

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

NO.	REVISION	UPDATES		REFERENCE				
		SECTION/ APPENDIX	DETAILS					
1.	July 2018 (Jan/Feb/ March updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p>Addition of the following safety information/ statements (as highlighted in yellow) on the adverse effects ie. anaphylaxis and severe cutaneous adverse reactions (SCARs);</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>130.</td> <td> MUCOLYTIC AGENT a) Ambroxol b) Bromhexine (Please refer Attachment 1) </td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	130.	MUCOLYTIC AGENT a) Ambroxol b) Bromhexine (Please refer Attachment 1)	<p>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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Anafilaksis Dan <i>Severe Cutaneous Adverse Reactions</i> (SCARs)</p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
130.	MUCOLYTIC AGENT a) Ambroxol b) Bromhexine (Please refer Attachment 1)							
2.	July 2018 (Jan/Feb/ March updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p>Addition of the following substance and the warning information/ statements regarding drug interactions between products containing cobicistat and corticosteroid (except products for external use);</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>51.</td> <td> COBICISTAT (Please refer Attachment 2) </td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	51.	COBICISTAT (Please refer Attachment 2)	<p>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 Bungkus dan Risalah Maklumat Ubat Untuk</p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
51.	COBICISTAT (Please refer Attachment 2)							

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			<table border="1"> <tr> <td>54.</td> <td> CORTICOSTEROID (Please refer Attachment 2) (changes as highlighted in yellow) </td> </tr> </table>	54.	CORTICOSTEROID (Please refer Attachment 2) (changes as highlighted in yellow)	Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat		
54.	CORTICOSTEROID (Please refer Attachment 2) (changes as highlighted in yellow)							
3.	July 2018 (Jan/Feb/ March updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p><u>Addition</u> of the following substance and the <u>safety information/ statements</u> on acute kidney injury, rhabdomyolysis/blood creatine phosphokinase increased and encephalopathy;</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>107.</td> <td> LEVETIRACETAM (Please refer Attachment 3) </td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	107.	LEVETIRACETAM (Please refer Attachment 3)	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 <i>Acute Kidney Injury, Rhabdomyolysis/ Blood Creatine Phosphokinase Increase Dan Encephalopathy</i>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
107.	LEVETIRACETAM (Please refer Attachment 3)							

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4.	July 2018 (Jan/Feb/ March updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p>Addition of the following substance and the safety information/ statements regarding drug reaction with eosinophilia and systemic symptoms (DRESS);</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>126.</td> <td>MINOCYCLINE (Please refer Attachment 4)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	126.	MINOCYCLINE (Please refer Attachment 4)	<p>Directive No. 6 Year 2018. (Ref: BPFK/PPP/07/25 (6) Jld.2) Direktif Untuk Semua Produk Yang Mengandungi Minocycline : Pengemaskinian Sisip Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Drug Reaction With Eosinophilia And Systemic Symptoms (DRESS)</i></p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
126.	MINOCYCLINE (Please refer Attachment 4)							
5.	July 2018 (Jan/Feb/ March updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p>Addition of the following safety information/ statements (as highlighted in yellow) regarding drug interactions between products containing propofol and sodium valproate;</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>157.</td> <td>PROPOFOL (Please refer Attachment 5)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	157.	PROPOFOL (Please refer Attachment 5)	<p>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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan</p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
157.	PROPOFOL (Please refer Attachment 5)							

NO.	REVISION	UPDATES		REFERENCE				
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			<table border="1"> <tr> <td>180.</td> <td>SODIUM VALPROATE (Please refer Attachment 5)</td> </tr> </table>	180.	SODIUM VALPROATE (Please refer Attachment 5)	Interaksi Ubat		
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6.	<p>July 2018 (Jan/Feb/ March updates)</p>	<p>APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)</p>	<p><u>Addition of the following substance and the safety information/ statements</u></p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>13.</td> <td>AMOXICILLIN (Please refer Attachment 6)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	13.	AMOXICILLIN (Please refer Attachment 6)	<p>Directive No. 8 Year 2018. (Ref: BPFK/PPP/07/25 (8) Jld.2) Direktif Untuk Semua Produk Yang Mengandungi Amoxicillin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Memperkukuhkan Maklumat Berkaitan <i>Severe Cutaneous Adverse Reactions (SCARs)</i> Pada Bahagian <i>Warnings & Precautions</i> Dan Amaran Berkaitan <i>Drug Reaction With Eosinophilia And Systemic Symptoms (DRESS)</i> Pada Bahagian <i>Side Effects</i></p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
13.	AMOXICILLIN (Please refer Attachment 6)							

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7.	July 2018 (Jan/Feb/ March updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p><u>Addition</u> of the following <u>substance</u> and the <u>safety information/ statements</u> on respiratory depression;</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>82.</td> <td>GABAPENTIN (Please refer Attachment 7)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	82.	GABAPENTIN (Please refer Attachment 7)	<p>Directive No. 9 Year 2018. (Ref: BPFK/PPP/07/25 (9) Jld.2) Direktif Untuk Semua Produk Yang Mengandungi Gabapentin : Pengemaskinian Sisip Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Respiratory Depression</i></p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
82.	GABAPENTIN (Please refer Attachment 7)							
8.	July 2018 (Jan/Feb/ March updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p><u>Replacement</u> of the following substance and <u>amendment</u> of description (as highlighted in yellow);</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>30.</td> <td>BOSWELLIA SERRATA BOSWELLIA SPP. The following statement shall be included on label and package inserts of health supplement for oral products containing <i>Boswellia serrata</i> spp. :</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	30.	BOSWELLIA SERRATA BOSWELLIA SPP. The following statement shall be included on label and package inserts of health supplement for oral products containing <i>Boswellia serrata</i> spp. :	<p>Directive No. 10 Year 2018. (Ref: BPFK/PPP/07/25 (10) Jld.2) Direktif Penambahan Kenyataan Amaran Bagi Semua Produk Yang Mengandungi <i>Boswellia Spp.</i></p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
30.	BOSWELLIA SERRATA BOSWELLIA SPP. The following statement shall be included on label and package inserts of health supplement for oral products containing <i>Boswellia serrata</i> spp. :							

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			<p>WARNING:</p> <p>Please consult your doctor/pharmacist before using this product if you are on other medicines.</p> <p>Reference : Directive No. 10 Year 2018. Ref. BPFK/PPP/07/25 (10) Jld 2. Direktif Penambahan Kenyataan Amaran Bagi Semua Produk Yang Mengandungi <i>Boswellia Spp.</i></p>					
9.	<p>July 2018</p> <p>(Jan/Feb/ March updates)</p>	<p>APPENDIX 9 : LABELLING REQUIREMENTS</p> <p>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</p>	<p>Addition of the following information/ statements on the limitation of use in liver imaging only (as highlighted in yellow);</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>83.</td> <td> <p>GADOBENIC ACID</p> <p>Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING</p> <p>Indication of products containing gadobenic acid shall be amended as follows:</p> </td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	83.	<p>GADOBENIC ACID</p> <p>Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING</p> <p>Indication of products containing gadobenic acid shall be amended as follows:</p>	<p>Drug Control Authority Meeting (DCA) No. 320</p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
83.	<p>GADOBENIC ACID</p> <p>Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING</p> <p>Indication of products containing gadobenic acid shall be amended as follows:</p>							

NO.	REVISION	UPDATES		REFERENCE				
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			<p>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.</p> <p>b) Other indications including use in MRI of the brain and spine, as contrast-enhanced MR- angiography & MRI of the breast shall be removed.</p>					
10.	<p>July 2018 (Jan/Feb/ March updates)</p>	<p>APPENDIX 8 : LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES</p> <p>(8.1 : LIST OF PROHIBITED AND RESTRICTED ACTIVE INGREDIENT AND</p>	<p>(i) Addition of the active ingredient <u>gadodiamide</u> in the list of prohibited active ingredients;</p> <p>8.1.1 LIST OF PROHIBITED ACTIVE INGREDIENTS AND COMBINATIONS</p> <p>a) Prohibited Active Ingredients</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>PROHIBITED ACTIVE INGREDIENTS</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> </tr> </tbody> </table>	NO.	PROHIBITED ACTIVE INGREDIENTS			<p>Drug Control Authority Meeting (DCA) No. 320</p>
NO.	PROHIBITED ACTIVE INGREDIENTS							

NO.	REVISION	UPDATES		REFERENCE						
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		COMBINATION)	<table border="1"> <tr> <td>20.</td> <td>Gadodiamide</td> </tr> </table> <p>(ii) Addition of the active ingredient <u>gadopentetic acid</u> in the list of restricted active ingredients;</p> <p>8.1.2 LIST OF RESTRICTED ACTIVE INGREDIENTS AND COMBINATIONS</p> <table border="1"> <thead> <tr> <th>Specific Active Ingredients</th> <th>Not Allowed in the Specified Preparation(s) or Condition</th> </tr> </thead> <tbody> <tr> <td>22. Gadopentetic acid</td> <td>All except Intra-articular Formulation</td> </tr> </tbody> </table>	20.	Gadodiamide	Specific Active Ingredients	Not Allowed in the Specified Preparation(s) or Condition	22. Gadopentetic acid	All except Intra-articular Formulation	
20.	Gadodiamide									
Specific Active Ingredients	Not Allowed in the Specified Preparation(s) or Condition									
22. Gadopentetic acid	All except Intra-articular Formulation									
11.	July 2018 (Jan/Feb/ March updates)	APPENDIX 4 : GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS SECTION F: SUPPLEMENTARY DOCUMENTS	<p>Addition on type of <u>dioxin test</u> and information on the <u>acceptable limits</u> at Section F: Supplementary Documents (as highlighted in yellow);</p> <ul style="list-style-type: none"> • Other Supporting documents <ul style="list-style-type: none"> ➤ For the submission of other supporting documents. 	Drug Control Authority Meeting (DCA) No. 320						

NO.	REVISION	UPDATES		REFERENCE
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		<ul style="list-style-type: none"> • Other Supporting Documents 	<ul style="list-style-type: none"> ➢ Additional requirement for safety and quality of active ingredient/ product (e.g.; dose for children, pregnant etc.). ➢ Quality testing for specific ingredient: <ul style="list-style-type: none"> - 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 tested for microcystin-LR using an acceptable method. ➢ Quality testing for specific product: <ul style="list-style-type: none"> - 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. <i>(The acceptable limit for these tests shall follow standard references such as United States Pharmacopoeia (USP) and European Regulation.)</i> - Certificate of Analysis for proof of hormone-free is required for product containing placenta. 	

