# LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JULY 2018

## (January, February, March 2018 Updates)

* Please note that this monthly list of updates will only be updated in the full version of DRGD in July 2018 revision. However, the effective dates are as stated below in the respective column.

<table>
<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>1.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS<br><br>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>safety information/ statements</u> (as highlighted in yellow) on the adverse effects ie. anaphylaxis and severe cutaneous adverse reactions (SCARs);<br><br><table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>MUCOLYTIC AGENT<br><br>Ambroxol and Bromhexine<br><br>(Please refer Attachment 1)</td></tr></table></td><td>1 February 2018</td><td>Directive No. 1 Year 2018. (Ref: BPFK/PPP/07/25 ( 1 ) Jld.2)<br>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)</td></tr>
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<tr><td>3.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS<br><br>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and the <u>safety information/ statements</u> on acute kidney injury, rhabdomyolysis/blood creatine phosphokinase increased and encephalopathy;</td><td>1 February 2018</td><td>Directive No. 3 Year 2018. (Ref: BPFK/PPP/07/25 ( 3 ) Jld.2)<br>Direktif Untuk Semua Produk Yang Mengandungi Levetiracetam : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat</td></tr>
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<tr><td>4.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS<br><br>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and the <u>safety information/ statements</u> regarding drug reaction with eosinophilia and systemic symptoms (DRESS);<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>MINOCYCLINE<br><br>(Please refer Attachment 4)</td></tr></table></td><td>1 March 2018</td><td>Directive No. 6 Year 2018. (Ref: BPFK/PPP/07/25 ( 6 ) Jld.2)<br>Direktif Untuk Semua Produk Yang Mengandungi Minocycline : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Drug Reaction With Eosinophilia And Systemic Symptoms (DRESS)</td></tr>
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<td>5.</td>
<td>APPENDIX 9 : LABELLING REQUIREMENTS<br><br>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Addition</u> of the following <u>safety information/ statements</u> (as highlighted in yellow) regarding drug interactions between products containing propofol and sodium valproate;
<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td></td><td>PROPOFOL<br>(Please refer Attachment 5)</td></tr>
<tr><td></td><td>SODIUM VALPROATE<br>(Please refer Attachment 5)</td></tr>
</table>
</td>
<td>1 March 2018</td>
<td>Directive No. 7 Year 2018. (Ref: BPFK/PPP/07/25 ( 7 ) Jld.2)<br>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</td>
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<td><u>Addition</u> of the following <u>substance</u> and the <u>safety information/ statements</u><br><br>
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<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td></td><td>AMOXICILLIN<br><br>(Please refer Attachment 6)</td></tr>
</table>
</td>
<td>1 March 2018</td>
<td>Directive No. 8 Year 2018. (Ref: BPFK/PPP/07/25 ( 8 ) Jld.2)<br>Direktif Untuk Semua Produk Yang Mengandungi Amoxicillin : 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</td>
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<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th><th rowspan="2">REFERENCE</th></tr>
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<td>APPENDIX 9 : LABELLING REQUIREMENTS<br><br>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Addition</u> of the following <u>substance</u> and the <u>safety information/ statements</u> on respiratory depression;<br><br>
<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td></td><td>GABAPENTIN<br><br>(Please refer Attachment 7)</td></tr>
</table>
</td>
<td>1 March 2018</td>
<td>Directive No. 9 Year 2018. (Ref: BPFK/PPP/07/25 ( 9 ) Jld.2)<br>Direktif Untuk Semua Produk Yang Mengandungi Gabapentin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Respiratory Depression</td>
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<td>8.</td>
<td>APPENDIX 9 : LABELLING REQUIREMENTS<br><br>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Replacement</u> of the following substance and <u>amendment</u> of description (as highlighted in yellow);<br><br>
<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td></td><td><s>BOSWELLIA SERRATA</s><br>BOSWELLIA SPP.<br><br>The following statement shall be included on label and package inserts <s>of health supplement</s> for oral products containing Boswellia <s>serrata</s> spp. :<br><br>WARNING:<br><br>Please consult your doctor/pharmacist before using this product if you are on other medicines.<br><br>Reference : Directive No. 10 Year 2018. Ref. BPFK/PPP/07/25 ( 10 ) Jld 2. Direktif Penambahan Kenyataan Amaran Bagi Semua Produk Yang Mengandungi Boswellia Spp.</td></tr>
</table>
</td>
<td>1 March 2018</td>
<td>Directive No. 10 Year 2018. (Ref: BPFK/PPP/07/25 (10) Jld.2)<br>Direktif Penambahan Kenyataan Amaran Bagi Semua Produk Yang Mengandungi Boswellia Spp.</td>
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<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th><th rowspan="2">REFERENCE</th></tr>
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<td>9.</td>
<td>APPENDIX 9 : LABELLING REQUIREMENTS<br><br>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Addition</u> of the following <u>information/ statements</u> on the limitation of use in liver imaging only (as highlighted in yellow);<br><br>
<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td></td><td>GADOBENIC ACID<br><br>Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING<br><br>Indication of products containing gadobenic acid shall be amended as follows:<br><br>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.<br><br>b) Other indications including use in MRI of the brain</td></tr>
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</td>
<td>1 April 2018</td>
<td>Drug Control Authority Meeting (DCA) No. 320</td>
</tr>
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<tr><td></td><td></td><td>and spine, as contrast-enhanced MR- angiography & MRI of the breast shall be removed.</td><td></td><td></td></tr>
<tr><td>10.</td><td>APPENDIX 8 : LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES<br><br>(8.1 : LIST OF PROHIBITED AND RESTRICTED ACTIVE INGREDIENT AND COMBINATION)</td><td>(i) <u>Addition</u> of the active ingredient <u>gadodiamide</u> in the list of prohibited active ingredients;<br><br>8.1.1 LIST OF PROHIBITED ACTIVE INGREDIENTS AND COMBINATIONS<br><br>a) Prohibited Active Ingredients<br><br><table><tr><th>NO.</th><th>PROHIBITED ACTIVE INGREDIENTS</th></tr><tr><td>20.</td><td>Gadodiamide</td></tr></table><br>(ii) <u>Addition</u> of the active ingredient <u>gadopentetic acid</u> in the list of restricted active ingredients;<br><br>8.1.2 LIST OF RESTRICTED ACTIVE INGREDIENTS AND COMBINATIONS</td><td>1 April 2018</td><td>Drug Control Authority Meeting (DCA) No. 320</td></tr>
</table>

