LIST OF UPDATES FOR

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(August 2025 Updates)

There are 14 amendments for the August 2025 DRGD Updates as follows:

Appendix of DRGD Third Edition, Tenth Revision July 2025

Appendix 18: List of Permitted, Prohibited and Restricted Substances

1. Amendment of information, 2.2 List of Restricted Excipients, Page 9
2. Amendment of information, 3.2 List of Restricted Colouring Agents, Page 14

Appendix 19: General Labelling Requirements

3. Amendment of information, Table 1, Page 2

Appendix 20: Specific Labelling Requirements

4. Addition of new ingredient and safety information, No. 222, TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 (EXCIPIENT), Page 220
5. Amendment of existing safety information, No. 81, DOXYCYCLINE, Page 81
6. Amendment of existing safety information, No. 48, CHLOROQUINE AND HYDROXYCHLOROQUINE, Page 48
7. Amendment of existing safety information, No. 121, LAMOTRIGINE, Page 120
8. Addition of new ingredient and safety information, No. 132, MEDROXYPROGESTERONE ACETATE, Page 131
9. Amendment of existing safety information, No. 213, SODIUM VALPROATE, Page 203

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Appendix 22: Educational Materials

10. Amendment of information, Table of Contents, Page 1
11. Amendment of information, 2.1 Patient Card, Page 8
12. Amendment of information, 2.2 Annual Risk Acknowledgement Form, Page 9
13. Amendment of information, 2.3 Guide for Healthcare Professionals, Page 11
14. Addition of information, 2.5 Guide for Male Patients, Page 14

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Amendment of Appendix 18 of List of Permitted, Prohibited and Restricted Substances

1. Amendment of information in 2.2 List of Restricted Excipients on page 9 by –

   (a) replacing the restriction, “Not allowed in the following preparations: Oral; Rectal; Vaginal or Nasal Preparations” with “Limited to not more than 7.5mg/kg body weight/day” for 1. a) Tartrazine (CI= 19140, FD & C Yellow No.5, E102).

2. Amendment of information in 3.2 List of Restricted Colouring Agents on page 14 by –

   (a) replacing “(external use only)” with “Limited to not more than 7.5mg/kg body weight/day” for 29. Tartrazine/ FD & C Yellow No. 5/MA Yellow A-2/ Aluminic Lake.

Amendment of Appendix 19: General Labelling Requirements

3. Amendment of information in Table 1 on page 2 by –

   (a) adding the following new parameter to “The following information in Table 1 below shall be present on the label of a product at the outer carton, immediate container or blister/ strips:”:

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
24.	Presence of tartrazine (if any) E.g. This product contains Tartrazine/ FD & C Yellow No. 5/ MA Yellow A-2/ Aluminic Lake	✓	✓	NA

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Amendment of Appendix 20: Specific Labelling Requirements

4. **Addition of new ingredient and safety information, No. 222, TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 (EXCIPIENT) on page 220** as follows in accordance with Directive No. 13, 2025: *Direktif berkenaan penetapan had harian dan pengemaskinian maklumat keselamatan bagi tartrazine* as decided in DCA Meeting No. 411, which takes effect on 18 August 2025 –

   Refer to **Attachment 1**

   Reference: Directive No. 13, 2025. *NPRA.600-1/9/13 (60)Jld.1* *Direktif berkenaan penetapan had harian dan pengemaskinian maklumat keselamatan bagi tartrazine*

5. **Amendment of existing safety information, No. 81, DOXYCYCLINE on page 81** as follows in accordance with Directive No. 18, 2025: *Direktif untuk semua produk yang mengandungi doxycycline: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko Fixed Eruption (FE)/ Fixed Drug Eruption (FDE)* as decided in DCA Meeting No. 411, which takes effect on 1 September 2025 –

   Refer to **Attachment 2**

   Reference: Directive No. 18, 2025. *NPRA.600-1/9/13 (65)Jld.1* *Direktif untuk semua produk yang mengandungi doxycycline : Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko Fixed Eruption (FE)/ Fixed Drug Eruption (FDE)*