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12.	July 2018 (April updates)	5. TYPES OF APPLICATION 5.1.4 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)	<p><u>Addition</u> of the following information;</p> <p>a) Registration of FEO product only applies to locally manufactured product, b) Imported product for pack/repack locally and for re-export falls under <i>Regulation 7(2)(b); Control of Drugs and Cosmetic Regulations 1984</i>, c) Documents required for FEO registration of pharmaceutical product includes: (i) COA of finished product for at least 1 pilot batch. (ii) Stability data (real time and accelerated stability study) for at least 1 pilot batch.</p> <p>(Please refer Attachment 8) (changes as highlighted in yellow)</p>	Directive No. 11 Year 2018. (Ref: BPFK/PPP/07/25 (11) Jld.2) Direktif Kaji Semula Pendaftaran Produk Untuk Tujuan Eksport Sahaja (FEO)
13.	July 2018 (April updates)	5. TYPES OF APPLICATION 5.1.4 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)	<p><u>Addition</u> of the following information;</p> <p>Conditions for the registration of FEO products: (i) Countries which do not impose specific regulatory requirements as Malaysia (e.g. formulation with banned/prohibited ingredients, zone IVB stability study, bioavailability/ bioequivalence study, API evaluation etc.); OR (ii) Countries which have different requirements such as different formulation (e.g. colour or strength of</p>	Policy Meeting No. 01 Year 2018

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			<p>ingredients), shape or manufacturing process, etc. as compared to a registered product; OR</p> <p>(iii) Difference in classification category of the products (e.g. as food in the importing country) for health supplements and traditional products.</p> <p>(Please refer Attachment 8) (changes as highlighted in yellow)</p>					
14.	<p>July 2018</p> <p>(April updates)</p>	<p>APPENDIX 9 : LABELLING REQUIREMENTS</p> <p>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</p>	<p><u>Addition</u> of the following substance and <u>warning information/ statements</u> on the adverse effect of photosensitivity;</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>118.</td> <td> <p>MESALAZINE</p> <p>(Please refer Attachment 9)</p> </td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	118.	<p>MESALAZINE</p> <p>(Please refer Attachment 9)</p>	<p>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 <i>Photosensitivity</i></p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
118.	<p>MESALAZINE</p> <p>(Please refer Attachment 9)</p>							
15.	<p>July 2018</p> <p>(April updates)</p>	<p>APPENDIX 9 : LABELLING REQUIREMENTS</p> <p>(9.2 : SPECIFIC LABELLING</p>	<p><u>Addition</u> of the following <u>information/ statements</u> on the risk of increased ALT level due to drug interaction between ethinylestradiol with the combination product containing ombitasvir / paritaprevir / ritonavir and dasabuvir;</p>	<p>Directive No. 13 Year 2018. (Ref: BPFK/PPP/07/25 (13) Jld.2) Direktif Untuk Semua Produk Yang Mengandungi</p>				

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		REQUIREMENTS)	<table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>72.</td> <td>ETHINYLESTRADIOL (Please refer Attachment 10) (changes as highlighted in yellow)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	72.	ETHINYLESTRADIOL (Please refer Attachment 10) (changes as highlighted in yellow)	Ethinylestradiol : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pegguna (RiMUP) Dengan Risiko Peningkatan Para Alanine Transaminase (ALT) Akibat Interaksi Dengan Produk Kombinasi Ombitasvir / Paritaprevir / Ritonavir Dan Dasabuvir
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
72.	ETHINYLESTRADIOL (Please refer Attachment 10) (changes as highlighted in yellow)							
16.	July 2018 (April updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p>Addition of the following substance and safety information/ statements regarding Anaphylactic/ Anaphylactoid Reaction and Severe Cutaneous Adverse Reactions (SCAR);</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>38.</td> <td>CARBOCISTEINE (Please refer Attachment 11)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	38.	CARBOCISTEINE (Please refer Attachment 11)	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 Pegguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Anaphylactic/ Anaphylactoid Reaction</i> Dan <i>Severe Cutaneous Adverse Reactions</i>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
38.	CARBOCISTEINE (Please refer Attachment 11)							

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				(SCAR)				
17.	July 2018 (April updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p><u>Addition</u> of the following substance and <u>safety information/ statements</u> regarding Anaphylactic/ Anaphylactoid Reaction and Severe Cutaneous Adverse Reactions (SCAR);</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>4.</td> <td>ACETYLCYSTEINE (Please refer Attachment 12)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	4.	ACETYLCYSTEINE (Please refer Attachment 12)	<p>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 Bungkus Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Anaphylactic/ Anaphylactoid Reaction</i> Dan <i>Severe Cutaneous Adverse Reactions</i> (SCAR)</p>
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18.	July 2018 (June updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p><u>Addition</u> of the following substance and <u>safety information/ statements</u> regarding Severe Cutaneous Adverse Reactions (SCARs);</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)			<p>Directive No. 16 Year 2018. (Ref: BPFK/PPP/07/25 (16) Jld.2) Direktif Untuk Semua Produk Yang Mengandungi Acetazolamide : Pengemaskinian Sisip Bungkus Dan Risalah Maklumat Ubat Untuk</p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							

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			<table border="1"> <tr> <td>3.</td> <td>ACETAZOLAMIDE (Please refer Attachment 13)</td> </tr> </table>	3.	ACETAZOLAMIDE (Please refer Attachment 13)	Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Severe Cutaneous Adverse Reactions</i> (SCARs)		
3.	ACETAZOLAMIDE (Please refer Attachment 13)							
19.	<p>July 2018</p> <p>(June updates)</p>	<p>APPENDIX 9 : LABELLING REQUIREMENTS</p> <p>(9.2 : SPECIFIC LABELLING REQUIREMENTS)</p>	<p><u>Addition</u> of the following substance and <u>safety information/</u> <u>statements</u> regarding Scleroderma Renal Crisis;</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>154.</td> <td>PREDNISONE AND PREDNISOLONE (EXCEPT TOPICAL PREPARATIONS) (Please refer Attachment 14)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	154.	PREDNISONE AND PREDNISOLONE (EXCEPT TOPICAL PREPARATIONS) (Please refer Attachment 14)	<p>Directive No. 17 Year 2018. (Ref: BPFK/PPP/07/25 (17) Jld.2)</p> <p>Direktif Untuk Semua Produk Yang Mengandungi Prednisone Dan Prednisolone (Kecuali Persediaan Topikal) : Pengemaskinian Sisip Bungkus Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Scleroderma Renal Crisis</i></p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
154.	PREDNISONE AND PREDNISOLONE (EXCEPT TOPICAL PREPARATIONS) (Please refer Attachment 14)							

NO.	REVISION	UPDATES		REFERENCE				
		SECTION/ APPENDIX	DETAILS					
20.	July 2018 (June updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p><u>Addition</u> of the following substances and <u>safety information/ statements</u> regarding QTc prolongation:</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>69.</td> <td>EFAVIRENZ (Please refer Attachment 15)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	69.	EFAVIRENZ (Please refer Attachment 15)	<p>Directive No. 18 Year 2018. (Ref: BPFK/PPP/07/25 (18) Jld.2) Direktif Untuk Semua Produk Yang Mengandungi Efavirenz : Pengemaskinian Sisip Bungkus Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan QTc <i>Prolongation</i></p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
69.	EFAVIRENZ (Please refer Attachment 15)							
21.	July 2018 (June updates)	APPENDIX 9 : LABELLING REQUIREMENTS (9.2 : SPECIFIC LABELLING REQUIREMENTS)	<p><u>Addition</u> of the following substances and <u>safety information/ statements</u> regarding Jarisch-Herxheimer Reaction;</p> <table border="1"> <thead> <tr> <th>NO.</th> <th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th> </tr> </thead> <tbody> <tr> <td>68.</td> <td>DOXYCYCLINE (Please refer Attachment 16)</td> </tr> </tbody> </table>	NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)	68.	DOXYCYCLINE (Please refer Attachment 16)	<p>Directive No. 19 Year 2018. (Ref: BPFK/PPP/07/25 (19) Jld.2) Direktif Untuk Semua Produk Yang Mengandungi Doxycycline : Pengemaskinian Sisip Bungkus Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Jarisch-Herxheimer Reaction</i></p>
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)							
68.	DOXYCYCLINE (Please refer Attachment 16)							

