LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JULY 2019

(February 2019 Updates)

*** Please note that this monthly list of updates will only be updated in the full version of DRGD in July 2019 revision. However, the effective dates are as stated below in the respective column.**

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
1.	**SECTION A: GENERAL OVERVIEW** **5.4.1 CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP)**	Amendment as below (online CPP application) : A CPP in ~~which follows~~ the format recommended by WHO for a registered product can be applied by the PRH where such certificate is required by any country importing such product. ~~shall be issued to locally manufactured products that are to be exported.~~ To apply a CPP, ~~For application of CPP, applicant~~ the PRH shall fill up completely and submit the online application form via the QUEST system. ~~in form BPFK 412.2: Permohonan Perakuan Keluaran Farmaseutikal.~~ A fee, as stated in **Appendix 1: Fees,** is payable on the issue of such certification.	**February 2017**

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>2.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following substance and safety information/ statements as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>LAMOTRIGINE

(Please refer Attachment 1)</td></tr></table></td><td>1 February 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th>EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th><th></th></tr>
<tr><td>3.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following substance and safety information/ statements as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>BETA LACTAM ANTIBIOTICS (INCLUDING COMBINATION PRODUCTS)
(Please refer Attachment 2)</td></tr></table>
Amendment of the following safety information/ statements (warning and precautions) as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>13.</td><td>AMOXICILLIN
(Please refer Attachment 3)</td></tr></table>
<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>152.</td><td>PENICILLIN
(Please refer Attachment 4)</td></tr></table></td><td>1 February 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>4.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following safety information/ statements on the adverse effects;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td><u>MYCOPHENOLATE</u>
(MYCOPHENOLATE MOFETIL DAN MYCOPHENOLIC ACID)

(Please refer Attachment 5)</td></tr></table></td><td>1 June 2016</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>5.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following safety information/ statements as below;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>BISPHOSPHONATE (ALENDRONATE, CLODRONATE, IBANDRONIC ACID, PAMIDRONATE, RISEDRONATE, ZOLEDRONIC ACID)
(Please refer Attachment 6)</td></tr></table></td><td>1 July 2016</td></tr>
</table>

Attachment 1

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

LAMOTRIGINE

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing lamotrigine;

Package Insert

a) Warnings and Precautions:

Hemophagocytic lymphohistiocytosis (HLH) has occurred in patients taking lamotrigine (see section Adverse Effects/Undesirable Effects). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lympha-denopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation. Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be discontinued unless an alternative aetiology can be established.

b) Adverse Effects/Undesirable Effects:

Post-marketing

Blood and lymphatic system disorders

Very rare: Hemophagocytic lymphohistiocytosis (see section Warnings and Precautions)

Consumer Medication Information Leaflet (RiMUP)

a) Side Effects:

Hemophagocytic lymphohistiocytosis (HLH)
There have been reports of a rare but very serious immune system reaction, in patients taking lamotrigine.
- Contact your doctor or pharmacist immediately if you experience any of the following symptoms while taking lamotrigine: fever, rash, neurological symptoms (e.g. shaking or tremor, confusional state).

Reference : Directive No. 3 Year 2019. Ref. BPFK/PPP/07/25 (3) Jld 3. *Direktif Untuk Semua Produk Yang Mengandungi Lamotrigine: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hemophagocytic Lymphohistiocytosis (HLH)*

Attachment 2

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

BETA-LACTAM ANTIBIOTICS (INCLUDING COMBINATION PRODUCTS)

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing beta-lactam antibiotics (including combination products);

Package Insert

a) Warnings and Precautions:

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with [product name], careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, [product name] must be discontinued immediately and appropriate alternative therapy instituted.

Consumer Medication Information Leaflet (RiMUP)

a) Side Effects:

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

- skin reddening, blisters, rash, fever, sore throat or eye irritation

Reference :
Directive No. 2 Year 2019. Ref. BPFK/PPP/07/25 (2) Jld 3 *Direktif Untuk Semua Produk Antibiotik Kumpulan Beta-Lactam Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (Rimup) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*

Attachment 3

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

AMOXICILLIN

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Amoxicillin (including combination products);

Package Insert

a) Warnings and Precautions:

~~Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.~~

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with [product name], careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, [product name] must be discontinued immediately and appropriate alternative therapy instituted.

b) Adverse Effects/ Undesirable Effects:

Skin and subcutaneous tissue disorders:
Frequency 'very rare': Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Consumer Medication Information Leaflet (RiMUP)

a) Side Effects:

Stop taking [product name] and contact your doctor immediately if you experience any of the following:
• Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature and enlarged lymph nodes.