6. **Amendment of existing safety information, No. 48, CHLOROQUINE AND HYDROXYCHLOROQUINE on Page 48** as follows in accordance with Directive No. 17, 2025: *Direktif untuk semua produk yang mengandungi hydroxychloroquine: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko major congenital malformation di kalangan kanak-kanak yang terdedah kepada hydroxychloroquine dalam kandungan, drug-induced phospholipidosis dan aggravation of myasthenia gravis (MG)* as decided in DCA Meeting No. 411, which takes effect on 1 September 2025 –

Refer to **Attachment 3**

Reference: Directive No. 17, 2025. *NPRA.600-1/9/13 (64)Jld.1* *Direktif untuk semua produk yang mengandungi hydroxychloroquine: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko major congenital malformation di kalangan kanak-kanak yang terdedah kepada hydroxychloroquine dalam kandungan, drug-induced phospholipidosis dan aggravation of myasthenia gravis (MG)*

7. **Amendment of existing safety information, No. 121, LAMOTRIGINE on Page 120** as follows in accordance with Directive No. 16, 2025: *Direktif untuk semua produk yang mengandungi Lamotrigine: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko Erythema Multiforme (EM)* as decided in DCA Meeting No. 411, which takes effect on 1 September 2025 –

   Refer to **Attachment 4**

   Reference: Directive No. 16, 2025. *NPRA.600-1/9/13 (63)Jld.1* *Direktif untuk semua produk yang mengandungi Lamotrigine : Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko Erythema Multiforme (EM)*

8. **Addition of new ingredient No. 132, MEDROXYPROGESTERONE ACETATE on page 131** as follows in accordance with Directive No. 14, 2025: *Direktif untuk semua produk yang mengandungi medroxyprogesterone acetate (MPA) bagi sediaan injeksi dan oral (dengan dos ≥100mg) : Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko meningioma* as decided in DCA Meeting No. 411, which takes effect on 1 September 2025 –

   Refer to **Attachment 5**

   Reference: Directive No. 14, 2025. *NPRA.600-1/9/13 (61)Jld.1* *Direktif untuk semua produk yang mengandungi medroxyprogesterone acetate (MPA) bagi sediaan injeksi dan oral (dengan dos ≥100mg) : Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko meningioma*

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9. **Amendment of existing safety information, No. 213, SODIUM VALPROATE on page 203** as follows in accordance with Directive No. 15, 2025: *Direktif Untuk Semua Produk Yang Mengandungi Valproate Termasuk Terbitannya (Sodium Valproate, Valproic Acid)* as decided in DCA Meeting No. 411, which takes effect on 1 September 2025 –

   Refer to **Attachment 6**

   Reference: Directive No. 15, 2025. *NPRA.600-1/9/13 (62)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Valproate Termasuk Terbitannya (Sodium Valproate, Valproic Acid)*

Amendment of Appendix 22: Educational Materials

10. Amendment of information in Table of Contents on page 1 by –

    (a) adding "2.5 Guide for Male Patients" to 2. Sodium Valproate.

    (b) adding "Directive No. 15, 2025, NPRA.600-1/9/13 (62)Jld.1: *Direktif Untuk Semua Produk Yang Mengandungi Valproate Termasuk Terbitannya (Sodium Valproate, Valproic Acid)* (18 August 2025)" to References.

11. Amendment of information, 2.1 Patient Card on page 8 by –

    (a) adding the following information:

Males (of reproductive potential) using valproate:

- There is a possible risk of movement and mental developmental disorders in children when valproate is taken by male patients in the 3 months before conception.
- Discuss this possible risk and the need for effective contraception with your doctor.
- Valproate is an effective medicine for epilepsy and bipolar disorder.
- Never stop taking valproate unless your doctor tells you to as your condition may become worse.
- If you are planning for a child, do not stop using valproate and contraception before you speak to your doctor.
- Ask your doctor for the patient guide.