NO.	REVISION	UPDATES		REFERENCE								
		SECTION/ APPENDIX	DETAILS									
22.	July 2018 (June updates)	<p>(i) APPENDIX 4: GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENT</p> <p>(ii) APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS</p> <p>(iii) APPENDIX 9: LABELLING REQUIREMENTS</p>	<p><u>Addition</u> of the word “graphics/ images” in the table for <u>Prohibited Visual/Graphics/Statements on Label/Packaging Material</u> as below;</p> <table border="1"> <thead> <tr> <th>No.</th> <th>Issue</th> <th>Example</th> <th>Note</th> </tr> </thead> <tbody> <tr> <td>16.</td> <td>Indecent photographs/ pornography/ graphics/ images</td> <td></td> <td>Prohibited on product label</td> </tr> </tbody> </table>	No.	Issue	Example	Note	16.	Indecent photographs/ pornography/ graphics/ images		Prohibited on product label	<p>Drug Evaluation Committee Meeting No. 10/2018</p> <p>(Memo from Complementary & Alternative Medicine Section, Ref: (1)dIm.BPFK/PPP/06/17 Jld.110)</p>
No.	Issue	Example	Note									
16.	Indecent photographs/ pornography/ graphics/ images		Prohibited on product label									
23.	July 2018	<p>APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS</p> <p>2.7.1 STATEMENTS TO BE STATED ON PRODUCT LABEL</p>	<p><u>Addition</u> of the following statement (permissible size of founder’s picture);</p> <p>2.7.1 STATEMENTS TO BE STATED ON PRODUCT LABEL</p> <ul style="list-style-type: none"> Any picture of the founder placed on the label must be decent and should not exceed 1/10th of the panel. 	<p>Drug Evaluation Committee Meeting No. 21/2017</p> <p>(Memo from Complementary & Alternative Medicine Section, Ref: (1)dIm.BPFK/PPP/06/17 Jld.110)</p>								

NO.	REVISION	UPDATES		REFERENCE						
		SECTION/ APPENDIX	DETAILS							
24.	July 2018	APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS 2.8 PARTICULARS OF PACKING	<p><u>Addition</u> of the following statement (sample pack size);</p> <p>2.8 PARTICULARS OF PACKING</p> <ul style="list-style-type: none"> • Sample pack size should not exceed 20 capsules/tablets 	<p>Drug Evaluation Committee Meeting No. 03/2018</p> <p>(Memo from Complementary & Alternative Medicine Section, Ref: (1)dIm.BPFK/PPP/06/17 Jld.110)</p>						
25.	July 2018	APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS 2.4 PRODUCT NAME	<p><u>Addition</u> of the following words (prohibited product names);</p> <p>Table 7:</p> <table border="1"> <thead> <tr> <th>No.</th> <th>Issue</th> <th>Example</th> </tr> </thead> <tbody> <tr> <td>16.</td> <td>Other prohibited product names</td> <td> <p>Example:</p> <p>Minda, IQ, Smart, Genius, Ultra Mega, Detox, Immune, Phase 2, Defense, Prime</p> </td> </tr> </tbody> </table>	No.	Issue	Example	16.	Other prohibited product names	<p>Example:</p> <p>Minda, IQ, Smart, Genius, Ultra Mega, Detox, Immune, Phase 2, Defense, Prime</p>	<p>Drug Evaluation Committee Meeting No. 21/2018, No. 22/2018 & No. 23/2018.</p> <p>(Memo from Complementary & Alternative Medicine Section, Ref: (1)dIm.BPFK/PPP/06/17 Jld.110)</p>
No.	Issue	Example								
16.	Other prohibited product names	<p>Example:</p> <p>Minda, IQ, Smart, Genius, Ultra Mega, Detox, Immune, Phase 2, Defense, Prime</p>								

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
26.	July 2018	APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS 2.6 STABILITY DATA	<p><u>Addition</u> of information for stability data;</p> <p>(i) Example of stability data</p> <ul style="list-style-type: none"> - Replaced with “RECOMMENDED PRESENTATION OF THE SUMMARY TABLE OF STABILITY RESULTS” - Please refer Attachment 17. <p>(ii) Tabulated list of stability indication parameters for traditional medicine</p> <ul style="list-style-type: none"> - Addition of a new table (Tabulated list of stability indicating parameters for traditional medicine). - Please refer Attachment 18. 	ASEAN Guidelines on Stability Study and Shelf-Life of Traditional Medicines
27.	July 2018	SECTION E: POST- REGISTRATION PROCESS 16.1 VARIATION	<p>Updating the application procedure from manual to <u>online</u> submission.</p> <p><u>Replacement</u> of the Table XV with the following statement (as highlighted in yellow);</p> <p>16.1.1 VARIATION APPLICATION FOR PHARMACEUTICAL PRODUCTS</p>	Policy Meeting No. 02 Year 2018

NO.	REVISION	UPDATES		REFERENCE								
		SECTION/ APPENDIX	DETAILS									
			<p>MODE OF SUBMISSION</p> <p><u>Table XV:</u></p> <table border="1"> <thead> <tr> <th>No</th> <th>Variation</th> <th>QUEST 2 Product</th> <th>QUEST 3 Product</th> </tr> </thead> <tbody> <tr> <td>1.</td> <td>Minor Variation Notification (MiV-N)</td> <td> <p>Applicant shall submit application for MiV-N via both <u>manual and online</u> QUEST 2 system.</p> <p>For manual submission, applicant can download <u>Form BPFK 416.3</u> from NPRA's website http://np.ra.moh.gov.my/, and shall submit to the respective Sections in Center for Product Registration, NPRA.</p> <p>For submission online, please scan the form and attach together with the revised draft of package insert and labelling as a single file.</p> </td> <td> <p>Applicant shall submit application <u>manually</u> to the respective Sections in Center for Product Registration, until further notice pertaining to online submission.</p> </td> </tr> </tbody> </table>	No	Variation	QUEST 2 Product	QUEST 3 Product	1.	Minor Variation Notification (MiV-N)	<p>Applicant shall submit application for MiV-N via both <u>manual and online</u> QUEST 2 system.</p> <p>For manual submission, applicant can download <u>Form BPFK 416.3</u> from NPRA's website http://np.ra.moh.gov.my/, and shall submit to the respective Sections in Center for Product Registration, NPRA.</p> <p>For submission online, please scan the form and attach together with the revised draft of package insert and labelling as a single file.</p>	<p>Applicant shall submit application <u>manually</u> to the respective Sections in Center for Product Registration, until further notice pertaining to online submission.</p>	
No	Variation	QUEST 2 Product	QUEST 3 Product									
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NO.	REVISION	UPDATES				REFERENCE
		SECTION/ APPENDIX	DETAILS			
			<p>2. Minor Variation Prior Approval (MiV-PA) & Major Variation (MaV)</p>	<p>Applicant shall submit application via <u>online</u> QUEST-2 system.</p>		
			<p>Applicant shall submit the variation application through the current online system.</p>			
28.	July 2018	SECTION E: POST-REGISTRATION PROCESS 16.3 CHANGE OF PRODUCT REGISTRATION HOLDER	<p>Updating the application procedure from manual to <u>online</u> submission.</p> <p>(Please refer Attachment 19) (changes as highlighted in yellow)</p>			Policy Meeting No. 02 Year 2018
29.	July 2018	SECTION E: POST-REGISTRATION PROCESS	<p>(i) Updating the application procedure from manual to <u>online</u> submission.</p> <p>(ii) Updating the requirements in accordance to current</p>			Policy Meeting No. 02 Year 2018

NO.	REVISION	UPDATES		REFERENCE												
		SECTION/ APPENDIX	DETAILS													
		14.1 RE-REGISTRATION APPLICATION	<p>directives.</p> <p>(Please refer Attachment 20) (changes as highlighted in yellow)</p>													
30.	July 2018	SECTION B: PRODUCT REGISTRATION PROCESS 8.4 EVALUATION OF APPLICATION	<p><u>Addition</u> of sub-section 8.4.2 PRIORITY REVIEW;</p> <p>(Please refer Attachment 21) (changes as highlighted in yellow)</p>	Policy Meeting No. 02 Year 2018												
31.	July 2018	APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS	<p><u>Additional</u> requirements for Package Insert (as highlighted in yellow);</p> <p>2.7 LABELLING REQUIREMENT</p> <table border="1"> <thead> <tr> <th>No.</th> <th>Items</th> <th>Immediate Label</th> <th>Outer Label</th> <th>Package Insert</th> <th>Blister Pack</th> </tr> </thead> <tbody> <tr> <td>12</td> <td>Name and address of product registration holder</td> <td>√</td> <td>√</td> <td>√</td> <td></td> </tr> </tbody> </table>	No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack	12	Name and address of product registration holder	√	√	√		<p>Memo from Complementary & Alternative Medicine Section, Ref: (1)dIm.BPFK/PPP/06/17 Jld.110)</p> <p>Policy Meeting No. 02 Year 2018</p>
No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack											
12	Name and address of product registration holder	√	√	√												

NO.	REVISION	UPDATES						REFERENCE																	
		SECTION/ APPENDIX	DETAILS																						
			(Example: Product Registration Holder: XXXXX)																						
			17 Name and content of alcohol, where present	√	√	√																			
			22 Product Description			√																			
			23 Date of Revision			√																			
32.	July 2018	SECTION C: QUALITY CONTROL	<p>Amendment (as highlighted in yellow) in Table X as below;</p> <p>10.2.2 PARTIAL VALIDATON FOR COMPENDIAL/ PHARMACOPOEIAL METHODS</p> <p>TABLE X:</p> <table border="1"> <thead> <tr> <th rowspan="3">Characteristic</th> <th colspan="4">Type of Analytical Method</th> </tr> <tr> <th rowspan="2">Identification</th> <th colspan="2">Testing for Impurities</th> <th rowspan="2">Assay: - dissolution (measurement only) - content/ potency</th> </tr> <tr> <th>Quantitation</th> <th>Limit</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>						Characteristic	Type of Analytical Method				Identification	Testing for Impurities		Assay: - dissolution (measurement only) - content/ potency	Quantitation	Limit						<p>Memo from Centre of Quality Control, Ref: NPRA.600-2/1/18 Bil.(2)</p> <p>Policy Meeting No. 02 Year 2018</p>
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NO.	REVISION	UPDATES				REFERENCE																			
		SECTION/ APPENDIX	DETAILS																						
			<table border="1"> <tr> <td>Precision Intermediate Precision</td> <td></td> <td>√ (1)</td> <td></td> <td>√ (1)</td> </tr> <tr> <td>Specificity (2)</td> <td>√</td> <td>√</td> <td>√</td> <td>√</td> </tr> <tr> <td>Detection Limit</td> <td></td> <td>(3)</td> <td>√</td> <td></td> </tr> <tr> <td>Quantitation Limit</td> <td></td> <td>√</td> <td></td> <td></td> </tr> </table>	Precision Intermediate Precision		√ (1)		√ (1)	Specificity (2)	√	√	√	√	Detection Limit		(3)	√		Quantitation Limit		√				
Precision Intermediate Precision		√ (1)		√ (1)																					
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Detection Limit		(3)	√																						
Quantitation Limit		√																							
<p>Note:</p> <p>√ signifies that this characteristic is normally evaluated.</p> <p>(1) In cases where reproducibility has been performed, intermediate precision is not needed.</p> <p>(2) Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).</p> <p>(3) May be needed in some cases.</p>																									

