There are eight (8) amendments for August 2020 DRGD Updates as below:

**Main Body of DRGD 3rd Edition**
1. Amendment of Section B, 10.3 Evaluation Timeline for Product Registration, Page 42
2. Amendment of Section C, Quality Control, Page 46

**Appendices of DRGD 3rd Edition**

**Appendix 20 : Specific Labelling Requirements**
3. Addition of new ingredient and safety information, No.141, Parenteral Nutrition Containing Amino Acids And/Or Lipids (Indicated For Use In Pediatric Population Aged Under 2 Years, Page 135
4. Amendment of existing ingredient and safety information, No.153, Propofol, Page 142
5. Amendment of existing ingredient and safety information, No.195, Topiramate, Page 189-190

**Appendix 32 : Change of Product Registration Holder**
6. Amendment of 1. Introduction, Page 1
7. Amendment of 2. Conditions, Page 2
8. Amendment of 5. Supporting Documents, Page 3
1. **Section B, 10.3 Evaluation Timeline for Product Registration on Page 42** is amended –
   
   (a) by inserting the words “Evaluation” before the words “Timeline for Product Registration” in the title.
   
   (b) by substituting the words “Duration (Inclusive screening process)” with the words “Evaluation Timeline” in the table.
   
   (c) by substituting the words “*Upon receipt of complete application.*” with the words “*Upon payment confirmation (Processing and Analysis Fee for Product Registration)*” below the table.

2. **The Section C : Quality Control on Page 46** is amended –
   
   (a) by substituting the words “Centre of Compliance & Quality Control” with the words “Centre of Product & Cosmetic Evaluation” at second paragraph.
   
   (b) by deleting the following paragraph after Para 2. E13 (b) under Documents to be submitted via online Quest system for finished product:

   “* For Biologics, all documents above mentioned except raw data.

   Documents to be submitted as hardcopy for finished product [applicable for Biologics]:
   1. Certificate of analysis for active drug substance (2 batches) and recent batches of finished product (local manufacturer 1 batch, overseas manufacturer 2 batches)
   2. Complete protocol of analysis for finished product (including preservatives and diluents, if any)

   **Note:**
   1. A cover letter consisting of the following information should be enclosed with every hard copy document submission:
      i) Name of product;
      ii) Reference Number/ Protocol Number;
      iii) Contact person (name/ email address/ telephone no.);
iv) Name and address of company.

2. Documents submitted should be well organized and indexed."

(c) by deleting the following paragraph after Para 2., S4.3:

“Documents to be submitted as CD [applicable for Active Pharmaceutical Ingredient, API]:
1. Certificate of analysis for active drug substance(s) (2 batches).
2. Complete protocol of analysis for drug substance(s).
3. Complete testing method for the AMV for drug substance(s).
4. Complete results for the AMV for drug substance(s) with all relevant validation parameters, including acceptance criteria and results.”

Amendment of Appendix 20: Specific Labelling Requirements


“141. PARENTERAL NUTRITION CONTAINING AMINO ACIDS AND/OR LIPIDS (INDICATED FOR USE IN PEDIATRIC POPULATION AGED UNDER 2 YEARS)

The following statements shall be included in the package insert of parenteral nutrition products containing amino acids and/or lipids (indicated for use in pediatric population aged under 2 years);

**Package Insert**

a) Dosage and Administration:
When used in neonates and children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (See Section Warnings and Precautions).

b) Warnings and Precautions:

Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, <product name> should be protected from ambient light until administration is completed (See Section Dosage and Administration).


(a) by inserting the following statement:

“c) ADVERSE EFFECTS/UNDESIRABLE EFFECTS:

Reproductive system and breast disorders:

Frequency “not known”: Priapism”

(a) by inserting the following information in c) Adverse Effects/Undesirable Effects under Package Insert

“Postmarketing data:
Eye disorders
Frequency "not known": Uveitis”

(b) by inserting the following information in a) Side Effects under Consumer Medication Information Leaflet (RiMUP)

“- sudden changes in your eyesight (e.g blurred vision)
- eye pain
- red eye”

Amendment of Appendix 32: Change of Product Registration Holder

6. Second paragraph under 1. Introduction on page 1 is amended –

(a) by substituting the statement “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” with the following statement:

‘Once NPRA deems the application is complete, the outcome of the change of PRH application shall be decided by the Drug Control Authority within forty five (45) working days.’
7. No. 9 under 2. Conditions on page 2 is amended –
   (a) by substituting the word “shall” with the word “may”

8. 5. Supporting Documents on page 3 is amended –
   (a) by deleting the words “letterhead of” after the words “The product owner name and address in” in 5.1 (i) (g)
   (b) by inserting the following item after 5.1 (i) (g):
       “h. The LOA must be submitted using the Product Owner’s official letterhead.”
There is one (1) amendment for September 2020 DRGD Updates as below:

Amendment of Appendix 21 : Special Conditions For Registration of A Particular Product or Group of Products on page 3.