Reference :
Directive No. 8 Year 2018. Ref. BPFK/PPP/07/25 (8) Jld 2. *Direktif Untuk Semua Produk Yang Mengandungi Amoxicillin Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (Rimup) Dengan Memperkukuhkan Maklumat Berkaitan Severe Cutaneous Adverse Reactions (Scars) Pada Bahagian Warnings & Precautions Dan Amaran Berkaitan Drug Reaction With Eosinophilia And Systemic Symptoms (Dress) Pada Bahagian Side Effects*

Attachment 4

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

PENICILLIN

The following statement shall be included on the **labels** of products containing penicillin:

'**Not to be used in patients with known hypersensitivity to Penicillin**'

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Amoxicillin (including combination products);

Package Insert

a) Warnings and Precautions:

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with [product name], careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, [product name] must be discontinued immediately and appropriate alternative therapy instituted.

b) Adverse Effects/ Undesirable Effects:

Skin and subcutaneous tissue disorders:
Frequency 'very rare': Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Consumer Medication Information Leaflet (RiMUP)

a) Side Effects:

Stop taking [product name] and contact your doctor immediately if you experience any of the following:
• Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature and enlarged lymph nodes.

Reference :
Directive No. 8 Year 2018. Ref. BPFK/PPP/07/25 (8) Jld 2. *Direktif Untuk Semua Produk Yang Mengandungi Amoxicillin Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (Rimup) Dengan Memperkukuhkan Maklumat Berkaitan Severe Cutaneous Adverse Reactions (Scars) Pada Bahagian Warnings & Precautions Dan Amaran Berkaitan Drug Reaction With Eosinophilia And Systemic Symptoms (Dress) Pada Bahagian Side Effects*

Attachment 5

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

MYCOPHENOLATE (MYCOPHENOLATE MOFETIL DAN MYCOPHENOLIC ACID)

The following statement shall be included in the package insert of product that contains mycophenolate (mycophenolate mofetil dan mycophenolic acid):

CONTRAINDICATIONS

- [Product name] is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see Use in Special Populations: Pregnancy).
- [Product name] is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see Use in Special Populations: Pregnancy).
- [Product name] is contraindicated in women who are breastfeeding (see Use in Special Populations: Breastfeeding).

USE IN SPECIAL POPULATIONS

Pregnancy

[Product name] is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. (see Contraindications).

Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning.

Prior to starting therapy with [product name], female patients of childbearing potential must have **two negative serum or urine pregnancy tests** with a sensitivity of at least 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting [product name]. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant.

Due to the mutagenic and teratogenic potential of mycophenolate, **women of child bearing potential** should use **two reliable forms of contraception** simultaneously, including at least one highly effective method, before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, **female partners of male patients** are recommended to use highly effective during treatment and for total of 90 days after the last dose of [product name].

Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

- *Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;*
- *Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos);*
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly);
- Cardiac abnormalities such as atrial and ventricular septal defects;
- Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations (such as spina bifida).

In the medical literature, malformations in children from mycophenolate-exposed pregnancies have been reported in 23% to 27% of live births. For comparison, the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosuppressants other than mycophenolate.

Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate, mainly in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.

Studies in animals have shown reproductive toxicity.

Breastfeeding
[Product name] is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Contraindications).

Studies in rats have shown mycophenolate to be excreted in milk. It is not known whether this medicine is excreted in human milk.

ADVERSE DRUG REACTIONS

Post-marketing experience:

Congenital Disorders
Congenital malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy (see Use in Pregnancy).

Pregnancy, Puerperium and Perinatal Conditions
Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported (see Use in Pregnancy).

Reference: **Directive No. 6 Year 2016 Ref. BPFK/PPP/07/25 (37).** *Direktif Untuk Semua Produk Yang Mengandungi Mycophenolate (Mycophenolate Mofetil Dan Mycophenolic Acid): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Teratogenik*

Attachment 6

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

BISPHOSPHONATE (ALENDRONATE, CLODRONATE, IBANDRONIC ACID, PAMIDRONATE, RISEDRONATE, ZOLEDRONIC ACID)

The following statement shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of product that contains Bisphosphonate (Alendronate, Clodronate, Ibandronic acid, Pamidronate, Risedronate, Zoledronic acid):

Package Insert :

SPECIAL WARNINGS AND PRECAUTIONS FOR USE :

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

ADVERSE DRUG REACTIONS :

Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Consumer Medication Information Leaflet (RiMUP)

POSSIBLE SIDE EFFECTS :

Very rare

- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

Reference : Directive No.7 Year 2016 . Ref : BPFK/PPP/07/25 (38). *Direktif Bagi Semua Produk Yang Mengandungi Bisphosphonate (Alendronate, Clodronate, Ibandronic Acid, Pamidronate, Risedronate, Zoledronic Acid) Dengan Risiko Kesan Advers Berkaitan Osteonecrosis Of The External Auditory Canal*

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JULY 2019

(April 2019 Updates)

*** Please note that this monthly list of updates will only be updated in the full version of DRGD in July 2019 revision. However, the effective dates are as stated below in the respective column.**

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
1.	**SECTION 8.4: EVALUATION OF APPLICATION** **8.4.2 PRIORITY REVIEW**	**<u>Addition</u>** of the following statement (highlighted in red) : 1. Priority review may be granted for new product application (in the category of New Drug Products, Biologics and Generics) which 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.) with no treatment options locally available, ii. Life-saving such as for treatment/ prevention of serious medical conditions (e.g. anticancer, antiretroviral, etc.) with no treatment options locally available, 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/ biosimilar product, or the first locally manufactured generic/biosimilar product.	**22nd January 2019**

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	DETAILS	
		No generic/ biosimilar product has been registered by DCA at point of consideration on granting Priority Review* **The priority review status granted **based on condition c) shall be cancelled during the duration of product application evaluation, in the event that a same/ similar first generic/biosimilar product or first locally manufactured generic/biosimilar product has been approved for registration.* 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.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
2.	**SECTION A: GENERAL OVERVIEW** **GENERAL CONDITIONS FOR REGISTRATION OF DRUG PRODUCTS UNDER THE CONTROL OF DRUGS AND COSMETICS REGULATIONS 1984**	**Addition** of the following statement (highlighted in red) : 6.5 INDICATIONS, SPECIAL CONDITIONS The registered product shall only be indicated for use as approved by the Authority. The importation, manufacture, sale and supply of the registered product shall comply with all other specific conditions imposed by the Authority. PRH may exclude any indication (s) protected by patents or exclusivities.	**4th April 2019**

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>3.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following substance and safety information/ statements as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>NORADRENALINE
(Please refer Attachment 1)</td></tr></table></td><td>15 April 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>4.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following substance and safety information/ statements as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>RETINOID (ORAL)

(Please refer Attachment 2)</td></tr></table></td><td>15 April 2019</td></tr>
</table>

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
5.	**SECTION B: PRODUCT REGISTRATION PROCESS** **8.1 PRE-SUBMISSION OF APPLICATION**	**Addition** of the following statement (highlighted in red); information on conditional registration and registration via abbreviated and verification review. Please refer Attachment 3	**27 March 2019**

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>6.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following safety information/ statements on the adverse effects;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td><u>MONTELUKAST</u>
(Please refer Attachment 4)</td></tr></table></td><td>1 May 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>7.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following safety information/ statements as below;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>FLUOROQUINOLONE
(Please refer Attachment 5)</td></tr></table></td><td>1 May 2019</td></tr>
</table>

Attachment 1

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

NORADRENALINE

The following statements shall be included in the package insert for products containing noradrenaline;

Package Insert

a) Adverse Effects/Undesirable Effects:

Cardiac disorders
Frequency 'not known': stress cardiomyopathy

Directive No. 5 Year 2019. Ref. BPFK/PPP/07/25 (5) Jld 3 *Direktif Untuk Semua Produk Yang Mengandungi Noradrenaline: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Stress Cardiomyopathy*

Attachment 2

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

RETINOID (ORAL)

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing retinoid (oral);

Package Insert

a) Warnings and Precautions:

Psychiatric symptoms

Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration.

*An additional statement should also be included in the package insert of oral isotretinoin: Suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Talk to your doctor before taking [product name] If you have ever had any kind of mental health problems. This includes depression, aggressive tendencies or mood changes.

*An additional statement should also be included in the RiMUP of oral isotretinoin: It also includes suicidal thoughts.

Mental health problems

Your mood may be affected while taking [product name]. You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that you are taking this medicine. They may notice these changes and help you quickly identify any problems that you need to talk to your doctor about.