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12. Amendment of information, 2.2 Annual Risk Acknowledgement Form on page 9 by –

    (a) adding **Attachment 7**

13. Amendment of information, 2.3 Guide for Healthcare Professionals on page 11 by –

    (a) adding **Attachment 8**

14. Addition of information, 2.5 Guide for Male Patients on page 14 by –

    (a) adding **Attachment 9**

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Attachment 1

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 (EXCIPIENT)*   The following statements shall be included in the package inserts and Consumer Medication Information Leaflet (RiMUP) of products containing TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 / Aluminic Lake: **Package Insert / Product label****   **a) Warnings and Precautions**   This preparation contains Tartrazine / FD & C Yellow No.5 / MA Yellow A-2 / Aluminic Lake that may cause allergic reactions in certain susceptible patients.   **Consumer Medication Information Leaflet (RiMUP)**   **a) Before you use (product name)**   Before you start to use it   (Product name) contains TARTRAZINE / FD & C YELLOW No.5 / MA Yellow A-2 / Aluminic Lake. This is a colouring agent, which may cause allergic reactions.   *This is not applicable to external use product   **In cases where a package insert and RiMUP are not available. For example; natural products, health supplements, or over-the-counter (OTC) products evaluated via abridge evaluation.

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Attachment 2

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
DOXYCYCLINE The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing doxycycline; **<u>Package Insert</u>** **a) Adverse Effects/ Undesirable Effects:** <u>Skin and subcutaneous tissue disorders:</u> Frequency 'rare': Fixed eruption **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side effects:** Round or oval patches of redness and swelling of the skin which reappear at the same site each time the medicine is taken (fixed eruption)

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Attachment 3

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
HYDROXYCHLOROQUINE The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing hydroxychloroquine; **<u>Package Insert</u>** **a) Warnings & Precautions:** <u>Drug Induced Phospholipidosis</u> Cases of hydroxychloroquine induced phospholipidosis have been reported during use of [product name] (see section Adverse Effects). Drug-induced phospholipidosis may occur in different organ systems such as cardiac, renal, or muscle. Monitoring for toxicity is advised. Discontinue [product name] if cardiac, renal, or muscle toxicity related to drug induced phospholipidosis is suspected or demonstrated by tissue biopsy. <u>Aggravation of Myasthenia Gravis</u> Aggravation of symptoms of myasthenia gravis (generalized weakness including shortness of breath, dysphagia, diplopia, ptosis etc.) have been reported in myasthenic patients receiving hydroxychloroquine therapy. Discontinue [product name] if aggravation of symptoms related to myasthenia gravis is suspected. **b) Pregnancy:** Data from a population-based cohort study including 2045 hydroxychloroquine exposed pregnancies suggests a small increase in the relative risk (RR) of congenital malformations associated with hydroxychloroquine exposure in the first trimester (n = 112 events). For a daily dose of ≥ 400 mg the RR was 1.33 (95% CI, 1.08 – 1.65). For a daily dose of < 400 mg the RR was 0.95 (95% CI, 0.60 – 1.50). **c) Adverse Effects/ Undesirable Effects:** <u>Metabolism and nutrition disorders</u> Frequency 'not known': phospholipidosis* *Cases of hydroxychloroquine induced phospholipidosis have been reported. Drug-induced phospholipidosis may occur in different organ systems such as cardiac, renal,

or muscle causing toxicity (see section Warnings and Precautions).

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

When you must not use it:

- [Product name] may be associated with a small increased risk of malformations and should not be used during pregnancy unless your doctor considers the benefits outweigh the risks.

Before you start to use it:

Take special care and check with your doctor if:

- You have or have had myasthenia (a disease with general muscle weakness including in some cases muscles used for breathing). You may notice aggravation of symptoms such as muscle weakness, difficulty in swallowing, double vision, drooping of the upper eyelid etc.
- Hydroxychloroquine may cause heart, kidney or muscle disorders. Please ask your doctor to inform you of signs and symptoms of drug induced phospholipidosis. Hydroxychloroquine may need to be stopped.

b) Side effects:

- Accumulation of a type of fat in tissues causing harm. The doctor may decide to stop the treatment with [product name].