Attachment 1

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
130.	<p>MUCOLYTIC AGENT</p> <p>1. The following <u>warning</u> shall be <u>included in the package inserts</u> of products containing:</p> <ul style="list-style-type: none">a) Acetylcysteineb) Carbocysteinec) Methylcarbocysteine (Mecysteine) <p>CONTRAINDICATIONS</p> <p>Contraindicated in children below two (2) years of age.</p> <p>2. The following <u>warning</u> shall be <u>included in the package insert, label and Consumer Medication Information Leaflet (RiMUP)</u> of products containing:</p> <ul style="list-style-type: none">a) Ambroxolb) Bromhexine <p><u>Package Insert</u></p> <p>a) Warnings and Precautions:</p> <p>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.</p> <p>b) Adverse Effects/Undesirable Effects:</p>

Immune System Disorders

Frequency not known: Anaphylactic reactions including anaphylactic shock.

Skin and Subcutaneous Skin Disorders

Frequency not known: Severe skin reactions (including Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP).

Consumer Medication Information Leaflet (RiMUP)

a) Side Effects

[Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms:

- 1) severe allergy: breathing difficulties, light headedness, skin swellings or rash
- 2) severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation

Reference:

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 Bungkus Semua Produk Carbocysteine, Acetylcysteine Dan Methylcarbocysteine (Mecysteine)
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 Bungkus Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Anafilaksis Dan *Severe Cutaneous Adverse Reactions* (SCARs)

Attachment 2

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)									
51.	<p>COBICISTAT</p> <p>The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Cobicistat;</p> <p><u>Package Insert</u></p> <p>a) Interactions with Other Medicaments:</p> <table border="1" data-bbox="345 726 1438 1803"> <thead> <tr> <th data-bbox="345 726 651 842"><i>Medicinal product by therapeutic areas</i></th> <th data-bbox="651 726 980 842"><i>Effects on medicinal product levels.</i></th> <th data-bbox="980 726 1438 842"><i>Recommendation concerning co-administration with [product name]</i></th> </tr> </thead> <tbody> <tr> <td colspan="3" data-bbox="345 842 1438 884"><i>All corticosteroids excluding cutaneous products</i></td> </tr> <tr> <td data-bbox="345 884 651 1803"><i>Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).</i></td> <td data-bbox="651 884 980 1803"><i>Interaction not studied with any of the components of [product name].</i> <i>Plasma concentrations of these medicinal products may be increased when co-administered with [product name], resulting in reduced serum cortisol concentrations.</i></td> <td data-bbox="980 884 1438 1803"><i>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.</i> <i>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.</i></td> </tr> </tbody> </table>	<i>Medicinal product by therapeutic areas</i>	<i>Effects on medicinal product levels.</i>	<i>Recommendation concerning co-administration with [product name]</i>	<i>All corticosteroids excluding cutaneous products</i>			<i>Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).</i>	<i>Interaction not studied with any of the components of [product name].</i> <i>Plasma concentrations of these medicinal products may be increased when co-administered with [product name], resulting in reduced serum cortisol concentrations.</i>	<i>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.</i> <i>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.</i>
<i>Medicinal product by therapeutic areas</i>	<i>Effects on medicinal product levels.</i>	<i>Recommendation concerning co-administration with [product name]</i>								
<i>All corticosteroids excluding cutaneous products</i>										
<i>Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).</i>	<i>Interaction not studied with any of the components of [product name].</i> <i>Plasma concentrations of these medicinal products may be increased when co-administered with [product name], resulting in reduced serum cortisol concentrations.</i>	<i>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.</i> <i>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.</i>								

	<p><u>Consumer Medication Information Leaflet (RiMUP)</u></p> <p>a) Before you use <product name>:</p> <p>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.</p> <p>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</p>
54.	<p>CORTICOSTEROID</p> <p>1. The following statements shall be <u>included in the package insert and RiMUP</u> of inhaled corticosteroid 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):</p> <p><u>Package Insert</u></p> <p>a) Special Warnings and Precautions for Use:</p> <p><u>Pneumonia in patients with COPD</u></p> <p>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.</p>

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 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**

	<p>Produk Inhalasi Kortikosteroid Yang Digunakan Untuk Rawatan <i>Chronic Obstructive Pulmonary Disease (COPD)</i> : Pengemaskinian Sisip Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Tambahan Berkenaan Peningkatan Risiko <i>Pneumonia</i></p> <p>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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat</p>
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Attachment 3

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
107.	<p data-bbox="321 367 594 401">LEVETIRACETAM</p> <p data-bbox="321 453 1433 569">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Levetiracetam;</p> <p data-bbox="321 663 548 697"><u>Package Insert</u></p> <p data-bbox="321 747 789 781">a) Warnings and Precautions:</p> <p data-bbox="375 833 1433 949">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.</p> <p data-bbox="321 1043 685 1077">b) Undesirable Effects:</p> <p data-bbox="375 1129 883 1205">Renal and urinary disorders: Frequency rare: acute kidney injury.</p> <p data-bbox="375 1257 1433 1373">Musculoskeletal and connective tissue disorders: Frequency rare: rhabdomyolysis and blood creatine phosphokinase increased.*</p> <p data-bbox="375 1383 1433 1459">* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.</p> <p data-bbox="375 1512 1433 1661">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.</p> <p data-bbox="321 1755 1084 1789"><u>Consumer Medication Information Leaflet (RiMUP)</u></p>

a) Side Effects:

Tell your doctor immediately if you notice any of the following:

- Symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, may be a sign of sudden decrease of kidney function.
- Signs or symptoms including muscleache, feeling of weakness and dark urine may indicate the side effect of rhabdomyolysis (breakdown of muscle tissue).
- If someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements, these could be symptoms of an encephalopathy.

Reference : Directive No. 3 Year 2018. Ref. [BPFK/PPP/07/25 \(3 \) Jld 2.](#) Direktif Untuk Semua Produk Yang Mengandungi Levetiracetam : Pengemaskinian Sisip Bungkus 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)
126.	<p data-bbox="321 373 548 407">MINOCYCLINE</p> <p data-bbox="321 453 1433 569">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> of products containing Minocycline:</p> <p data-bbox="321 663 548 697"><u>Package Insert</u></p> <p data-bbox="321 747 792 781">a) Warnings and Precautions:</p> <p data-bbox="375 831 1328 865"><u>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)</u></p> <p data-bbox="375 915 1433 1241">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.</p> <p data-bbox="321 1291 943 1325">b) Adverse Effects/ Undesirable Effects:</p> <p data-bbox="375 1362 951 1396">Skin and subcutaneous tissue disorders:</p> <p data-bbox="375 1434 1328 1467">Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)</p> <p data-bbox="321 1551 1084 1585"><u>Consumer Medication Information Leaflet (RiMUP)</u></p> <p data-bbox="321 1623 570 1656">a) Side Effects:</p> <p data-bbox="375 1694 1433 1770">Stop taking <product name> and contact your doctor immediately if you experience any of the following:</p>

- 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 Semua Produk Yang Mengandungi Minocycline : Pengemaskinian Sisip Bungkus 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)
157.	<p data-bbox="321 373 505 407">PROPOFOL</p> <p data-bbox="321 457 1433 533">The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Propofol:</p> <p data-bbox="321 583 532 617">a) WARNING</p> <p data-bbox="375 667 1433 1037">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.</p> <p data-bbox="375 1087 1433 1192">There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction or emergence from anaesthesia induced by propofol.</p> <p data-bbox="321 1234 570 1268">b) Interactions:</p> <p data-bbox="375 1310 1433 1423">A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.</p> <p data-bbox="321 1507 1433 1625">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</p>

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 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

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.
- 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.

Pregnancy Exposure Risk related to valproate

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.

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to 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.

Developmental disorders

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.

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).