This is in accordance with Directive No.17, 2020: Direktif Berkenaan Pindaan Syarat Pendaftaran Khas Bagi Produk Yang Mengandungi Oral Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit as decided in DCA Meeting No. 348. This directive takes effect on 10th September 2020.

The existing special conditions for no.2 ETRETINATE/ ACITRETIN and no.4 ISOTRETINOIN/ TRETINOIN are deleted and substituted with the following information:

7. RETINOIDS INDICATED FOR THE TREATMENT OF SKIN DISEASES (ORAL)
   a) The product registration holder shall ensure that the product shall only be sold or supplied to, and prescribed by:
      i. Dermatologists registered in the National Specialist Register; or
      ii. Dermatologists serving in any government health facilities.

   b) The product registration holder shall submit a proper record containing the following information to the Authority upon request.
      i. Name of product;
      ii. Product registration number;
      iii. Date & quantity of product manufactured/ imported and supplied; and
      iv. Name, address & contact number of purchaser (prescriber).

   c) The prescriber shall keep and maintain proper patient records for audit purpose, if any.


September 2020 DRGD Updates
There are five (5) amendments for November 2020 DRGD Updates as below:

**Main Body of DRGD 3rd Edition**
1. Amendment of Section B, 14. Guideline for the Submission of Product Samples for Laboratory Testing, Page 47
2. Flowchart under Section B: Product Registration Process, Page 24

**Appendices of DRGD 3rd Edition**
3. Amendment of Table I, Page 11 and Page 13

**Appendix 7 : Guideline on Registration of Natural Products**
4. Amendment of 2. General Requirements for Registration of Natural Products, 2.7 Quality Control, Page 54 and 57

**Appendix 9 : Fees**

(a) by substituting the whole paragraph under the title 14.Guideline for the Submission of Product Samples for Laboratory Testing as below:

“The submission of sample for laboratory testing is as part of the registration process. This guideline consists of the general and specific requirements for the submission of samples to the Centre of Compliance & Quality Control for laboratory testing. The general requirements define the condition of the samples to be submitted whereas the specific requirements illustrate the additional details needed according to the category of product.

The applicant is given a period of 14 working days from the date of screening approval to send samples for laboratory testing. If the samples are not submitted within the specified time frame, the application will be rejected.

The applicants shall comply with these requirements and failure to meet any of these requirements may cause rejection of the samples.

11.1 GENERAL REQUIREMENTS

a) After the screening has been approved, applicants must make appointment with the Laboratory Services Unit for the submission of registration samples for laboratory testing.

b) Requirements for samples:

i) A cover letter consisting of the following information should enclosed with every sample submission:

- Name and reference no of product;
- Name and address of holder;
- Name, email address and contact number of authorized person;

ii) Samples submitted must be in their original packaging & labeling.
iii) Samples submitted must be from the same manufacturing premise as stated in the application for registration.

iv) Samples submitted must have an expiry date of least one (1) year from the date of submission and must be from the same batch number.

c) For imported products, applicants are required to submit the original import permit together with the samples for laboratory testing. The import permit will be issued by the Centre of Product & Cosmetic Evaluation for natural product and Centre of Compliance & Quality Control for pharmaceutical products. The applicant should ensure that the import permit is endorsed by the enforcement officer at the entry point.