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Attachment 4

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
LAMOTRIGINE The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing lamotrigine; **<u>Package Insert</u>** **a) Adverse Effects/ Undesirable Effects:** <u>Skin and subcutaneous tissue disorders</u> Frequency 'rare': erythema multiforme **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side effects:** • Skin rashes or redness, which may develop into severe skin reactions including red spots or patches that may look like a target or "bulls-eye" with a dark red centre surrounded by paler red rings (Erythema multiforme)

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Attachment 5

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

MEDROXYPROGESTERONE ACETATE

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing medroxyprogesterone acetate (all injectable and oral preparations with dosage ≥ 100mg);

Package Insert

a) Contraindication:

Patient with meningioma or history of meningioma (for non-oncological indications)

b) Warnings & Precautions:

Meningioma

Cases of meningioma (single and multiple) have been reported in patients treated with medroxyprogesterone acetate for a prolonged time (several years). Patients treated with medroxyprogesterone acetate should be monitored for signs and symptoms of meningioma in accordance with clinical practice.

In some cases, shrinkage of meningioma was observed after treatment discontinuation of depot medroxyprogesterone acetate. If a patient treated for a non-oncological indication is diagnosed with meningioma, medroxyprogesterone acetate must be stopped, as a precautionary measure.

If a patient treated for an oncological indication is diagnosed with meningioma, the need for further treatment with medroxyprogesterone acetate should be carefully considered on a case-by-case basis taking into account individual benefits and risks.

c) Adverse Effects/ Undesirable Effects:

Neoplasms benign, malignant & unspecified

Frequency (Unknown): meningioma

d) Pharmacodynamics:

Based on results from a French epidemiological case-control study, an association between medroxyprogesterone acetate and meningioma has been observed. This study was based on data from the French National health data system (SNDS –

Système National des Données de Santé) and included a population of 18,061 women who had intracranial surgery for meningioma and 90,305 women without meningioma. The exposure to medroxyprogesterone acetate 150 mg/3ml injectable was compared between women who had intracranial surgery for meningioma and women without meningioma. Analyses showed an excess risk of meningioma with the use of medroxyprogesterone acetate 150 mg/3 ml (9/18,061 (0.05%) v 11/90, 305 (0.01%), OR 5.55 (95%CI 2.27 to 13.56)). This excess risk seems to be driven primarily by prolonged use (≥3 years) of medroxyprogesterone acetate.

Consumer Medication Information Leaflet (RiMUP) (oral preparations with dosage ≥ 100mg only)

a) Before you use [product name]:

When you must not use it:

Do not use [product name], if you have meningioma or have ever been diagnosed with a meningioma (a usually benign tumour of the tissue layer surrounding the brain and spinal cord) unless you use [product name] for cancer.

Before you start to use it:

Meningioma

Use of medroxyprogesterone acetate has been linked to the development of a usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma). The risk increases especially when you use it for longer duration (several years). If you are diagnosed with meningioma, your doctor will reconsider your treatment with [product name]. If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

b) Side effects:

Usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma) with a frequency not known.

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Attachment 6

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

SODIUM VALPROATE

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing sodium valproate and related substances, including valproic acid;

Package Insert

a) Warnings & Precautions:

Use in male patients of reproductive potential

A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam (see Pregnancy). Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk. The prescribers should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment. The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.

The male patient should be advised:

- not to donate sperm during treatment and for 3 months after stopping the treatment,

- of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception,

- that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception.

The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use (Annual Risk Acknowledgement Form). Educational materials are available for healthcare professionals and male patients. A patient guide should be

provided to all men of reproductive potential using valproate

b) Reproduction:

Teratogenicity and developmental effects from female and male exposure

Risk to children of fathers treated with valproate

A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam. The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07).

Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see Warnings/Precautions)

Fertility

Valproate administration may also impair fertility in men (see Section Adverse Reactions). In the few cases in which valproate was switched/discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed.

c) Adverse Effects/ Undesirable Effects:

Reproductive system and breast disorders:

Rare: male infertility

d) Nonclinical Safety Data:

Reproductive and developmental toxicity

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits.

In published literature, behavioural abnormalities have been reported in first generation offspring of mice and rats after in utero exposure to clinically relevant doses/exposures of valproate. In mice, behavioural changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute in utero exposure of the first generation. The relevance of these findings for humans is unknown.