Reference : Directive No. 6 Year 2019. Ref. BPFK/PPP/07/25 (6) Jld 3 *Direktif Untuk Semua Produk Yang Mengandungi Retinoid (Oral): Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Neuropsychiatric Disorders*

Attachment 3

8.1.2 METHOD OF EVALUATION

Method of evaluation for registration of a product is divided into four (4) types, which are:

a) **Full Evaluation**;

b) Full Evaluation (conditional registration)

- Applies to new registration applications for New Drug Products and Biologics
- At the point of submission, the product must be registered in at least one Drug Control Authority (DCA) reference agencies
- A conditional registration does not apply to additional indications submitted post-registration
- Once a product has been granted a full registration that is not subjected to any specific conditions, the full registration approval cannot be reverted into a conditional registration approval. However, the approval of additional indication with less than comprehensive clinical data may be considered on case-to-case basis
- A conditional registration is valid for two years. Thereafter, the conditional registration may be renewed 2 times (with the possibility of 2 extensions of 2 years each)
- Please refer to the **Guidelines On Conditional Registration For New Chemical Entities And Biologics** for further details

c) Full Evaluation via abbreviated and verification review;

- Applies to New Drug Products and Biologics including biosimilars
- Abbreviated Review applies to a product that has been evaluated and approved by one (1) reference drug regulatory agency
- Verification Review applies to a product that has been evaluated and approved by two (2) reference drug regulatory agencies
- For details, please refer to **Guidelines on facilitated registration pathway: abbreviated and verification review**. The guideline provides information on the eligibility criteria, procedures and requirements for submitting application to register a product via abbreviated or verification review. The implementation of the guideline was on 1 April 2019 as stated in the Directive No.7 Year 2019. Ref BPFK/PPP/07/25(7) Jld 3: Direktif Untuk Melaksanakan Guidelines On Facilitated Registration Pathway: Abbreviated And Verification Review.

d) Abridged Evaluation

Attachment 4

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

MONTELUKAST

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing montelukast;

Package Insert

a) Adverse Effects/Undesirable Effects:

Postmarketing Experience:

Blood and lymphatic system disorders : thrombocytopenia

Psychiatric disorders:

obsessive-compulsive symptoms

Consumer Medication Information Leaflet (RiMUP)

a) Side Effects:

Tell your healthcare provider right away if you notice any of the following behavior and mood-related changes:

- Obsessive-compulsive symptoms

Reference :
Directive *(31)dlm.bpfk/ppp/07/25 ;* *Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 6 Year 2015 : Direktif Untuk Semua Produk Yang Mengandungi Montelukast : Pengemaskinian Sisip Bungkusan Dengan Maklumat Kesan Advers Berkaitan Thrombocytopenia*

Directive No. 8 Year 2019 Ref. BPFK/PPP/07/25 (8). *Direktif Untuk Semua Produk Yang Mengandungi Montelukast: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Obsessive-Compulsive Symptoms*

Attachment 5

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

FLUOROQUINOLONE (ORAL AND INJECTION ONLY)

The following statement shall be included in the package inserts of products containing fluoroquinolones:

WARNING AND PRECAUTION

Exacerbation of myasthenia gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with flouroquinolones use in persons with myasthenia gravis. Avoid flouroquinolones in patients with known history of myasthenia gravis

ADVERSE REACTIONS/SIDE EFFECTS

Exacerbation of myasthenia gravis

Post Marketing Experience

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing fluoroquinolone (oral and injection only);

Package Insert

a) Warnings and Precautions:

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Before you start to use it:

- Tell your healthcare providers if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).
- Tell your healthcare providers if you have experienced a previous episode of aortic dissection (a tear in the aorta wall).
- Tell your healthcare providers if you have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet´s disease, high blood pressure, or known atherosclerosis).

b) While you are using it:

Things to be careful of:

- If you feel sudden, severe pain in your abdomen, chest or back, go immediately to the emergency department.

Reference:

Circular Bil (20) dlm BPFK/PPP/01/03 Jld 1: *Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Exacerbation of Myasthenia Gravis dalam Sisip Bungkusan Semua Produk Antibiotik dalam Kumpulan Fluoroquinolones*

Directive No.9 Year 2016 . Ref : BPFK/PPP/07/25 (9). *Direktif Untuk Semua Produk Yang Mengandungi Fluoroquinolone (Sediaan Oral Dan Injeksi Sahaja): Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (Rimup) Dengan Maklumat Keselamatan Berkaitan Risiko Aortic Aneurysm Dan Aortic Dissection*

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JULY 2019

(June 2019 Updates)

*** Please note that this monthly list of updates will only be updated in the full version of DRGD in July 2019 revision. However, the effective dates are as stated below in the respective column.**