Female children, female adolescents and woman of childbearing potential (see above and Special Warnings and Precautions for use)

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 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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat

Attachment 6

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
13.	<p data-bbox="321 373 532 405">AMOXICILLIN</p> <p data-bbox="321 447 1437 552">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> of products containing Amoxicillin (including combination products);</p> <p data-bbox="321 604 548 636"><u>Package Insert</u></p> <p data-bbox="370 678 833 709">a) Warnings and Precautions:</p> <p data-bbox="418 751 1437 867">Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.</p> <p data-bbox="370 919 987 951">b) Adverse Effects/ Undesirable Effects:</p> <p data-bbox="418 1003 1437 1119">Skin and subcutaneous tissue disorders: Frequency 'very rare': Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)</p> <p data-bbox="321 1171 1084 1203"><u>Consumer Medication Information Leaflet (RiMUP)</u></p> <p data-bbox="370 1255 613 1287">a) Side Effects:</p> <p data-bbox="418 1329 1437 1392">Stop taking [product name] and contact your doctor immediately if you experience any of the following:</p> <ul data-bbox="435 1413 1437 1570" style="list-style-type: none">• 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. <p data-bbox="321 1612 1437 1812">Reference : Directive No. 8 Year 2018. Ref. BPFK/PPP/07/25 (8) Jld 2. Direktif Untuk Semua Produk Yang Mengandungi Amoxicillin Termasuk Kombinasi: Pengemaskinian Sisp Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (Rimup) Dengan Memperkukuhkan Maklumat Berkaitan <i>Severe Cutaneous Adverse Reactions (Scars)</i> Pada Bahagian <i>Warnings & Precautions</i> Dan Amaran Berkaitan <i>Drug Reaction With Eosinophilia And Systemic Symptoms (Dress)</i> Pada Bahagian Side Effects</p>

Attachment 7

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
82.	<p data-bbox="321 373 535 407">GABAPENTIN</p> <p data-bbox="321 449 1430 554">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> of products containing Gabapentin;</p> <p data-bbox="321 632 548 665"><u>Package Insert</u></p> <p data-bbox="370 705 829 739">a) Warnings and Precautions:</p> <p data-bbox="418 779 748 812"><u>Respiratory depression</u></p> <p data-bbox="418 863 1430 1106">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.</p> <p data-bbox="370 1150 984 1184">b) Adverse Effects/ Undesirable Effects:</p> <p data-bbox="418 1224 1081 1257">Respiratory, thoracic and mediastinal disorders</p> <p data-bbox="418 1297 992 1331">Frequency 'rare': Respiratory depression</p> <p data-bbox="321 1413 1084 1446"><u>Consumer Medication Information Leaflet (RiMUP)</u></p> <p data-bbox="370 1486 769 1520">a) While You Are Using It:</p> <p data-bbox="418 1560 764 1593"><u>Before you start to use it</u></p> <p data-bbox="418 1644 1430 1761">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.</p>

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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Respiratory Depression*

Attachment 8

5.1.4 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)

- a) Refers to locally manufactured products for export only which are not marketed locally with a different formulation (e.g. colour or strength of ingredients) or shape compared to a registered product; exporting purpose only and not marketed locally. This does not apply to imported products meant to be packed/repacked locally and to be re-export (the application falls under Regulation 7(2)(b), Control of Drugs and Cosmetic Regulations 1984. A separate [application form](#) may be obtained from the NPRA website).
- b) For products containing ingredients/ formulations which are not allowed by the Authority for local use, applicant shall submit a confirmation in writing from the competent authority of the importing country that there is no objection to the importation and sale of the said ingredients/ formulations. Evidence of registration of the said formulation with the competent authority in importing country may be submitted as supporting data;
Applications for registration of FEO products are only accepted in the following condition(s) and to be supported with evidence issued by the competent Authority of the importing countries (self-declaration is not accepted):
- (i) Countries which do not impose specific regulatory requirements as Malaysia (e.g. formulation with banned/ prohibited ingredients, zone IVB stability study, bioavailability/ bioequivalence study, API evaluation etc.); OR
 - (ii) Countries which have different requirements such as different formulation (e.g. colour or strength of ingredients), shape or manufacturing process, etc. as compared to a registered product; OR
 - (iii) Difference in classification category of the products (e.g. as food in the importing country) for health supplements and traditional products.
- c) Upon application, Applicant may apply for a Certificate of Pharmaceutical Product (CPP) will be issued to the applicant for the registered FEO products.
- d) For a registered product intended for exportation as well as to be sold in Malaysia:
- New application for registration for export only will NOT be required if there is no change in the formulation and appearance of the registered product.
 - Applicant may apply a CPP will be issued to the applicant for the registered product and together with an explanation/ declaration letter of any difference(s) to the importing country (e.g. a product exported with a different product name), upon application.
- e) For a registered product, now intended to be for export only and no longer for sale in Malaysia:
- Application for registration as a FEO product is required.

- The existing registration number (i.e. MAL number) will remain the same but with the addition of the administrative code E (For Export Only)
- f) Applications for registration of FEO products are processed based on abridged evaluation. However, the additional following requirements must be fulfilled for pharmaceutical products (not applicable to health supplements and traditional products):
- (i) Certificate of Analysis (COA) of finished product for at least 1 pilot batch; AND
 - (ii) Minimum 6 months stability data (real time and accelerated stability study) for at least 1 pilot batch.
- g) Applications shall be submitted by using an application form [BPFK 438.1](#) (for Generic Medicines/ Health Supplements) and [BPFK 438.1 \(T\)](#) (for Traditional Products).
Note: The applicant must first register membership for QUEST system with NPRA and subsequently purchase a USB Token that contains a User Digital Certificate, from MSC Trustgate.com Sdn. Bhd. This is to enable the applicant to access the system for product updating once the application for registration is approved. For further detail, please refer Section A General Overview under [3.3 How To Apply](#). Application is via online submission in QUEST system.

Reference: [Bil \(11\)d/m.BPFK/07/25 Jld.2](#) Direktif Kaji Semula Pendaftaran Produk Untuk Tujuan Eksport Sahaja (FEO)

Attachment 9

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
118.	<p data-bbox="321 380 532 415">MESALAZINE</p> <p data-bbox="321 449 1433 569">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing mesalazine;</p> <p data-bbox="321 642 548 678"><u>Package Insert</u></p> <p data-bbox="370 726 831 762">a) Warnings and Precautions:</p> <p data-bbox="418 812 1433 932">Photosensitivity More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.</p> <p data-bbox="370 980 984 1016">b) Adverse Effects/ Undesirable Effects:</p> <p data-bbox="418 1066 1003 1142">Skin and Subcutaneous Tissue Disorders Frequency “rare”: Photosensitivity</p> <p data-bbox="321 1220 1084 1255"><u>Consumer Medication Information Leaflet (RiMUP)</u></p> <p data-bbox="370 1306 610 1341">a) Side Effects:</p> <p data-bbox="418 1392 1433 1467">Photosensitivity: Itchy eruption and exaggerated sunburn on patches of sun-exposed skin</p> <p data-bbox="321 1549 1433 1669">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 <i>Photosensitivity</i></p>

Attachment 10

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
72.	<p data-bbox="326 380 643 411">ETHINYLESTRADIOL</p> <p data-bbox="326 464 1430 579">Please refer to CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION for products containing cyproterone acetate 2mg with ethinylestradiol 0.035mg in combination.</p> <p data-bbox="326 674 1430 789">The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing ethinylestradiol;</p> <p data-bbox="326 863 548 894"><u>Package Insert</u></p> <p data-bbox="370 947 699 978">a) Contraindications:</p> <p data-bbox="418 1031 1430 1178">[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).</p> <p data-bbox="370 1220 829 1251">b) Warnings and Precautions:</p> <p data-bbox="418 1304 1430 1787">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).</p>

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.

Consumer Medication Information Leaflet (RiMUP)

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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Risiko Peningkatan Paras Alanine Transaminase (ALT) Akibat Interaksi Dengan Produk Kombinasi Ombitasvir / Paritaprevir / Ritonavir Dan Dasabuvir

Attachment 11

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
38.	<p data-bbox="321 422 586 453">CARBOCISTEINE</p> <p data-bbox="321 506 1437 621">The following statements shall be <u>included in the label, package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing carbocisteine;</p> <p data-bbox="321 699 407 730"><u>Label</u></p> <p data-bbox="337 783 1437 898"><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:</p> <ul data-bbox="337 926 1437 1066" style="list-style-type: none">• Severe allergy: breathing difficulties, light headedness, skin swellings or rash.• Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. <p data-bbox="321 1157 548 1188"><u>Package Insert</u></p> <p data-bbox="370 1241 1003 1272">a) Adverse Effects / Undesirable Effects:</p> <p data-bbox="418 1325 943 1398"><u>Immune System Disorders:</u> Anaphylactic / anaphylactoid reaction</p> <p data-bbox="418 1430 1437 1650"><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.</p> <p data-bbox="321 1734 1084 1766"><u>Consumer Medication Information Leaflet (RiMUP)</u></p>

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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Anaphylactic/ Anaphylactoid Reaction* Dan *Severe Cutaneous Adverse Reactions* (SCAR)

Attachment 12

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
4.	<p data-bbox="321 380 610 415">ACETYLCYSTEINE</p> <p data-bbox="321 464 1437 583">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing acetylcysteine;</p> <p data-bbox="321 659 1385 737">1. Injectable products with the indication as antidote for paracetamol overdose</p> <p data-bbox="375 770 605 806"><u>Package Insert</u></p> <p data-bbox="375 852 889 888">a) Warnings and Precautions:</p> <p data-bbox="415 938 795 974"><u>Hypersensitivity Reactions</u></p> <p data-bbox="415 980 1437 1268">Serious acute hypersensitivity reactions during acetylcysteine administration including rash, hypotension, wheezing, and/or shortness of breath, have been observed in patients receiving intravenous acetylcysteine for paracetamol overdose and occurred soon after initiation of the infusion (see Adverse Effects/Undesirable Effects). If a severe hypersensitivity reaction occurs, immediately stop the infusion of acetylcysteine and initiate appropriate treatment.</p> <p data-bbox="415 1318 1437 1562">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.</p> <p data-bbox="415 1612 1437 1814">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</p>

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:

Immune System Disorders:

Anaphylactic/anaphylactoid reaction

Skin and Subcutaneous Tissue Disorders:

Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects.

