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JANUARY 2024
(November 2023 Updates)

There are five (5) amendments for the November 2023 DRGD Updates as follows:

Main Body of DRGD Third Edition, Sixth Revision October 2023

Section B: Product Registration Process

1. Addition of information, 7.9.1 Shrink wrapping, Page 40
2. Addition of information, 7.9 Packaging, Page 40

Appendix of DRGD Third Edition, Sixth Revision October 2023

Appendix 6: Guideline on Registration of Health Supplements

3. Addition of information, Table 7, 5.28 Prohibited Visual/ Graphics on Label, Page 29

Appendix 7: Guideline on Registration of Natural Products

4. Addition of information, Table 11, 2.6.4 Prohibited Visual/ Graphics/ Statement on Packaging Materials (Label, Box, Package Insert or Consumer Medication Information Leaflet), Page 49

Appendix 19A: Prohibited Visual / Graphics / Statements on Label

5. Addition of information, Table, Page 1

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Amendment of Section B: Product Registration Process

1. Amendment of information in 7.9.1 Shrink wrapping on Page 40 by –

   (a) adding the statement, "g) Use of shrink wrapping in promotional pack – refer to 7.9.2 Promotional Pack."

2. Amendment of information in 7.9 Packaging on Page 40 by –

   (a) adding the following paragraph,

"7.9.2 Promotional Pack

a) Promotional packs use material such as a sleeve band or a sticker that is attached to the primary packaging (only if outer packaging is not available), outer packaging or shrink wrapping of finished product.

b) Promotional packs are allowed provided that the following conditions are met:

(i) This only applies to registered Health Supplements, Traditional Medicines and Non-scheduled Poisons (OTC) products (category N, T and X).
(ii) The promotional pack is intended for temporary use only.
(iii) There are no qualitative or quantitative changes to the approved primary packaging and the outer packaging.
(iv) The promotional packaging shall not obscure the label content on the immediate container or outer carton of the product.
(v) The shrink wrap used as packaging must be completely transparent and does not contain any wordings/ graphics except for (vi).
(vi) Examples of promotional wordings allowed on the sleeve band or sticker are Value Pack, Free XX Pack Size, Buy 1 Free 1, Bonus Pack, Hari Raya, Chinese New Year, Deepavali, etc. Such wordings used on promotional pack must fulfil requirement for (iv).

(vii) Promotional wording deemed to be superlative is not allowed."

Amendment of Appendix 6: Guideline on Registration of Health Supplements

3. Amendment of information in Table 7 in 5.28 Prohibited Visual/ Graphics on Label on Page 29 by –

(a) adding the phrase, "for immediate container, outer carton, package insert or Consumer Medication Information Leaflet." to "Such statements are prohibited on labels" in the Note for No. 1 Marketing Strategy.

Amendment of Appendix 7: Guideline on Registration of Natural Products

4. Amendment of information in Table 11 in 2.6.4 Prohibited Visual/ Graphics/ Statement on Packaging Materials (Label, Box, Package Insert or Consumer Medication Information Leaflet) on Page 49 by –

(a) adding the phrase, "for immediate container, outer carton, package insert or Consumer Medication Information Leaflet." to "Such statements are prohibited on labels" in the Notes for No. 1 Marketing Strategy.

Amendment of Appendix 19A: Prohibited Visual / Graphics / Statements on Label

5. Amendment of information in Table on Page 1 by –

(a) adding the statement, "Such statements are prohibited on labels for immediate container, outer carton, package insert or Consumer Medication Information Leaflet." in the Note for No. 1 Marketing Strategy.