<table>
<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>1.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following substance and safety information/ statements as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS
(Please refer Attachment 1)</td></tr></table></td><td>30 May 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>2.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td>Amendment of the safety information/ statements as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>FLUOROQUINOLONE

(Please refer Attachment 2)</td></tr></table></td><td>15 April 2019</td></tr>
</table>

Attachment 1

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS The following statements shall be included in the Consumer Medication Information Leaflet (RiMUP) for products containing Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors : **Consumer Medication Information Leaflet (RiMUP)** 'Seek immediate medical attention when symptoms such as nausea, vomiting, decreased appetite, abdominal pain, excessive thirst, difficulty in breathing, confusion, unusual fatigue or sleepiness, frequent urination and fruity-smelling breath occur'.

Attachment 2

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

FLUOROQUINOLONE (ALL DOSAGE FORM)

The following statement shall be included in the package inserts :

~~**FLUOROQUINOLONE (ORAL AND INJECTION ONLY)**~~

~~The following statement shall be included in the package inserts of products containing fluoroquinolones:~~

Package Inserts

WARNING AND PRECAUTION

Exacerbation of myasthenia gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with flouroquinolones use in persons with myasthenia gravis. Avoid flouroquinolones in patients with known history of myasthenia gravis

ADVERSE REACTIONS/SIDE EFFECTS

Exacerbation of myasthenia gravis

Post Marketing Experience

FLUOROQUINOLONE (ORAL AND INJECTION ONLY)

i) The following statement shall be included in the package inserts :

~~The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing fluoroquinolone (oral and injection only);~~

Package Insert

a) Warnings and Precautions:

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

ii) The following statements shall be included in the Consumer Medication Information Leaflet (RiMUP) for products containing fluoroquinolone (oral and injection only);

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Before you start to use it:

Tell your healthcare providers if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).

Tell your healthcare providers if you have experienced a previous episode of aortic dissection (a tear in the aorta wall).

Tell your healthcare providers if you have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet´s disease, high blood pressure, or known atherosclerosis).

b) While you are using it:

Things to be careful of:

· If you feel sudden, severe pain in your abdomen, chest or back, go immediately to the emergency department.

Reference:

Circular Bil (20) dlm BPFK/PPP/01/03 Jld 1: *Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Exacerbation of Myasthenia Gravis dalam Sisip Bungkusan Semua Produk Antibiotik dalam Kumpulan Fluoroquinolones*

Directive No.9 Year 2016 . Ref : BPFK/PPP/07/25 (9). *Direktif Untuk Semua Produk Yang Mengandungi Fluoroquinolone (Sediaan Oral Dan Injeksi Sahaja): Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (Rimup) Dengan Maklumat Keselamatan Berkaitan Risiko Aortic Aneurysm Dan Aortic Dissection*

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JULY 2019

(July 2019 Updates)

*** Please note that this monthly list of updates will only be updated in the full version of DRGD in July 2019 revision. However, the effective dates are as stated below in the respective column.**

<table>
<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>1.</td><td>APPENDIX 8 :
LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES

8.3.2
List of Restricted Colouring Agents</td><td><u>Addition</u> of the following colouring agents in the List of Restricted Colouring Agents as below :

8.3.2 List of Restricted Colouring Agents
The following colouring agents are ALLOWED in preparations as stated in the parentheses:
<table><tr><th>NO.</th><th>COLOURING AGENTS</th><th>COLOUR INDEX NUMBER (CI)</th></tr><tr><td>10.</td><td>Mica coated with titanium dioxide and/or iron oxide (internal use only)

• for solid dosage form, not more than 3% of the preparation (in the case where the preparation was made using iron oxides, the preparation shall not contain more than 55% iron oxides)</td><td></td></tr></table></td><td>31 July 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>2.</td><td>SECTION A: GENERAL OVERVIEW

5. TYPES OF APPLICATION

5.1 REGISTRATION OF PRODUCTS

5.1.3 REGISTRATION OF STARTER PACK/ PATIENT INITIATION PACK</td><td><u>Addition</u> of the statement dose adjustment pack (to apply same policy as Starter Pack/ Patient Initiation Pack)

5.1.3 REGISTRATION OF STARTER PACK/ PATIENT INITIATION PACK/ DOSE ADJUSTMENT PACK

a) Starter pack/patient initiation pack/dose adjustment pack may consist of:
i) Combination of products with different strengths which are packed together in one packaging such as blister or calendar pack.
ii) Combination of more than one pre-filled pen containing different strengths of preparation in one packaging.
iii) Must be registered under the same product owner and PRH.

