.** **Reference:** *a) **Circular 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* *b) **Circular 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*

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189.	**TESTOSTERONE** The following statements shall be <u>included in the package insert</u> and <u>Consumer Medication Information Leaflet (RiMUP)</u> for products containing Testosterone; **<u>Package Insert</u>** **a) Warnings and Precautions:** <u>Drug Abuse and Dependence</u> 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. **c) Overdose:** <u>Chronic Overdose Caused by Abuse</u> Chronic overdose caused by abuse of testosterone and other anabolic androgenic steroids (AAS) can lead to serious adverse outcomes

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	particularly cardiovascular and psychiatric adverse events (See Sections Warnings and Precautions and Adverse Effects/ Undesirable Effects). **d) Adverse Effects/Undesirable Effects:** <u>Abuse-Related Adverse Reactions</u> Serious adverse reactions have been reported in individuals who abuse testosterone and anabolic androgenic steroids (AAS) and include cardiac arrest, 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>** **b) 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

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	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 Year 2017. Ref.** 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 Dan Kebergantungan Ubat
190.	**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**
191.	**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: Circular Bil (34)dlm BPFK/02/5/1.3:*** *Penggunaan Thiomersal Dalam Persediaan Vaksin*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
192.	**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": **WARNING** 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 prevention of reocclusion may increase the risk of intracranial haemorrhage. Close monitoring of patients is strongly recommended.
193.	**TIAPROFENIC ACID** The following statement shall be included in the package inserts of products containing Tiaprofenic acid: **PRECAUTION** 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.

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194.	**TOPIRAMATE** The following statement shall be included in the package inserts of products containing Topiramate: **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. **Reference Circular : (22) BPFK/PPP/07/25. Directive No. 15 Year 2014 Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Amaran Berkaitan Risiko Gangguan Penglihatan**
195.	**TRAMADOL** (Please also refer to OPIOID) The following statements shall be included in the package insert and RiMUP of products containing Tramadol: **Package Insert** **a) Recommended Dosage:** Adults and adolescents (12 years and older) <Product name> is not approved for use in patients below 12 years old. Paediatric population 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.

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	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, 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. <u>Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism</u> 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:** <u>Pregnancy</u> Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has

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	not been established. <Product name> is not recommended for pregnant women. <u>Lactation</u> 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) **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **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. **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 Year 2017. Ref.** 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

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196.	**TRETINOIN TOPICAL** The following statement shall be included in the package inserts of products containing Tretinoin used topically: **USE IN PREGNANCY:** Studies in animal have shown that oral tretinoin is fetotoxic in rats given 500 times the topical human dose and teratogenic in rats given 1,000 times the topical human dose. Topical tretinoin has caused delayed ossification in a number of bones in the offspring of rats and rabbits given 100 to 320 times the topical human dose, respectively. There has been increasing incidence of foetal malformation following topical administration of tretinoi. Use of topical tretinoin is not recommended during pregnancy, especially the first trimester.
197.	**TRIAZOLAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE
198.	**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) At part of ***Dosage and method of administration*****:**

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	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 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.*** For products containing Trimetazidine 35mg: ***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.*** ***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 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***

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	with caution. b) At part of ***Contraindications*****:** - ***Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders*** - ***Severe renal impairment (creatinine clearance < 30ml/min).*** c) At part of ***Special warnings and precautions for use*****:** ***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.*** ***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) At part of ***Side 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.***

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 5 Year 2013, (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*
199.	**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:*** ***Circular 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)*
200.	**VARENICLINE** The following statement shall be included in the package inserts of products containing Varenicline: **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** 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. **UNDESIRABLE EFFECTS** Post marketing cases of MI, depression and suicidal ideation have been reported in patients taking varenicline. ***Reference:*** ***Circular Bil (83) dlm. BPFK/17/FV/28:*** *Maklumat daripada European Medicines Agency (EMEA) berkaitan penggunaan produk Champix (Varenicline) untuk rawatan berhenti merokok (smoking cessation).*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
201.	**VITAMIN K** 149.1 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.** 149.2 The following statement shall be included in the package inserts of products containing Vitamin K1 (phytomenadione) as single ingredient used intravenously: **WARNING** 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.
202.	**WARFARIN** a) The following statements shall be included in the package insert of products containing Warfarin: **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).

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	Special Warnings and Precautions for Use: • 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). **Interactions** The following drugs have been reported to potentiate the warfarin effect (increase INR): • Miconazole **Adverse Drug Reactions**: Skin and subcutaneous tissue disorders Frequency 'not known': Calciphylaxis b) The following statements shall be included in the RiMUP of products containing Warfarin: **Possible Side Effects**: 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.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	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 **Reference :** **1. Directive No. 15 Year 2016. Rujukan BPFK/PPP/07/25 (1) Jld 1.** DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI WARFARIN DENGAN RISIKO KESAN ADVERS CALCIPHYLAXIS **2. Directive No. 12 Year 2017. Ref. 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
203.	**ZIPRASIDONE** Please refer to ANTIPSYCHOTIC AGENT
204.	**ZOLPIDEM TARTRATE** Please refer to SEDATIVE – HYPNOTIC PRODUCTS
205.	**ZOPICLONE** Please refer to SEDATIVE – HYPNOTIC PRODUCTS