Impairment of fertility

In sub-chronic/ chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs. In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Relevance of the testicular findings to pediatric population is unknown.

Consumer Medication Information Leaflet (RiMUP)

a) While you are using it:

Important advice for male patients able to father a child

Potential risk related to taking valproate in the 3 months prior to conception

A study suggests that if you take valproate in the 3 months prior to conception, your child may have a higher risk for impaired mental and/or motor development compared to children born to fathers who used lamotrigine or levetiracetam, other medicines that can be used to treat your disease. In this study, around 5 children in 100 had such disorders when born from fathers treated with valproate, and around 3 children in 100 when born from fathers treated with the other medicines. There are no data on this potential risk to children fathered more than 3 months after stopping valproate treatment (the time needed for new sperm to be formed).

As a precautionary measure, your doctor will discuss with you

- The potential risk when fathering a child if you are treated with valproate,

- The need to use effective contraception (birth control) for you and your female partner

during the treatment and for 3 months after stopping valproate

-The need to consult your doctor to discuss alternative treatment options, as soon as you are planning to father a child and before discontinuing contraception (birth control),

- To not donate sperm during treatment and for 3 months after stopping treatment.

Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse. If your female partner becomes pregnant while you used valproate in the 3 months prior to conception, both of you should contact the doctor for counselling

You should get regular (at least annual) appointments with your doctor. During this visit your doctor will make sure you acknowledge the risk and precautions associated with valproate use. Make sure you read the patient guide that you will receive from your doctor.

b) Side effects:

- male infertility (may be reversible after dose reduction or discontinuation)

Attachment 7

Annual Risk Acknowledgment Form for male patients of reproductive potential treated with valproate (*Product Name*)

Read, complete and sign this form during a visit with the specialist: at treatment initiation and at the annual visit. This is to make sure that after discussion with their specialist, male patients or their caregiver acknowledged the potential risk and understood the precautions associated with valproate use.

Part A. To be completed and signed by the Specialist

Name of patient or caregiver: _____

I have discussed the following information with the above-named patient or caregiver:

The potential risk of neurodevelopmental disorders (NDDs) in children born to males treated with valproate in the 3 months prior to conception: • A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam. • The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07). • Due to study limitations, it is not possible to determine which of the studied NDDs subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. • The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.	☐
The need for regular (at least annual) review of the treatment and consideration of alternative therapeutic options.	☐
The need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment.	☐
That the patient should not donate sperm during treatment and for 3 months after stopping the treatment.	☐
The need for patient to consult his doctor to discuss alternative treatment options as soon as he is planning to father a child, and before discontinuing contraception.	☐
The need for patient and his female partner to contact their doctor for counselling in case a child was conceived while he used valproate within 3 months prior to conception.	☐
That the patient should not stop taking valproate without talking to their doctor, as the epilepsy or bipolar disorder could become worse.	☐
I have given the patient or caregiver a copy of the patient guide.	☐

Name of Specialist

Signature Date

Annual Risk Acknowledgment Form for male patients of reproductive potential treated with valproate (*Product Name*)

Read, complete and sign this form during a visit with your specialist: at treatment initiation and at the annual visit. This is to make sure that after discussion with your specialist, you or your caregiver acknowledged the potential risk and understood the precautions associated with valproate use.

Part B. To be completed and signed by the Patient or caregiver.

That I should visit a specialist regularly (at least annually) to review whether valproate treatment remains the best option for me	☐
The potential risk of taking valproate in male patients when planning to have a child: • A study suggests that if I take valproate in the 3 months prior to conception, my child may have a higher risk for impaired mental and/or motor development compared to children born to males who used lamotrigine or levetiracetam, other medicines that can be used to treat my disease. • In this study, around 5 children in 100 had such disorders when born from male patients treated with valproate, and around 3 children in 100 from male treated with the other medicines. • There are no data on this potential risk to children of male patients conceived more than 3 months after stopping valproate treatment (the time needed for new sperm to be formed).	☐
That I and my female partner should use effective contraception (birth control) while I am treated with valproate and for 3 months after stopping treatment.	☐
That I need to consult my doctor to discuss alternative treatment options, as soon as I plan for a child, and before discontinuing contraception (birth control).	☐
That I should not donate sperm during treatment with valproate and for 3 months after stopping treatment.	☐
The need for both me and my female partner to contact the doctor for counselling in case we conceived a child while I was using valproate in the 3 months prior to conception.	☐
That I should not stop my treatment without talking to my doctor. If I stop my treatment, my symptoms may become worse.	☐
I have received a copy of the patient guide	☐