e) Labelling requirement specifically for starter pack /patient initiation/ dose adjustment pack is shown in Table V:
<table><tr><th>No.</th><th>Outer Label</th><th>Immediate Label</th></tr><tr><td>1.</td><td>Statement of starter pack/patient initiation pack/dose adjustment pack

Individual name for each products</td><td>Individual name for each products</td></tr></table></td><td>31 July 2019</td></tr>
</table>

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	DETAILS	
		Note: *These labelling requirements for a starter pack/ patient initiation pack/ dose adjustment shall as well be subjected to other labelling requirements as stated in Appendix 9.1: Label (mock-up) for Immediate Container, Outer Carton and Proposed Package Insert)*	

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>3.</td><td>16.5
APPLICATION FOR A CONVENIENT PACK</td><td>i) Additional information on differentiation from Combination Pack (Combo Pack) and Starter Pack/ Patient Initiation Pack/ Dose Adjustment Pack:

<u>Table XX:</u>
<table><tr><th>No.</th><th>Particulars</th><th>Convenient Pack</th><th>Combination Pack

(Combo Pack)</th><th>Starter Pack/ Patient Initiation Pack/ Dose Adjustment Pack</th></tr><tr><td>1.</td><td>New registration number (MAL No.) to be assigned upon approval</td><td>No</td><td>Yes</td><td>No</td></tr></table></td><td>31 July 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>4.</td><td>APPENDIX 9 :
LABELLING REQUIREMENTS

9.2 :
SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the safety information/ statements (highlighted in red) as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>FLUOROQUINOLONES
(Please refer Attachment 1)</td></tr></table></td><td>1 August 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>5.</td><td>APPENDIX 9 :
LABELLING REQUIREMENTS

9.2 :
SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the following substance and safety information/ statements as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>HYDROCHLOROTHIAZIDE
(Please refer Attachment 2)</td></tr></table></td><td>1 August 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>6.</td><td>APPENDIX 9 :
LABELLING REQUIREMENTS

9.2 :
SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the safety information/ statements (highlighted in red) as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>TOPIRAMATE
(Please refer Attachment 3)</td></tr></table></td><td>1 August 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>7.</td><td>APPENDIX 9 :
LABELLING REQUIREMENTS

9.2 :
SPECIFIC LABELLING REQUIREMENTS</td><td>Addition of the safety information/ statements (highlighted in red) as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>LAMOTRIGINE
(Please refer Attachment 4)</td></tr></table></td><td>1 August 2019</td></tr>
</table>

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	DETAILS	
8.	**16.4 NEW/ ADDITIONAL INDICATION**	**Addition** of the following sentence: “An application to add a new indication that is deemed not feasible for submission to DCA’s reference agencies can be considered for evaluation at NPRA on a case-by-case basis.” Please refer Attachment 5.	**31 July 2019**

Attachment 1

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

FLUOROQUINOLONE (ALL DOSAGE FORM)

The following statement shall be included in the package inserts :

WARNING AND PRECAUTION

Exacerbation of myasthenia gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with flouroquinolones use in persons with myasthenia gravis. Avoid flouroquinolones in patients with known history of myasthenia gravis

ADVERSE REACTIONS/SIDE EFFECTS

Exacerbation of myasthenia gravis

Post Marketing Experience

FLUOROQUINOLONE (SYSTEMIC FORMULATIONS INCLUDING ORAL AND INJECTION DOSAGE FORMS)

i) The following statement shall be included in the **package inserts** :

Package Insert

a) **Indication:**

(i) The following statement should be included:

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

(ii) The following indication(s), if relevant, should be deleted:

- Acute bronchitis
- Laryngitis
- Pharyngitis-tonsillitis
- Prophylaxis of infectious gastroenteritis / traveller's diarrhoea
- Selective decontamination of gastrointestinal tract in patients with compromised immune system
- Vaginal infections

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

- Acute bacterial rhinosinusitis*
- Acute exacerbation of chronic obstructive pulmonary disease including chronic bronchitis*
- Nosocomial pneumonia / Hospital-acquired pneumonia*

- Acute otitis media*
- External otitis*
- Endocarditis*
- Infection of cerebrospinal fluid*
- Meningitis*
- Septicaemia*
- Uncomplicated acute cystitis / uncomplicated cystitis*
- Prevention of exacerbations in women with recurring urinary tract infections*
- Prevention of infection in surgical procedures in the urogenital system*,#
- Pre-operative preparations for chronic cholesteatomatous otitis and chronic otitis spreading to bone*

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

*<Product name> should be only used :

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

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

a) Warnings and Precautions:

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

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

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. [INN] should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids*. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with [INN] should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

*[For systemically administered levofloxacin-containing products, the listing of risk factors should additionally include: "in patients receiving daily doses of 1000 mg levofloxacin".]