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There is one (1) amendment for the December 2023 DRGD Updates as follows:

Appendix of DRGD Third Edition, Sixth Revision October 2023

Appendix 14: Evaluation Routes

1. Amendment of information, 3) Full Evaluation via Abbreviated and Verification Review, Page 2

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Amendment of Appendix 14: Evaluation Routes

1. Amendment of information in 3) Full Evaluation via Abbreviated and Verification Review on Page 2 by –

(a) substituting the following paragraph,

"3) **Full Evaluation via Abbreviated and Verification Review**

- This applies to New Drug Products and Biologics, including biosimilars.
- Abbreviated Review applies to a product that has been evaluated and approved by one (1) DCA reference agency.
- Verification Review applies to a product that has been evaluated and approved by two (2) DCA reference agencies.
- Refer to *Guidelines on Facilitated Registration Pathway: Abbreviated and Verification Review*. (Effective 1 April 2019)

Reference: Directive No. 7, 2019, *BPFK/PPP/07/25 (7) Jld.3*: *Direktif Untuk Melaksanakan* Guidelines on Facilitated Registration Pathway: Abbreviated and Verification Review (27 March 2019)"

with the following paragraph,

"3) **Full Evaluation via Facilitated Registration Pathway (Abbreviated and Verification Review)**

- This applies to New Drug Products, Generic Medicines, and Biologics, including cell and gene therapy products (CGTPs).
- Abbreviated Review involves a limited independent assessment of specific parts of the dossier, or submission for suitability of use under local conditions and regulatory requirements, while relying on prior assessment and inspection outcomes from a reference authority or trusted institution to inform the local decision. This applies to a product that has been evaluated and approved by:

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i) WHO Collaborative Registration Procedure (CRP)
   a) Products authorised by WHO Stringent Regulatory Authorities (SRAs)/ WHO Listed Authorities (WLA)
   b) WHO prequalified medicines and vaccines

ii) Products approved by any of the following regulatory agencies*
   a) European Medicines Agency (EMA)
   b) Health Canada
   c) Pharmaceuticals and Medical Devices Agency (PMDA), Japan
   d) Swissmedic, Switzerland
   e) Therapeutic Goods Administration (TGA), Australia
   f) United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA)
   g) United States Food and Drug Administration (US FDA)

   *at least one agency approval or more

- Verification Review is a review of the sameness of the product dossier to ensure that the medical product is the same as the one that has been assessed by ASEAN Joint Assessment. This applies to a product that has been evaluated and approved by ASEAN Joint Assessment (JA) procedure.
- Refer to Guideline for Facilitated Registration Pathway (FRP), Revision 1, 2023 (Effective 1 January 2024)

Reference: Directive No. 13, 2023, *NPRA.600-1/9/13 (31)Jld.1*: *Direktif Berkenaan Pengemaskinian dan Pelaksanaan Guideline for Facilitated Registration Pathway (FRP), Revision 1, 2023* (16 November 2023)"

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There are four (4) amendments for the January 2024 DRGD Updates as follows:

Appendix of DRGD Third Edition, Sixth Revision October 2023

Appendix 20: Specific Labelling Requirements

1. Amendment of existing safety information, No. 127, Metformin, Page 126
2. Addition of new ingredient and safety information, No. 104, Imatinib, Page 104
3. Addition of new ingredient and safety information, No. 184, Rivastigmine, Page 179

Appendix 21: Special Conditions for Registration of a Particular Product or Group of Products

4. Amendment of information, no. 5, Midazolam, Page 2

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Amendment of Appendix 20: Specific Labelling Requirements

1. **The specific labelling requirements for existing ingredient, No. 127, Metformin on page 126** is amended as follows in accordance with Directive No. 1, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Metformin (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Risiko Kekurangan Vitamin B12 (Vitamin B12 Deficiency)* as decided in DCA Meeting No. 392, which takes effect on 1 February 2024 –

"**127. METFORMIN**

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

Package Insert

a) Warnings & Precautions:

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

b) Adverse Effects/ Undesirable Effects:

Metabolism and nutrition disorders

Common: Vitamin B12 decrease/deficiency

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a) Side effects:

Common side effects (may affect up to 1 in 10 people):

- Decreased or low vitamin B12 levels in the blood (symptoms may include extreme tiredness (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin). Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.