2. All other products (not indicated for treatment of paracetamol overdose)

Package Insert

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 weeks following completion of treatment with this combination drug regimen.

Consumer Medication Information Leaflet (RiMUP)

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. 14 Year 2018. Ref. [BPFK/PPP/07/25 \(14 \) Jld 2.](#) Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine Dan Acetylcysteine : Pengemaskinian Label, Sisip Bungkus Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Anaphylactic/ Anaphylactoid Reaction* Dan *Severe Cutaneous Adverse Reactions* (SCAR)

Attachment 13

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
3.	<p data-bbox="321 380 602 415">ACETAZOLAMIDE</p> <p data-bbox="321 464 1437 583">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Acetazolamide;</p> <p data-bbox="321 674 553 709"><u>Package Insert</u></p> <p data-bbox="321 758 792 793">a) Warnings and Precautions:</p> <p data-bbox="375 842 1437 1045">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.</p> <p data-bbox="321 1094 954 1129">b) Adverse Effects / Undesirable Effects:</p> <p data-bbox="375 1178 964 1213"><u>Skin and Subcutaneous Tissue Disorders</u></p> <p data-bbox="375 1262 1437 1381">Frequency not known: Severe skin reactions [including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP)]</p> <p data-bbox="321 1461 1084 1497"><u>Consumer Medication Information Leaflet (RiMUP)</u></p> <p data-bbox="321 1545 574 1581">b) Side Effects:</p> <p data-bbox="375 1629 1437 1749">[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:</p> <ul data-bbox="375 1797 1437 1833" style="list-style-type: none">• 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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Severe Cutaneous Adverse Reactions* (SCARs)

Attachment 14

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
154.	<p>PREDNISONE AND PREDNISOLONE (EXCEPT TOPICAL PREPARATIONS)</p> <p>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);</p> <p><u>Package Insert</u></p> <p>a) Warnings and Precautions:</p> <p><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.</p> <p><u>Consumer Medication Information Leaflet (RiMUP)</u></p> <p>a) Before you start to use it:</p> <p>Talk to your doctor before taking <product name>, if you have:</p> <p>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.</p> <p>Reference: Directive No. 17 Year 2018. Ref. BPFK/PPP/07/25 (17) Jld 2. Direktif Untuk Semua Produk Yang Mengandungi Prednisone Dan Prednisolone (Kecuali Persediaan Topikal) : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Schleroderma Renal Crisis</i></p>

Attachment 15

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
69.	<p data-bbox="321 390 506 422">EFAVIRENZ</p> <p data-bbox="321 474 1430 590">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Efavirenz;</p> <p data-bbox="321 684 548 716"><u>Package Insert</u></p> <p data-bbox="321 768 789 800">a) Warnings and Precautions:</p> <p data-bbox="375 852 1430 1052">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.</p> <p data-bbox="321 1104 691 1136">b) Pharmacodynamics:</p> <p data-bbox="375 1188 748 1220">Cardiac Electrophysiology</p> <p data-bbox="375 1272 1430 1808">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).</p>

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 and Precautions). Consider alternatives to [Product name] when coadministered with a drug with a known risk of Torsade de Pointes.

Consumer Medication Information Leaflet (RiMUP)

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 Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan QTc *Prolongation*

Attachment 16

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
68.	<p data-bbox="321 390 553 422">DOXYCYCLINE</p> <p data-bbox="321 474 1414 594">The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Doxycycline;</p> <p data-bbox="321 684 548 716"><u>Package Insert</u></p> <p data-bbox="321 768 789 800">a) Warnings and Precautions:</p> <p data-bbox="375 852 1414 1014">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.</p> <p data-bbox="321 1062 935 1094">b) Adverse Effects/Undesirable Effects:</p> <p data-bbox="375 1146 743 1178"><u>Immune system disorders</u></p> <p data-bbox="375 1230 1414 1308">Frequency not known: Jarisch-Herxheimer reaction (see Section Warnings and Precautions)</p> <p data-bbox="321 1398 1081 1430"><u>Consumer Medication Information Leaflet (RiMUP)</u></p> <p data-bbox="321 1482 570 1514">a) Side Effects:</p> <p data-bbox="375 1566 1365 1728">[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.</p> <p data-bbox="334 1776 1414 1833">Reference: Directive No. 19 Year 2018. Ref. BPFK/PPP/07/25 (19) Jld 2. Direktif Untuk Semua Produk Yang Mengandungi Doxycycline : Pengemaskinian Sisip Bungkus Dan</p>

	Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan <i>Jarisch-Herxheimer Reaction</i>
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Attachment 17

Stability data as shown in the following example shall be submitted for evaluation.

RECOMMENDED PRESENTATION OF THE SUMMARY TABLE OF STABILITY RESULTS

Product Name	:	Storage Temperature,	:	Relative Humidity
Dosage Form	:	Batch No.	:	
Strength	:	Manufacturing Date	:	
Container/Packaging	:	Date Of Report	:	
Pack Size	:	Period Of The Study	:	

Testing Parameters (as applicable)	Specifications	Testing Frequency (Months)							
		0	3	6	9	12	18	24	36
Appearance/ Organoleptic characteristics: Odour Colour	To describe the characteristics								
Disintegration	DRGD								
Uniformity of weight	DRGD								
Assay: (All standardized compounds claimed on label, if applicable)	To specify								
Microbial Contamination Test -Total Aerobic Microbial Count	-NMT 2 x 10 ⁴ CFU/g or CFU/mL								
-Total Yeasts & Moulds Count	-NMT 2 x 10 ² CFU/g or CFU/mL								
-Test for Specified Microorganisms	-NMT 1 x 10 ² CFU of bile-tolerant gram-negative bacteria in 1g or 1mL -Absence of Salmonella in 25g or 25mL -Absence of Escherichia coli in 1g or 1mL -Absence of Staphylococcus aureus in 1g or 1mL								
Heavy Metal Contamination -Lead (Pb) -Cadmium (Cd) -Mercury (Hg)	-NMT 10 ppm -NMT 0.3 ppm -NMT 0.5 ppm								

-Arsenic (As)	-NMT 5 ppm								
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NMT = Not More Than

Conclusion:

Prepared by: (signature)

Name:

Designation:

Date:

Checked by: (signature)

Name:

Designation:

Date:

Approved by: (signature)

Name:

Designation:

Date:

Attachment 18

The tabulated list of parameters for each dosage form is presented as a guide for the following types of tests to be included in a stability study.

Tabulated list of stability indicating parameters for traditional medicine

Testing Parameters Dosage Form	Organoleptic characteristics	Assay	Hardness/ friability	Dissolution/ Disintegration	Water content	Viscosity	pH	Microbial content	Granules/ Particle Seize variation	Resuspendability	Adhesiveness
Oral powder	√	√			√			√			
Hard capsule	√	√		√	√			√			
Soft capsule	√	√		√				√			
Coated and Uncoated Tablet	√	√	√	√	√			√			
Coated and Uncoated Pill/ Pellet	√	√		√	√			√			
Suspension	√	√				√	√	√	√	√	
Solution	√	√				√	√	√			
Emulsion	√	√				√	√	√			
Semi Solid Preparations (Ointment/ Cream/ Gel/ Lotion/ Paste)	√	√				√	√	√			
Plaster	√	√						√			√
Granules	√	√			√			√	√		

Herbal Infusion Bag/ Herbal Tea Bag	√	√			√			√			
Pastilles	√	√			√			√			

Attachment 19

16.3 CHANGE OF PRODUCT REGISTRATION HOLDER

[Reference: [Directive \(3\)d/m.BPFK/PPP/07/25](#)]

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 4 Tahun 2013: Direktif Untuk Meminda Prosedur Permohonan Pertukaran Pemegang Pendaftaran Produk (03 June 2013)

16.3.1 INTRODUCTION

A transfer procedure for the purpose of changing the existing product registration holder (PRH) that is authorized to market a registered product in Malaysia to another holder. This procedure allows the registered product to maintain the same registration number.

Upon receipt of complete online application via QUEST system and hardcopy of original documents, the change of PRH application shall be processed within forty-five (45) working days.

16.3.2 CONDITIONS

The application is subjected to the following conditions:

- 1) An application to transfer the marketing authorization of a registered product shall be submitted by the existing PRH.
- 2) The new PRH shall be a registered company/ business with Companies Commissioner of Malaysia and a registered QUEST user with National Pharmaceutical Regulatory Division (NPRA).
- 3) The registered product intended to be transferred to a new PRH shall have a remaining registration validity period of at least six (6) months. If the registration validity is less than six (6) months, the existing PRH shall first apply for the renewal of this registered product.
- 4) No change/s can be made to the technical data or approved pharmaceutical / pharmacological information, including the texts of the product label and leaflet, **except** the name and address of the approved PRH.
- 5) In the interim, the existing PRH shall still bear the marketing authorization responsibility of the said registered product.

- 6) The transfer shall come into effect on the day the DCA makes a decision on the **outcome of the Change of PRH** application. Upon the transfer of product registration to the new PRH, the authorization issued to the previous PRH will be cancelled as the product cannot be marketed simultaneously by two different PRHs. The new PRH shall **then** bear responsibility for the said product.
- 7) However, the existing PRH is allowed to deplete the stocks and **will still be held liable should any** pharmacovigilance issues or quality defects associated with the product arise during the interim **of the** transfer.
- 8) The existing PRH or newly approved PRH shall submit a written request to deplete the existing stocks after DCA approval **has been obtained** for the transfer. The PRH **that submits** the request shall **be held** responsible **for the batches and quantity requested** in the event any pharmacovigilance issues or quality defects associated with those product **batches arise**.
- 9) Application shall be rejected if the applicant fails to provide satisfactory required documents within 30 working days starting from the first date of correspondence **by the evaluator**.