<table>
<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th><th rowspan="2">REFERENCE</th></tr>
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<tr><td></td><td></td><td>
<table>
<tr><th colspan="2">Specific Active Ingredients</th><th>Not Allowed in the Specified Preparation(s) or Condition</th></tr>
<tr><td>22.</td><td>Gadopentetic acid</td><td>All except Intra-articular Formulation</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>11.</td><td>APPENDIX 4 : GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS<br><br>SECTION F: SUPPLEMENTARY DOCUMENTS<br><br>• Other Supporting Documents</td><td><u>Addition</u> on type of <u>dioxin test</u> and information on the <u>acceptable limits</u> at Section F: Supplementary Documents (as highlighted in yellow);<br><br>• Other Supporting documents<br><br>➢ For the submission of other supporting documents.<br><br>➢ Additional requirement for safety and quality of active ingredient/ product (e.g.; dose for children, pregnant etc.).<br><br>➢ Quality testing for specific ingredient:<br>- For product containing Aphanizomenon flos-aquae, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been</td><td>1 April 2018</td><td>Drug Control Authority Meeting (DCA) No. 320</td></tr>
</table>

| NO. | UPDATES | | EFFECTIVE DATE | REFERENCE |
|---|---|---|---|---|
| | SECTION/ APPENDIX | DETAILS | | |
| | | tested for microcystin-LR using an acceptable method.<br><br>➢ Quality testing for specific product:<br>- Certificate of Analysis for ~~Dioxin level~~ the level of dioxin (PCDDs and PCDFs) and dioxin-like polychlorinated biphenyls (PCBs) is required for product containing ingredient(s) derived from seafood.<br>*(The acceptable limit for these tests shall follow standard references such as United States Pharmacopoeia (USP) and European Regulation.)*<br>- Certificate of Analysis for proof of hormone-free is required for product containing placenta. | | |