Reference: Directive No. 1, 2024. *NPRA.600-1/9/13 (32)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Metformin (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Risiko Kekurangan Vitamin B12 (Vitamin B12 Deficiency)"*

2. **Addition of new ingredient 104. Imatinib and safety information on page 104** as follows in accordance with Directive No. 2, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Imatinib: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Thrombotic Microangiopathy (TMA)* as decided in DCA Meeting No. 392, which takes effect on 1 February 2024 –

"**IMATINIB**

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

Package Insert

a) Warnings & Precautions:

Thrombotic microangiopathy

BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA), including individual case reports for Imatinib. If laboratory or clinical findings associated with TMA occur in a patient receiving Imatinib, treatment should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If antiADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with Imatinib should not be resumed.

b) Adverse Effects/ Undesirable Effects:

Blood and lymphatic system disorders

Frequency 'rare': thrombotic microangiopathy

Consumer Medication Information Leaflet (RiMUP)

a) Before you start to use [product name]:

Before taking [product name], tell your doctor:

- if you experience bruising, bleeding, fever, fatigue and confusion when taking [product name]. This may be a sign of damage to blood vessels known as thrombotic microangiopathy (TMA).

b) Side effects:

Rare:

- blood clots in small blood vessels (thrombotic microangiopathy).

Reference: Directive No. 2, 2024. *NPRA.600-1/9/13 (33)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Imatinib: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Thrombotic Microangiopathy (TMA)"*

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3. **Addition of new ingredient 184. Rivastigmine and safety information on page 179** as follows in accordance with Directive No. 3, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Rivastigmine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko QT Prolongation dan Torsade de Pointes (TdP)* as decided in DCA Meeting No. 392, which takes effect on 1 February 2024 –

"**RIVASTIGMINE**

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

Package Insert

a) Warnings & Precautions:

QT Prolongation and torsade de pointes

Electrocardiogram QT prolongation may occur in patients treated with certain cholinesterase inhibitor products including rivastigmine. Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, hypokalemia or hypomagnesemia, personal or family history of QT prolongation, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. Clinical monitoring may also be required.

b) Interactions:

Medicinal products known to prolong the QT interval

Caution is advised when rivastigmine is used in combination with other medicinal products known to prolong the QT interval (including but not limited to quinidine, amiodarone, pimozide, halofantrine, cisapride, citalopram, mizolastin, moxifloxacin, erythromycin). Clinical monitoring may also be required.

Consumer Medication Information Leaflet (RiMUP)

a) Before you start to use [product name]:

Tell the doctor if you have, or have ever had heart conditions such as irregular or slow heartbeat, QTc prolongation, a family history of QTc prolongation, torsade de pointes, or have low potassium or magnesium. Your doctor may need to monitor you more closely while you are on this medicine.

b) Taking other medicines:

Caution when [product name] is taken together with medicinal product know to prolong the heart's electrical system (QT interval) [including but not limited to quinidine (medicine used to treat irregular heartbeat), amiodarone (medicine used to treat serious /fatal irregular heartbeat), pimozide (medicine works on central nervous system), halofantrine (antimalaria medicine), cisapride (medicine used to treat symptoms of night-time heartburn), citalopram (medicine used to treat depression), mizolastin (antihistamine medicine), medicine used to treat bacterial infection such as moxifloxacin, erythromycin]. Your doctor may also monitor your clinical condition as needed.

Reference: Directive No. 3, 2024. ***NPRA.600-1/9/13 (34)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Rivastigmine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko QT Prolongation dan Torsade de Pointes (TdP)"*

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Amendment of Appendix 21: Special Conditions for Registration of a Particular Product or Group of Products

4. Amendment of information for no. 5, Midazolam on Page 2 by –

(a) inserting the phrase, “in tablet form” after “products containing midazolam”.