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with [INN] should be advised to inform their doctor and pharmacist prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section Adverse Effects/Undesirable Effects).

b) Adverse Effects/Undesirable Effects:

Musculoskeletal and connective tissue disorders*
Nervous system disorders*
General disorders and administrative site conditions*
Psychiatric disorders*
Eye disorders*
Ear and labyrinth disorders*

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see section Warnings and Precautions).

ii)The following statements shall be included in the **Consumer Medication Information Leaflet (RiMUP)** :

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Before you start to use it:

- Tell your healthcare providers if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).
- Tell your healthcare providers if you have experienced a previous episode of aortic dissection (a tear in the aorta wall).
- Tell your healthcare providers if you have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet´s disease, high blood pressure, or known atherosclerosis).
- You should not take fluoroquinolone antibacterial medicines, including <product name>, if you have experienced any serious adverse reaction in the past when taking a fluoroquinolone (see section Things to be careful of and Side effects). In this situation, you should inform your healthcare providers as soon as possible.

b) While you are using it:

Things to be careful of:

If you feel sudden, severe pain in your abdomen, chest or back, go immediately to the emergency department.

Prolonged, disabling and potentially irreversible serious side effects
Fluoroquinolone antibacterial medicines, including <product name>, have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible.

Stop taking your fluoroquinolone antibiotic and contact your healthcare providers immediately if you have the following signs of a side effect:

- Tendon pain or swelling, often beginning in the ankle or calf. If this happens, rest the painful area until you can see your healthcare providers.
- Pain in your joints or swelling in your shoulder, arms, or legs.
- Abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in your body, especially in the legs or arms, or difficulty walking.
- Severe tiredness, depressed mood, anxiety, problems with your memory, or severe problems sleeping.
- Changes in your vision, taste, smell, or hearing.

Tell your healthcare providers if you have had one of the above effects during or shortly after taking a fluoroquinolone – this means you should avoid them in the future. You and your healthcare providers will decide on continuing the treatment considering also an antibiotic from another class.

Tendinitis and tendon rupture

Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping of <product name> therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking <product name>, contact your healthcare providers and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

Peripheral neuropathy

You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking <product name> and inform your healthcare providers immediately in order to prevent the development of potentially irreversible condition.

c) Side Effects:

Fluoroquinolones have been reported to cause serious side effects involving tendons, muscles, joints, and the nerves – in a small proportion of patients, these side effects caused long-lasting or permanent disability (see section Before you start to use it and Things to be careful of).

References:

Circular Bil (20) dlm BPFK/PPP/01/03 Jld 1: *Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Exacerbation of Myasthenia Gravis dalam Sisip Bungkusan Semua Produk Antibiotik dalam Kumpulan Fluoroquinolones*

Directive No.9 Year 2019. Ref: BPFK/PPP/07/25 (9). *Direktif Untuk Semua Produk Yang Mengandungi Antibiotik Kumpulan Fluoroquinolone (Sediaan Oral Dan Injeksi Sahaja): Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Aortic Aneurysm Dan Aortic Dissection*

Directive No.12 Year 2019. Ref: BPFK/PPP/07/25 (12). *Direktif Untuk Semua Produk Yang Mengandungi Fluoroquinolone (Sediaan Oral Dan Injeksi): Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berikut : a) Membatalkan dan Menghadkan Indikasi Antibiotik Kumpulan Fluoroquinolone b) Amaran Berkaitan Disabling and Potentially Permanent Side Effects (tendinitis, tendon rupture, peripheral neuropathy & central nervous system/ neuropsychiatric effects)*

Attachment 2

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

HYDROCHLOROTHIAZIDE

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing hydrochlorothiazide;

Package Insert

a) Warnings and Precautions:

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

b) Adverse Effects/Undesirable Effects:

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

c) Pharmacodynamic:

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for

both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg).