16.3.3 APPLICATION

The existing PRH shall submit the following documents and payment to NPRA:

1. ~~Application Form BPFK-430.5~~ **Fill and submit application online via the current QUEST system**
2. ~~Borang Penyerahan Permohonan BPFK-001~~
3. Processing Fee (refer 16.3.4)
4. Original Supporting Documents (refer 16.3.5)

16.3.4 PROCESSING FEE

1. NON-REFUNDABLE processing fee.

- For a Traditional Product	: RM 500.00
- For a Poison or Non-Poison Pharmaceutical Product (including Health Supplement)	: RM 1,000.00
2. ~~The processing fee shall be paid in the form of a bank draft/ money order/ postal order, made payable to "Biro Pengawasan Farmaseutikal~~

~~Kebangsaan~~ online via QUEST immediately after the change of PRH application has been submitted.

3. ~~Application/s without correct processing fee will not be accepted for processing.~~ Foreign currency is not accepted.

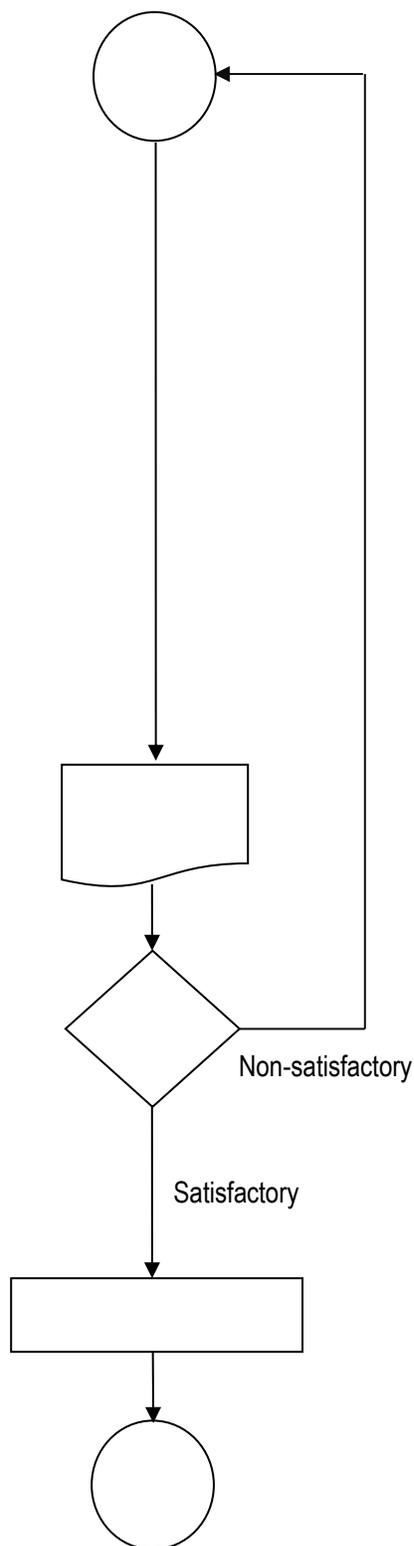
16.3.5 SUPPORTING DOCUMENTS

1. List of required supporting documents:
 - i) Letter of Authorization (LOA) issued by the Product Owner. **If the Product Owner is an entity registered outside of Malaysia then the LOA must be certified by the Notary Public from the country of origin of said Product Owner. However, if the Product Owner is a Malaysian registered entity then the LOA must be certified by a local Commissioner for Oaths** **The LOA shall consist** of the following information:
 - a. The registered name and registration number of the product(s) concerned.
 - b. Company name, business registration number and address of the proposed new PRH **as registered in QUEST.**
 - c. Company name, business registration number and address of the existing PRH **as registered in QUEST.**
 - d. Effective date of the appointment and termination given by the product owner. If the effective date is not mentioned, the date of the LOA issued will be considered as the effective date.
 - e. Signature of the Managing Director/ Director/ President/ Chief Executive Officer/ General Manager who has overall responsibility for the company or organization.
 - f. Full and complete **name,** address, email address (if available), telephone and fax number (if available) of the Product Owner **as registered in QUEST.**
 - g. **The Product Owner name and address in the letterhead of the LOA must be identical to the information of the Product Owner registered in QUEST for the product(s) concerned.**
 - ii) **Resolution by the Company Board of Directors of local Product Owner verifying that ALL the Board of Directors/ Partners have given their consent to the Change of PRH. This resolution must be signed by ALL the Board of Directors/ Partners. If the Product Owner is not a local entity, please omit.**
 - iii) **Latest document indicating details of director/s and shareholder/s of local Product Owner (e.g. ~~Form 24 and Form 49.~~ Corporate Information, Summary of Share Capital, Directors/Officers, Shareholders/Members from the MyData SSM website). These documents must be certified by the Commissioner for Oaths (i.e. Statutory Declaration). If the Product Owner is not a local entity, please omit.**

**Note:* LOA format example (Please refer 16.3.6 Supporting Document Format Example)

- iv) Resolution by the Company Board of Directors of **existing PRH** verifying that ALL the Board of Directors/ Partners have given their consent to the Change of PRH. This resolution must be signed by ALL the Board of Directors/ Partners.
 - v) ~~Certified by Commissioner for Oath of the latest document indicating details of director/s and shareholder/s of existing PRH; e.g. Form 24 and Form 49.~~ Latest document indicating details of director/s and shareholder/s of **existing PRH** (e.g. Corporate Information, Summary of Share Capital, Directors/Officers, Shareholders/Members from the MyData SSM website). These documents must be certified by the Commissioner for Oaths (i.e. Statutory Declaration).
 - vi) The Company/ Business Registration Certificate of the proposed new PRH certified true copy by a MAICSA accredited company secretary or by the Companies Commission of Malaysia (e.g. Form 9 and/ or Form 13).
 - vii) Statement of Acceptance as Product Registration Holder, [NPRA-430.5\(3\)](#) to be filled by the proposed new PRH.
2. The ORIGINAL documents listed above shall be submitted to the Centre of Product Registration, NPRA once payment for the application has been made. Photocopies of documents will not be accepted.
 3. Date of the documents including date of stamps/signatures of certifying bodies must be recent, i.e. not exceeding six (6) months from the date of application.
 4. Each page of attachment (if any) i.e. product list must be endorsed by the signatory.
 5. The Secretariat, if necessary, has the right to request further supplementary information or documentation. Failure to provide these additional information or documentation(s) will result in the rejection of the transfer application.

16.3.7 FLOWCHART FOR THE CHANGE OF PRODUCT REGISTRATION HOLDER



Company (Existing PRH)

Submit complete application to NPRA as below;

1. ~~Application Form BPFK-430.5~~
2. ~~Borang Penyerahan Permohonan BPFK-001~~
1. Fill and submit application online via QUEST system
2. Processing Fee (refer 16.3.4)
3. Submit Original Supporting Documents ~~consisting of;~~ (refer 16.3.5) to Centre for Product Registration
 - ~~LOA from product owner certified by Notary Public for overseas company or Commissioner For Oath for local company~~
 - ~~Resolution by Company Board of Directors of local product owner~~
 - ~~The latest Form 24 and Form 49 of local product owner certified by Commissioner for Oath~~
 - ~~Resolution by Company Board of Directors of existing PRH~~
 - ~~The latest Form 24 and Form 49 of existing PRH certified by Commissioner for Oath~~
 - ~~Company/ Business Registration Certificate of proposed new PRH~~
 - ~~Statement of Acceptance As Product Registration Holder; BPFK-430.5(3) completed by proposed new PRH~~

Secretariat

Receive and evaluate application and original documents ~~documentations and evaluation of application~~

Secretariat

Processing of evaluated application;

1. Satisfactory:
 - a) Table to DCA meeting for approval
2. Non-satisfactory:
 - b) Table to DCA meeting for rejection (processing fee is NON-REFUNDABLE in the event the application is rejected)

DCA Meeting

Secretariat

Processing of DCA meeting outcome;

1. Notification of transfer approval to new proposed PRH and termination notification to existing PRH for approved application; OR
2. Notification of transfer rejection to existing PRH for rejected application

SECTION E: POST-REGISTRATION PROCESS

14. MAINTENANCE OF REGISTRATION

Registration of a product shall be valid for **five (5) years** or such period as specified in the Authority database (unless the registration is suspended or cancelled by the Authority).

Application for re-registration (renewal of product registration) of a product shall be submitted **within six (6) months prior to the expiry** of the validity period of a product registration. A letter of reminder for product re-registration will be issued to the product registration holder 3 months prior to the expiry date of a product registration.

After the expiry date, the status of product registration shall be automatically changed to 'expired', and applicant will not be able to submit the application for product re-registration. Any form of appeal **shall not be considered** if re-registration application is not submitted before the expiry date of a product registration since reminder letter is issued 3 months prior to the expiry date. A new registration application shall be submitted if applicant wishes to continue to market the product.

After the expiry of product registration date, the product is deemed **unregistered**. Products of which their re-registration is on hold due to unmet requirements but has passed its registration expiry date, the new registration date shall be updated according to the DCA Meeting date where the re-registration application is approved by the DCA.

The application for product re-registration **shall only be submitted when all of the registration requirements have been complied with. Failure to do so shall result in the re-registration application being rejected by the Authority.**

14.1 REQUIREMENT

The requirements for product re-registration as aforementioned are as follows:

- a) Patient dispensing pack size for pharmaceutical product containing scheduled poison or non-scheduled poison with tablet/capsule dosage form, including oral liquid preparation and dermatological preparation.

Note: Please refer Appendix 10: Guideline on Patient Dispensing Pack for Pharmaceutical.