11.2 SPECIFIC REQUIREMENTS

11.2.1 NATURAL PRODUCTS

a) Quantity of samples submitted must be:
   i. a minimum of 6 separate containers of all dosage forms with total contents of not less than 200 g or 200 mL;
      OR
   ii. a minimum of 60 pieces of plasters or patches with total of not less than 200g.

b) Centre of Compliance & Quality Control will conduct testing for Heavy Metals, Microbial Contamination Test, Disintegration Test, Uniformity Of Weight and screening for adulteration for the samples submitted.

c) The result of the tested sample is final and there is no provision for appeal."
with the new paragraph as below:

“14.1 Natural Products

a) In accordance with Directive No. 8 2020, BPFK/PPP/07/25 (8) Jld.4. *Direktif Penerimaan Keputusan Pengujian Pra-Pendaftaran Produk Semulajadi dari Makmal Swasta yang Telah Diiktiraf oleh Bahagian Regulatori Farmasi Negara (NPRA) dan Makmal Kawalan Kualiti Pengilang Tempatan*, starting from 1st December 2020, the applicant is no longer required to submit samples of natural product for laboratory testing to NPRA.

b) The PRH shall submit a Certificate of Analysis (CoA) for the purpose of product registration evaluation.

c) For further details regarding submission of the CoA, refer to Appendix 7: Guideline on Registration of Natural Products, 2.7.7 Certificate of Analysis (Finished Product).”

2. The flowchart under Section B: Product Registration Process on Page 24 is amended –

(a) by deleting the box “**Sample testing**” after the box Submission of Registration Application and Screening Process

3. Amendment of Appendix 2: Medical Device-Drug-Cosmetic Interphase (MDDCI) and Combination Products, Table I: Medical Device-Drug-Cosmetic Interphase (MDDCI) Product Classification Decision

The product No.16 *In Vivo Diagnostic Agents* on page 11 is amended –

(a) by inserting new information under *Intended Purpose/ Indication And Mode of Action (MOA), Category, and Custodian Agency* as follows:
### INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)

<table>
<thead>
<tr>
<th></th>
<th>CATEGORY</th>
<th>CUSTODIAN AGENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Topical/ intraocular/ intravitreal ophthalmic staining agents/ dyes for diagnostic purpose, enhance visualisation during ophthalmic procedures and/or contact lens fitting; e.g. fluorescein ophthalmic strips, trypan blue, brilliant blue, methylene blue.</td>
<td>MEDICAL DEVICE</td>
<td>MDA</td>
</tr>
</tbody>
</table>

(b) by inserting the words “other than No.16.a.” after the words “b. For diagnostic purposes”.

(c) by deleting the following paragraph after – NMR enhancing agents:

“- Ophthalmic diagnostic agents, e.g. staining agent such as fluorescent ophthalmic strips for diagnostic purposes”

**The product No.19 Medicinal Gases, on page 13** is amended –

(a) by substituting the following information in a. and b. as below:

<table>
<thead>
<tr>
<th></th>
<th>CATEGORY</th>
<th>CUSTODIAN AGENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. To be used in anaesthesia and inhalation therapy, including their primary containers.</td>
<td>DRUG</td>
<td>NPRA</td>
</tr>
<tr>
<td>b. For in-vivo diagnostic purposes including lung function tests.</td>
<td>DRUG</td>
<td>NPRA</td>
</tr>
</tbody>
</table>
(November 2020 Updates)

With the following information:

<table>
<thead>
<tr>
<th>Intended Purpose/Indication and Mode of Action (MOA)</th>
<th>Category</th>
<th>Custodian Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Gases or gas mixtures which mode of action is achieved primarily based on pharmacological, immunological or metabolic action in/on the body, such as gases for hypoxia (oxygen gas) and anaesthetic (nitrous oxide gas)</td>
<td>Drug</td>
<td>NPRA</td>
</tr>
<tr>
<td>b. Gases or gas mixtures which mode of action is achieved primarily by physical in nature and not achieved primarily based on pharmacological, immunological or metabolic action in/on the body, such as gases for insufflation of the abdominal cavity for laparoscopy and gases for removal of warts (e.g. liquid nitrogen)</td>
<td>Medical Device</td>
<td>MDA</td>
</tr>
</tbody>
</table>

4. Appendix 7: Guideline on Registration of Natural Products is amended –

(a) by deleting the first paragraph under 2.7 QUALITY CONTROL on page 54 as below:

“SAMPLE FOR TESTING

Sample for testing shall be submitted to the Center of Quality Control, NPRA within 14 working days from the screening approval date. Import permit will be issued after screening approval for imported products.

Applicant need to proceed for payment within 30 days once the sample is submitted.

Delay in submission / payment will result in rejection of the new product registration application.”
For further information, please refer Section C: Guideline for Submission of Product Samples for Laboratory Testing in the main DRGD."