Name of patient or caregiver Signature Date

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Attachment 8

GUIDE FOR HEALTHCARE PROFESSIONALS
RISK OF NEURODEVELOPMENTAL DISORDERS (NDDs) FOLLOWING USE OF SODIUM VALPROATE IN MALE PATIENTS OF REPRODUCTIVE POTENTIAL

Note: This guide is to inform you of important information and strengthened warnings related to this risk

BACKGROUND INFORMATION: SAFETY DATA

A retrospective observational study was conducted using data from multiple registry databases in Denmark, Sweden and Norway to investigate the risk of NDDs in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment, in the 3 months period prior to conception. The main outcome of interest was NDDs (composite endpoint including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, movement disorders) in offspring up to 11 years of age. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

1. Risk of Neurodevelopmental Disorders (NDDs)

- The meta-analysis of data from the 3 countries resulted in a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07) for NDDs in children from males treated with valproate monotherapy in the 3 months prior to conception compared to the composite lamotrigine/levetiracetam monotherapy group.
- The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group monotherapy versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group.
- Due to study limitations, it is not possible to determine which of the studied NDD subtypes(autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs.
- The risk to children born to male patients stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known

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Recommendations for valproate use in male patients of reproductive potential

- **The use of sodium valproate in male patients is initiated and supervised by a specialist experienced in treatment of epilepsy or bipolar disorder.**
- **Male patients should be informed about the potential risk of Neurodevelopmental Disorders (NDDs) and the need to consider effective contraception, including for a female partner, while using valproate and for 3 months after stopping the treatment;**
- **Treatment with valproate in male patients should be regularly reviewed by prescribers to evaluate whether valproate remains the most suitable treatment for the patient.**
- **For male patients planning to have a child, suitable alternative treatment options should be considered and discussed with the patient. Individual circumstances should be evaluated for each patient. It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar should be sought as appropriate.**
- **The male patients should be advised to not donate sperm during treatment and for at least 3 months after treatment discontinuation.**

COU

NSELLING POINT

- advise patient/ caregiver on the risk of neurodevelopmental disorders associated with children from men taking sodium valproate three (3) months prior to conception.
- advise patient and his female partner to use effective contraception without interruption throughout the entire duration of sodium valproate treatment and three (3) months after stopping the drug.
- Inform patient not to donate sperm during treatment and for three (3) months after stopping the treatment
- inform patient also about the risks of untreated seizure or bipolar disorder and advise patient not to stop treatment abruptly.
- ensure that patient/ caregiver acknowledges the potential risk and understands the precautions associated with sodium valproate using the annual risk acknowledgement form for males and receives the patient card and patient guide provided by the product registration holder of sodium valproate.

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(August 2025 Updates)

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8. Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* 2013 Mar; 12(3):244-52.
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Attachment 9
GUIDE FOR MALE PATIENTS
RISK OF NEURODEVELOPMENTAL DISORDERS (NDDs) FOLLOWING USE OF SODIUM VALPROATE IN MALE PATIENTS OF REPRODUCTIVE POTENTIAL

This guide contains key information about the potential risk of sodium valproate when used by male patients of reproductive potential in the three (3) months before conception of a child.
Ask your doctor or pharmacist if you have any questions.

INFORMATION ABOUT THE RISK:

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to males treated with valproate in the 3 months before conception. In this study, around 5 children in every 100 had such disorders when born to males treated with valproate, as compared to around 3 children in every 100 when born to males treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease).