Consumer Medication Information Leaflet (RiMUP)

a) Before you start to use it:

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

b) Side Effects:

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

Directive No.11 Year 2019. Ref: BPFK/PPP/07/25 (11). *Direktif Untuk Semua Produk Yang Mengandungi Hydrochlorothiazide Termasuk kombinasi : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Non-Melanoma Skin Cancer*

Attachment 3

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

TOPIRAMATE

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing topiramate;

Package Insert

a) Special Warnings And Precautions For Use

Visual field defects

Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible following topiramate discontinuation, however some cases were not. In a large proportion of postmarketing case reports reversibility was unknown, but in cases where an outcome was reported, the majority were reversible. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.

b) **Warnings and Precautions:**

Chronic, untreated metabolic acidosis may increase the risk of nephrocalcinosis

c) **Adverse Effects/Undesirable Effects:**

Renal and urinary disorders
Very rare: Nephrocalcinosis

Consumer Medication Information Leaflet (RiMUP)

a) Side Effects:

There is a potential significant risk for metabolic acidosis that may have no symptoms and if left untreated may be associated with adverse effects on kidneys (e.g. kidney stone/ nephrocalcinosis).

Reference Circular : (22) BPFK/PPP/07/25. Directive No. 15 Year 2014 *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Amaran Berkaitan Risiko Gangguan Penglihatan*

Directive No.13 Year 2019. Ref : BPFK/PPP/07/25 (13). *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Nephrocalcinosis*

Attachment 4

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

LAMOTRIGINE

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing lamotrigine;

Package Insert

a) Warnings and Precautions:

Hemophagocytic lymphohistiocytosis (HLH) has occurred in patients taking lamotrigine (see section Adverse Effects/Undesirable Effects). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lympha-denopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation. Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be discontinued unless an alternative aetiology can be established.

Brugada-type ECG

A very rare association with Brugada-type ECG has been observed, although a causal relationship has not been established. Therefore, careful consideration should be given before using <product name> in patients with Brugada syndrome.

b) Adverse Effects/Undesirable Effects:

Post-marketing

Blood and lymphatic system disorders

Very rare: Hemophagocytic lymphohistiocytosis (see section Warnings and Precautions)

Consumer Medication Information Leaflet (RiMUP)

a) Before you use <product name>:

Before you start to use it

Talk to your healthcare providers before taking <product name>:

- If you have a condition called Brugada syndrome (a genetic disease that affects the heart)

b) Side Effects:

Hemophagocytic lymphohistiocytosis (HLH)

There have been reports of a rare but very serious immune system reaction, in patients taking lamotrigine.

- Contact your doctor or pharmacist immediately if you experience any of the following symptoms while taking lamotrigine: fever, rash, neurological symptoms (e.g. shaking or tremor, confusional state).

Reference :

Directive No. 3 Year 2019. Ref. BPFK/PPP/07/25 (3) Jld 3. *Direktif Untuk Semua Produk Yang Mengandungi Lamotrigine: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hemophagocytic Lymphohistiocytosis (HLH)*

Directive No. 14 Year 2019. Ref. BPFK/PPP/07/25 (14) Jld 3. *Direktif Untuk Semua Produk Yang Mengandungi Lamotrigine: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Brugada-Type ECG*

Attachment 5

16.4 NEW/ ADDITIONAL INDICATION

New/ additional indication is defined as an indication which is not initially approved for a registered pharmaceutical product. This shall include new therapeutic indication or indication for new age group, such as usage in children, and shall not include changing/ rephrasing of sentences.

There are two (2) types of evaluation process available for a new/ additional indication application:

16.4.1 FULL EVALUATION PROCESS

For new indication which has been registered in any one of the Authority's eight (8) reference countries (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan and Switzerland).

This application will require specialists' comments.

16.4.2 VERIFICATION PROCESS

For new indication which has been registered by any two reference country's authorities (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan, Switzerland and EMA).

Note: The approved new indication in these countries should be the same as that of the proposed new indication.

An application to add a new indication that is deemed not feasible for submission to DCA's reference agencies can be considered for evaluation at NPRA on a case-by-case basis.

Other supporting documents that are deemed necessary shall be submitted upon request to support the efficacy and safety of the proposed additional indication.

The supporting documents may include but not limited to the following:
a) Approval of Additional Indication(s) in country of origin;
b) Approval status in reference countries, its corresponding approval letter and approved Package Insert;
c) Approval Indication status in ASEAN Member States and its approved corresponding package insert;
d) Revised Package Insert;
e) World Wide Approval status;
f) Consumer Medication Information Leaflet (RiMUP);
g) Clinical Expert Reports;
h) Synopsis of Individual Studies;
i) Clinical Studies Report/ In-House Clinical Trials;
j) Published Clinical Papers;
k) Current Periodic Safety Update Report (PSUR).