(a) by substituting the whole information under 2.7.7 Certificate of Analysis (Finished Product) on page 57 as below:

“Starting from 1st January 2018, 2 batches of Certificate of Analysis (COA) for Finished Product must be submitted upon submission of new product registration for Natural Product / Health Supplement with the general claim.


with the following information :

“The PRH shall submit a Certificate of Analysis (CoA) for the purpose of product registration evaluation. The CoA submitted to NPRA must meet the following requirements:

i) CoA from panel laboratories (certified by NPRA) or local manufacturers’ laboratories
   - Only local laboratories can be accepted as a panel laboratory
   - Refer to NPRA website for the list of panel laboratories
   - Local manufacturers are allowed to issue CoA for their own products only

ii) CoA for one (1) batch of local or imported product to be submitted during product evaluation with NPRA’s product reference number from Quest 3+ system.

iii) CoA from multiple laboratories for different tests may be accepted, provided that the same batch of the products is submitted to the laboratories

November 2020 Updates
iv) The following compulsory testing parameters shall be stated in the CoA:

<table>
<thead>
<tr>
<th>Testing parameters</th>
<th>Panel laboratories/manufacturers’ laboratories</th>
<th>Other laboratories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organoleptic</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>Disintegration</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>Uniformity of weight</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>Microbial Contamination Test</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>Heavy Metal Contamination</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>Lovastatin (product containing Red Yeast Rice; Monascus purpureus)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Microcystin (product containing Aphanizomenon flosaquae)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Assay (for all standardize compounds claimed on label)</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

v) For imported products, applicants are required to submit CoA from panel laboratories. Import permit issued by the Centre of Product & Cosmetic Evaluation is required to bring in samples for the purpose of laboratory testing. The applicant shall ensure that the import permit is endorsed by the enforcement officer at the entry point.

5. The timeline in 6. Charges For Product Classification under Appendix 9 : Fees on Page 6 is amended –

(a) by substituting the words “7-14 working days” with the words “14 working days”. 
There are two (2) amendments for December 2020 DRGD Updates as below:

1. **Amendment of Appendix 4 : Guideline on Registration of Biologics**

   The 1.1 *Definitions* on page 4 is amended -

   (a) by inserting the following information after the paragraph *For details, please refer to Guidance Document and Guidelines for Registration of Cell and Gene Therapy (CGTPs)*. This document provides information for manufacturers, applicants, healthcare professionals and the public on legal arrangements in Malaysia for the registration of CGTPs. The implementation of the guideline will be compulsory on 1 January 2021 as stated in the Directive No. 6 Year 2017:

   “Please also refer to Directive No.19/2020 regarding the details of mechanism for registration and enforcement of CGTPs in stages.

   References:

2. **Amendment of Appendix 14 : Evaluation Routes**

   Part 2) *Full Evaluation (Conditional Registration)* in Appendix 14 on page 1 is amended -

   (a) by deleting the following information in point no.3 before the word *However*:

   “When a product has been granted full registration that is not subjected to any specific condition, the full registration approval shall not be reverted into a conditional registration approval.”
(b) by inserting new paragraph in point no.6:

“For medicinal products or vaccines to be used during disaster, the guideline must be read in conjunction with Guidance and Requirements on Conditional Registration of Pharmaceutical Products During Disaster. The validity of conditional registration is one year. Thereafter, the conditional registration may be renewed two (2) times (with the possibility of 2 extension of 1 year each).

References:

LIST OF UPDATES FOR
DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, JANUARY 2021
(January 2021 Updates)

There are eight (8) amendments for January 2021 DRGD Updates as below:

Appendices of DRGD 3rd Edition

Appendix 20 : Specific Labelling Requirements
1. Addition of new ingredient and safety information, No.2, Abiraterone, Page 11
2. Addition of new ingredient and safety information, No.48, Clozapine, Page 45-47
3. Amendment of existing ingredient and safety information, No.68, Efavirenz, Page 66-67
4. Amendment of existing ingredient and safety information, No.112, Mesalazine, Page 108-109
5. Amendment of existing ingredient and safety information, No.135, Ondansetron, Page 126-128
6. Addition of new ingredient and safety information, No.137, Oseltamivir, Page 132-133
7. Amendment of existing ingredient and safety information, No.184, Sulfasalazine, Page 181-182