- b) Bioequivalence study report for all registered generic products containing scheduled poison with immediate release, oral, solid dosage form (came into force starting from 1st January 2013)

Reference:

(10) dlm.BPFK/PPP/01/03 Jld.1

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 1 Tahun 2011 : Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens Bagi Semua Produk Generik "Immediate Release, Oral, Solid Dosage Form" Yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian BioEkuivalens (2 March 2011)

- c) Bioequivalence study report for all registered generic products containing scheduled poison with effervescent, dispersible, orodispersible, sublingual, buccal and chewable dosage form (comes into force for product registration which is expiring starting from 1st January 2019)

Reference:

(27) dlm.BPFK/PPP/07/25

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 3 Tahun 2015 : Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens (BE) Bagi Semua Produk Generik Dalam Bentuk Dos Oral Tablet/Kapsul Yang Bersifat *Effervercent, Dispersible, Orodispersible, Sublingual, Buccal Dan Chewable* Yang Mengandungi Bahan Aktif Racun Berjadual (23 February 2015)

(45) dlm.BPFK/PPP/01/03 Jld.3

Lanjutan Tarikh Penguatkuasaan Untuk Memenuhi Keperluan Kajian Bioekuivalens (BE) Bagi Produk Generik Dalam Bentuk Dos Oral Tablet/Kapsul Yang Bersifat *Effervescent, Dispersible, Orodispersible, Sublingual, Buccal dan Chewable* Yang Mengandungi Bahan Aktif Racun Berjadual (31 May 2016)

- d) Regulatory control of active pharmaceutical ingredient (API) for all dosage form of registered pharmaceutical products containing scheduled poison (comes into force for product registration which is expiring starting from 1st January 2020)
- API information shall be submitted at **least one year prior to the product registration expiry date.**
 - Please refer also Appendix 6: Guideline on Regulatory Control of Active Pharmaceutical Ingredients

Reference:

(7) dlm.BPFK/PPP/07/25

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 8 Tahun 2013 : Direktif Perluasan Skop Pelaksanaan Kawalan Regulatori Ke Atas Bahan Aktif Farmaseutikal Bagi Produk Generik Yang Mengandungi Racun Berjadual (Fasa II) (16 January 2014)

(11) dlm.BPFK/PPP/01/03 Jld.3

Lanjutan Tarikh Pelaksanaan Pengawalan Bahan Aktif Farmaseutikal (API) Bagi Produk Farmaseutikal Berdaftar Yang Mengandungi Racun Berjadual (27 June 2014)

- e) For pharmaceutical products which were submitted for registration before the year 2009, applicants shall ensure that stability study for the products at zone IV B has been conducted and granted variation approval before submission of re-registration application.

Reference:

(1) dlm. BPFK/PPP/01/03 Jld.3

Keperluan Data Kajian Stabiliti Dalam Zon IV B Bagi Produk Farmaseutikal Berdaftar (05 April 2013)

(5) dlm. BPFK/PPP/01/03

Lanjutan Tarikh Berkuatkuasa Untuk Memenuhi Keperluan Data Kajian Stabiliti Dalam Zon IV B Bagi Produk Farmaseutikal Berdaftar (14 August 2013)

For pharmaceutical products that required exemption from zone IV B requirements, applicants shall submit the exemption request via variation application MiV-PA through the current online system.

- f) Valid GMP document/certificate for imported product (came into force starting from 1st January 2014)

To maintain the registration of an imported product, the PRH shall comply with GMP requirement as stated in the directive issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984.

Note: Please refer also Guidance Document for Foreign GMP Inspection (5th Edition March 2018)

Reference:

Bil (25) dlm BPFK/PPP/01/03 Jld.1

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 1 Tahun 2012 : Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (09 February 2012)

Bil (96) dlm. BPFK/PPP/01/03 Jld.2

Surat Pekeliling Bagi Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (28 December 2012)

(32) dlm. BPFK/PPP/07/25

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil.1 Tahun 2016: Direktif Mengenai Keperluan Pemeriksaan Amalan Perkilangan Baik (APB) Luar Negara Bagi Tujuan Pendaftaran/Pendaftaran Semula Produk Farmaseutikal Berdaftar Dengan Pihak Berkuasa Kawalan Dadah (PBKD) (22 January 2016)

(123) dlm. BPFK/30/05/1 Bahagian 4

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil.11 Tahun 2016: Direktif Mengenai Penerimaan Pengesahan Pematuhan Amalan Perkilangan Baik (APB) Bagi Tujuan Pendaftaran Semula Produk Farmaseutikal Berdaftar dengan Pihak Berkuasa Kawalan Dadah (PBKD) (30 June 2016)

Bil (15) dlm. BPFK/PPP/06/06 Jld.47

Pendaftaran Bersyarat Bagi Produk-Produk Dengan Sijil Amalan Perkilangan Baik (APB) dari Ministry of Economic Affairs, Taiwan (1 February 2017)

Bil. (4) dlm. BPFK/PPP/07/25 Jld.2

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil.4 Tahun 2018: Direktif Mengenai Penerimaan Pengesahan Pematuhan Amalan Perkilangan Baik (APB) Bagi Pengilang Farmaseutikal Bagi Tujuan Pendaftaran Baru/Pendaftaran Semula Produk Farmaseutikal Berdaftar Dengan Pihak Berkuasa Kawalan Dadah (PBKD) (16 May 2018)

- g) Amendment of product name consisting only generic name for registered pharmaceutical product containing scheduled poison and non-scheduled poison (came into force starting 1 January 2017)

Reference:

(39) dlm. BPFK/PPP/01/03 Jld.3

Pekeliling Penggunaan Nama Generik Pada Nama Produk Bagi Produk Farmaseutikal (21 December 2015)

- h) Endorsement letter of ancillary medical device component (from Medical Device Authority, Malaysia) for re-registration of drug-medical device combination product (comes into force for product registration which is expiring starting from 1 July 2019)

Note: Please refer also Guideline for Registration of Drug-Medical Device and Medical-Device-Drug Combination Products.

Reference:

(9) dlm. BPFK/PPP/07/25 Jld.1

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil.4 Tahun 2017: Direktif Kkuatkuasa Pemakaian Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products (10 March 2017)

14.2 APPLICATION FOR PRODUCT RE-REGISTRATION

- a) The application for product re-registration shall be submitted and herein paid via the current online system.
- b) The non-refundable processing fees for product re-registration are as follow:
 - i. Traditional Product : RM 500.00 per product
 - ii. Pharmaceutical Product (including Health Supplement) : RM1,000.00 per product

~~14.1 RE-REGISTRATION APPLICATION~~

- ~~a) For a product registered under the QUEST 2 system, the application for re-registration of the product shall be submitted online via the QUEST 2 system.~~
- ~~b) For a product registered under the QUEST 3 system, the application for re-registration of the product shall be submitted manually to NPRA with the following documents;
 - ~~i) Re-registration Application Form; BPFK 420.1~~
 - ~~ii) Processing Fee (refer Subsection 14.2 as below)~~~~

~~Please refer the following circulars for more information:~~

~~(37)d/m.BPFK/PPP/01/03Jld.3~~

~~Permohonan Pendaftaran Semula Produk QUEST 3 Melalui Prosedur Manual (29 May 2015)~~

~~14.2 RE-REGISTRATION PROCESSING FEE~~

- ~~a) Traditional Product : RM 500.00 per product~~
- ~~b) Poison/ Non-Poison product : RM 1,000.00 per product~~
- ~~c) The processing fee shall be paid in the form of a bank draft/ money order/ postal order, made payable to "Biro Pengawasan Farmaseutikal Kebangsaan".~~

~~All processing fees submitted to NPRA are NON-REFUNDABLE.~~

8. FLOW OF REGISTRATION PROCESS

8.4 EVALUATION OF APPLICATION

8.4.1 INITIATION OF REVIEW

Upon confirmation of payment, the application with the submitted data shall be evaluated. Review of applications shall follow a queue system. There shall be separate queues for the different categories of products and/or according to level of claims (~~i.e.~~ e.g. general, medium or high claim **for health supplements**).

8.4.2 PRIORITY REVIEW

1. Priority review may be granted for **new product application** (in the category of **New Drug Products, Biologics and Generics**) which ~~is intended for treatment of a serious or life-threatening disease, where the likelihood of death is high unless the course of the disease is interrupted.~~ **fulfils either one of the following conditions;**
 - a) **Product which is intended for:**
 - (i) **Unmet medical needs (e.g. medicines for rare diseases, new vaccines, etc.),**
 - (ii) **Life-saving such as for treatment/ prevention of serious medical conditions (e.g. anticancer, antiretroviral, etc.),**
 - (iii) **Treatment/ prevention in pandemic/ endemic situations, for the interest of public health,**
 - (iv) **Emergency supply/ crucial for treatment purpose according to the current needs in the country,**
 - (v) **Supply to the Ministry of Health Malaysia under circumstances where alternative product with the same active ingredient is unavailable,**

- b) Product which involves a change in the formulation due to the decision/instruction by the Drug Control Authority (DCA), for the purpose of formulation improvement with appropriate scientific justification(s),
 - c) Product which is the first generic product, or the first locally manufactured generic product.
2. An application for Priority Review should be submitted via a formal letter addressed to the Director of NPRA once the screening has been approved.
 3. The approval of Priority Review is subjected to the decision of the Drug Evaluation Committee Meeting upon submission of complete product registration documentation and does not exempt applicant from any product registration requirements.
 4. The timeline for evaluation for product granted Priority Review is as below;

No.	Product Category	Duration (Starting from the date of approval of Priority Review)
(A)	Full Evaluation	
1.	New Drug Products	120 working days
2.	Biologics	120 working days
3.	Generics (Scheduled Poison)	100 working days
4.	Generics (Non-Scheduled Poison)	100 working days