**Attachment 1**

| NO. | SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC) |
|---|---|
| | **MUCOLYTIC AGENT**<br><br>1. The following warning shall be included in the package inserts of products containing:<br><br>a) Acetylcysteine<br>b) Carbocysteine<br>c) Methylcarbocysteine (Mecysteine)<br><br>**CONTRAINDICATIONS**<br><br>Contraindicated in children below two (2) years of age.<br><br>2. The following warning shall be included in the package insert, label and Consumer Medication Information Leaflet (RiMUP) of products containing:<br><br>a) Ambroxol<br>b) Bromhexine<br><br>**Package Insert**<br><br>**a) Warnings and Precautions:**<br><br>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.<br><br>**b) Adverse Effects/Undesirable Effects:** |

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| | Immune System Disorders<br>Frequency not known: Anaphylactic reactions including anaphylactic shock.<br><br>Skin and Subcutaneous Skin Disorders<br>Frequency not known: Severe skin reactions (including Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP).<br><br>**Consumer Medication Information Leaflet (RiMUP)**<br><br>**a) Side Effects**<br><br>[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:<br>1) severe allergy: breathing difficulties, light headedness, skin swellings or rash<br>2) severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation<br><br>**Reference:**<br>1. **Circular Bil (7) dlm BPFK/PPP/01/03 Jld 1:** Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip Bungkusan Semua Produk Carbocysteine, Acetylcysteine Dan Methylcarbocysteine (Mecysteine)<br>*2.* **Directive No. 1 Year 2018. Ref. BPFK/PPP/07/25 ( 1 ) Jld 2.** Direktif Untuk Semua Produk Yang Mengandungi Ambroxol Dan Bromhexine : Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Anafilaksis Dan *Severe Cutaneous Adverse Reactions* (SCARs) |

**Attachment 2**

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td></td><td>
COBICISTAT<br><br>
The following statements shall be <u>included in the package insert</u> and <u>Consumer Medication Information Leaflet (RiMUP)</u> for products containing Cobicistat;<br><br>
<u>Package Insert</u><br><br>
a) Interactions with Other Medicaments:
<table>
<tr><th>Medicinal product by therapeutic areas</th><th>Effects on medicinal product levels.</th><th>Recommendation concerning co-administration with [product name]</th></tr>
<tr><td colspan="3">All corticosteroids excluding cutaneous products</td></tr>
<tr><td>Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).</td><td>Interaction not studied with any of the components of [product name].<br><br>Plasma concentrations of these medicinal products may be increased when co-administered with [product name], resulting in reduced serum cortisol concentrations.</td><td>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.<br><br>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</td></tr>
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| | | | *should be considered, particularly for long-term use.* |

**Consumer Medication Information Leaflet (RiMUP)**

**a) Before you use <product name>:**

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

**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

**CORTICOSTEROID**

1. The following statements shall be included in the package insert and RiMUP of inhaled corticosteriod used for treatment of Chronic Obstructive Pulmonary Disease (COPD) such as **budesonide** and **fluticasone** (product containing single active ingredient and in combination) and **beclomethasone** (only for combination product):

**Package Insert**

**a) Special Warnings and Precautions for Use:**

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an

increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patient with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking status, older age, low body mass index (BMI) and severe COPD.

**b) 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.

**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

| | |
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| | medicines (including some medicines for HIV such as cobicistat).<br><br>**Reference :**<br>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*<br>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 |

**Attachment 3**

| NO. | SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC) |
|---|---|
| | **LEVETIRACETAM**<br><br>The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Levetiracetam;<br><br>**Package Insert**<br><br>**a) Warnings and Precautions:**<br><br>Acute kidney injury<br>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.<br><br>**b) Undesirable Effects:**<br><br>Renal and urinary disorders:<br>Frequency rare: acute kidney injury.<br><br>Musculoskeletal and connective tissue disorders:<br>Frequency rare: rhabdomyolysis and blood creatine phosphokinase increased.*<br>* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.<br><br>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.<br><br>**Consumer Medication Information Leaflet (RiMUP)** |