Appendix 13 : Designation and Registration of Orphan Medicines
8. Addition of new Appendix
Amendment of Appendix 20: Specific Labelling Requirements

1. **Addition of new ingredient**
   2. **Abiraterone and safety information on page 11** as follows in accordance with Directive No.2, 2020: Direktif Untuk Semua Produk Yang Mengandungi Abiraterone: Pengemaskinian Sisip Bungkus dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hypoglycaemia Akibat Interaksi Ubat as decided in DCA Meeting No. 352, which takes effect on 1st February 2021 –

   **“2. ABIRATERONE”**

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

**Package Insert**

**a) Warnings and Precautions**

**Hypoglycaemia**

Cases of hypoglycaemia have been reported when [product name] was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide; therefore, blood sugar should be measured frequently in patients with diabetes.

**b) Interactions:**

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1000mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide.
Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Taking other medicines

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is important because [product name] may increase the effects of a number of medicines including some medicines for diabetes. Your doctor may want to change the dose of these medicines."


“48. CLOZAPINE

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

Package Insert

a) Contraindications

Paralytic ileus
b) Warnings and Precautions

Clozapine exerts anticholinergic activity, which may produce undesirable effect throughout the body. Probably on account of its anticholinergic properties, [product name] has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, paralytic ileus, megacolon and intestinal infarction/ischaemia. On rare occasions these cases have proved fatal. Careful monitoring during treatment with [product name] to identify early, the onset of constipation, followed by effective management of constipation are recommended to prevent complications.

c) Adverse Effects/ Undesirable Effects:

Gastrointestinal disorders: (very rare) intestinal obstruction, ileus, faecal impaction

Post-marketing: megacolon*, intestinal infarction/ischaemia*, intestinal necrosis*, intestinal ulceration*, intestinal perforation*, colitis

( *These adverse drug reactions were sometimes fatal)

d) Interactions

Due to the possibility of additive effects, caution is essential when substances possessing anticholinergic effects are given concomitantly with [product name].

Consumer Medication Information Leaflet (RiMUP)

a) When you must not use it:

Do not take [product name] if you suffer or have ever suffered from severe constipation, obstruction of the bowel or any other condition which has affected your large bowel.
b) Taking other medicines:

Tell your doctor or pharmacist if you are taking or have recently taken medicines which cause constipation (such as anticholinergic, which are used to relieve stomach cramps, spasms and travel sickness).

c) While you are using [product name]:

Tell your doctor or pharmacist if you have experienced constipation, abdominal pain, abdominal tenderness, fever, bloating and/or bloody diarrhea. Your doctor will need to examine you.

d) Side effects:

Abdominal pain, cramping, swollen abdomen, vomiting, constipation and failure to pass gas which may be signs and symptoms of bowel obstruction.”

3. The specific labelling requirements for existing ingredient no. 68. Efavirenz on page 66 to 67 is amended in accordance with Directive No.4, 2021: Direktif Untuk Semua Produk Yang Mengandungi Efavirenz (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Late Onset Neurotoxicity as decided in DCA Meeting No. 352, which takes effect on 1st February 2021 –

(a) by inserting the following information in a) Warnings and Precautions under Package Insert
“Nervous System Symptoms:
Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms, which are associated with increased efavirenz levels despite standard dosing of [product name]. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of [product name] is warranted.”

(b) by inserting the following information under Package Insert

“d) Adverse Effects/ Undesirable Effects:
Postmarketing experiences: encephalopathy”

(c) by inserting the following information under Consumer Medication Information Leaflet (RiMUP)

“b) Side effects:
Some nervous system symptoms [e.g. confusion, slow thoughts and physical movement and delusions (false beliefs) or hallucinations (seeing or hearing things that others do not see or hear)] may occur months to years after beginning [product name] therapy. Always notify your doctor or pharmacist if you have these symptoms or any side effects while taking [product name].”
4. **The specific labelling requirements for existing ingredient no.112 Mesalazine on page 108 to 109** is amended in accordance with Directive No.1, 2021: *Direktif Untuk Semua Produk Yang Mengandungi Mesalazine Dan Sulfasalazine: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Nephrolithiasis* as decided in DCA Meeting No. 352, which takes effect on 1st February 2021 –

(a) **by inserting** the following information in *a) Warnings and Precautions under Package Insert*

   “Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment.”