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| | **a) Side Effects:**<br><br>Tell your doctor immediately if you notice any of the following:<br>• 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.<br>• Signs or symptoms including muscleache, feeling of weakness and dark urine may indicate the side effect of rhabdomyolysis (breakdown of muscle tissue).<br>• 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.<br><br>**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* |

**Attachment 4**

| NO. | SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC) |
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| | **MINOCYCLINE**<br><br>The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Minocycline:<br><br>**Package Insert**<br><br>**a) Warnings and Precautions:**<br><br>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)<br><br>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.<br><br>**b) Adverse Effects/ Undesirable Effects:**<br><br>Skin and subcutaneous tissue disorders:<br><br>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)<br><br>**Consumer Medication Information Leaflet (RiMUP)**<br><br>**a) Side Effects:**<br><br>Stop taking <product name> and contact your doctor immediately if you experience any of the following: |

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| | • 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.<br><br>**Reference : Directive No. 6 Year 2018. Ref. BPFK/PPP/07/25 ( 6 ) Jld 2.** Direktif Untuk Semua Produk Yang Mengandungi Minocycline : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Drug Reaction With Eosinophilia And Systemic Symptoms* (DRESS) |

**Attachment 5**

| NO. | SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC) |
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| | **PROPOFOL**<br><br>The following statement shall be included in the package inserts of products containing Propofol:<br><br>**a) WARNING**<br><br>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.<br><br>There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction orbemergence from anaesthesia induced by propofol.<br><br>**b) Interactions:**<br><br>A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.<br><br>**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 |

**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 ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.

**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

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| | 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.<br><br>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.<br><br>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).<br><br>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.<br><br>In particular the prescriber must ensure the patient understands:<br>• The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.<br>• The need to use effective contraception.<br>• The need for regular review of treatment.<br>• The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.<br><br>In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible:<br><br>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.<br><br>**c) Fertility, Pregnancy and Lactation:**<br><br>[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. |

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| | In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.<br><br>Pregnancy Exposure Risk related to valproate<br>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.<br><br>Congenital malformations<br>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.<br><br>Developmental disorders<br>Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.<br><br>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.<br><br>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 |

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| | 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.<br><br>There are limited data on the long term outcomes.<br><br>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.<br><br>Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).<br><br><u>Female children, female adolescents and woman of childbearing potential (see above and Special Warnings and Precautions for use)</u><br><br>If a Woman wants to plan a Pregnancy<br>• 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.<br>• In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed<br>• In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.<br><br>Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a 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:<br>- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day.<br>- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.<br>- Folate supplementation before the pregnancy may decrease the risk of |

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| | 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.<br>- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.<br><br>**d) Interactions:**<br><br>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.<br><br>**Consumer Medication Information Leaflet (RiMUP)**<br><br>**a) Taking other medicines:**<br><br>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.<br><br>**Reference :**<br>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<br>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 |

**Attachment 6**

| NO. | SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC) |
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| | **AMOXICILLIN**<br><br>The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Amoxicillin (including combination products);<br><br>**Package Insert**<br><br>**a) Warnings and Precautions:**<br><br>Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.<br><br>**b) Adverse Effects/ Undesirable Effects:**<br><br>Skin and subcutaneous tissue disorders:<br>Frequency 'very rare': Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)<br><br>**Consumer Medication Information Leaflet (RiMUP)**<br><br>**a) Side Effects:**<br><br>Stop taking [product name] and contact your doctor immediately if you experience any of the following:<br>• 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.<br><br>**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 |

**Attachment 7**

| NO. | SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC) |
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| | **GABAPENTIN**<br><br>The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Gabapentin;<br><br>**Package Insert**<br><br>**a) Warnings and Precautions:**<br><br>Respiratory depression<br><br>Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.<br><br>**b) Adverse Effects/ Undesirable Effects:**<br><br>Respiratory, thoracic and mediastinal disorders<br><br>Frequency 'rare': Respiratory depression<br><br>**Consumer Medication Information Leaflet (RiMUP)**<br><br>**a) While You Are Using It:**<br><br>Before you start to use it<br><br>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. |

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| | 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.<br><br>**b) Side Effects:**<br><br>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.<br><br>**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* |