(b) **by inserting** the following information in *b) Adverse Effects/ Undesirable Effects under Package Insert*

   “Renal and urinary disorders
   Frequency ‘not known’: Nephrolithiasis”

(c) **by inserting** the following information under *Consumer Medication Information Leaflet (RiMUP)*

   “a) **Before you use [product name]:**

   Before you start to use it

   - Kidney stones may develop with the use of [product name]. Symptoms may include pain in the sides of the abdomen and blood in the urine. Take care to drink a sufficient amount of liquid during treatment with [product name].”

(d) **by inserting** the following information in *b) Side Effects under Consumer Medication Information Leaflet (RiMUP)*

   “Kidney stones and associated pain”
5. **The specific labelling requirements for existing ingredient no. 135 Ondansetron on page 126 to 128** is amended in accordance with Directive No.5, 2021: *Direktif Untuk Semua Produk Yang Mengandungi Ondansetron: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Kecacatan Kelahiran (Birth Defects) Susulan Penggunaan Ketika Hamil* as decided in DCA Meeting No. 352, which takes effect on 1st February 2021 –

(a) by inserting the following information under *Package Insert*

“**b) Pregnancy and Lactation:**

**Pregnancy**

The use of ondansetron in pregnancy is not recommended.

In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformations, the epidemiological studies showed conflicting results.

Three epidemiological studies in the US assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in offspring born to mothers exposed to ondansetron during the first trimester of pregnancy.

- One cohort study with 88,467 pregnancies exposed to ondansetron showed an increased risk of oral clefts (3 additional cases per 10,000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03-1.48)) without an apparent increase in risk of cardiac malformations. A separately published subgroup analysis of 23,877 pregnancies exposed to intravenous ondansetron did not find an increased risk of either oral clefts or cardiac malformations.
- One case-control study using population-based birth defect registries with 23,200 cases across two datasets showed an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study.
- The second cohort study with 3,733 pregnancies exposed to ondansetron found an increased risk of ventricular septal defect, adjusted RR 1.7 (95%CI 1.0-2.9), but no statistically significant increase in risk of cardiac malformations.
Reproductive studies in rats and rabbits did not show evidence of harm to the fetus.

Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with [product name].

Females of reproductive potential should be advised that it is possible that [product name] can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) when using [product name] during the treatment and for two days after stopping treatment with [product name]."

(b) by inserting the following information

“Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

[Product name] is not recommended for use during pregnancy.

- Tell your doctor if you are pregnant or planning to become pregnant. [Product name] may harm your unborn baby.
- If you do become pregnant during treatment with [product name], tell your doctor.

If you are a woman of childbearing age, your doctor will check if you are pregnant and perform a pregnancy test if necessary before starting treatment with [product name]. If you may become pregnant, you should use effective birth control during treatment and for at least 2 days after stopping [product name]. Ask your doctor about options of effective birth control.”
6. **Addition of new ingredient no. 137. Oseltamivir and safety information on page 132 to 133** as follows in accordance with Directive No.6, 2020: Direktif Untuk Semua Produk Yang Mengandungi Oseltamivir: Pengemaskinan Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Thrombocytopenia as decided in DCA Meeting No. 352, which takes effect on 1st February 2021 –

“**137. OSELTAMIVIR**

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

**Package Insert**

**a) Adverse Effects/Undesirable Effects:**

Blood and lymphatic system disorders  
Frequency ‘Rare’ : Thrombocytopenia

**Consumer Medication Information Leaflet (RiMUP)**

**a) Side effects:**

Rare side effects:

- thrombocytopenia (low platelet count)”
7. The specific labelling requirements for existing ingredient no. 184. Sulfasalazine on page 181 to 182 is amended in accordance with Directive No.1, 2021: Direktif Untuk Semua Produk Yang Mengandungi Mesalazine Dan Sulfasalazine: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Nephrolithiasis as decided in DCA Meeting No. 352, which takes effect on 1st February 2021 –

   (a) by inserting the following information under Package Insert

   “c) Adverse Effects/Undesirable Effects:

       Renal and urinary disorders

       Frequency 'not known': Nephrolithiasis*

       * Adverse effects identified post-marketing.”

   (b) by inserting the following information under Consumer Medication Information Leaflet (RiMUP)

   “b) Side effects:

       - kidney stones and associated pain”

Addition of new appendix, Appendix 13 : Designation and Registration of Orphan Medicines.

8. The new appendix as in Attachment A.