However, the study has limitations and therefore it is not entirely clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. A wide range of movement and mental developmental disorders were investigated in the study. However, the study was not large enough to show which particular type of disorder children may be at risk of developing. For example, problems with your child's movement and mental development as they grow up may include :

- Movement problems
- Lower intelligence than other children of the same age
- Poor speech and language skills
- Autism or autistic spectrum problems
- Attention Deficit and/or Hyperactivity Disorder

What you must do if you are being prescribed sodium valproate:

- Use **effective contraception** (birth control) for you and your female partner during valproate use and for three (3) months after stopping valproate (the time needed for new sperm to be formed).
- Consult your doctor when you **are planning to conceive a child** and before stopping contraception.
- Ask your doctor of the possibility of **other treatments** that can be used to treat your disease, depending on your individual situation.
- **Do not donate sperm** when taking valproate and for three (3) months after stopping valproate treatment.
- **Talk to your doctor** if you are planning a child.
- If your **female partner becomes pregnant** while you used valproate in the three (3) months before conception and you have questions, **contact your doctor.**
- **Do not stop your treatment** without talking to your doctor. If you stop your treatment, your symptoms may become worse.
- Follow your **regular appointments** with your prescriber.
- Discuss with your doctor if you have any concerns and report any side effects.

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(September 2025 Updates)

There are three (3) amendments for the September 2025 DRGD Updates as follows:

Appendix of DRGD Third Edition, Tenth Revision July 2025

Appendix 4: Guideline on Registration of Biologics

1. Amendment of existing information, 1.1 Definitions, Page 4

Appendix 7C: Guideline on Natural Products With Therapeutic Claim

2. Amendment of existing information, 3.1 Therapeutic Claim, Page 3

Appendix 20: Specific Labelling Requirements

3. Addition of new ingredient and safety information, No. 102, Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists, Page 103

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(September 2025 Updates)

Amendment of Appendix 4: Guideline on Registration of Biologics

1. Amendment of existing information in 1.1 Definitions on page 4 by –

   (a) replacing "Guidance Document and Guidelines for Registration of Cell and Gene Therapy (CGTPs) in Malaysia**"** in the statement, **"**For details, please refer to Guidance Document and Guidelines for Registration of Cell and Gene Therapy (CGTPs) in Malaysia." with "Guidance Document and Guidelines for Registration of Cell and Gene Therapy (CGTPs) in Malaysia, Second Edition – September 2025"

   (b) replacing "iii) Good Tissue Practice Guideline, 2nd Edition, December 2015 " with "iii) *NPRA.600-1/9/12 (30) Pekeliling Berkenaan Pengemaskinian Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia (Second Edition)* (19 September 2025)" in References.

Amendment of Appendix 7C: Guideline on Natural Products With Therapeutic Claim

2. Amendment of existing information in 3.1 Therapeutic Claim on page 3 by –

   (a) replacing "Directive No. 9, 2016, *Bil. (40) dlm.BPFK/PPP/07/25 Keperluan* Good Laboratory Practice (GLP) *bagi Kajian Keselamatan Bukan Klinikal Untuk Tujuan Pendaftaran Produk* New Chemical Entity (NCE)*, Biologik dan Produk Herba Dengan Tuntutan Terapeutik Tinggi"* in the statement, "Non-clinical safety studies for therapeutic claims must be conducted in a facility which complies to Organisation for Economic Cooperation and Development (OECD) Good Laboratory Practice (GLP) requirement as mentioned in Directive No. 9, 2016, *Bil. (40) dlm.BPFK/PPP/07/25 Keperluan* Good Laboratory Practice (GLP) *bagi Kajian Keselamatan Bukan Klinikal Untuk Tujuan Pendaftaran Produk* New Chemical Entity (NCE)*, Biologik dan Produk Herba Dengan Tuntutan Terapeutik Tinggi"* with *"*Directive No. 20, 2025, ***NPRA.600-1/9/13 (67) Jld.1*** *Direktif Berkenaan Pengemaskinian Keperluan Amalan Makmal Baik (Good Laboratory Practice, GLP) dan Pelaksanaan Pemeriksaan GLP Study-Specific Ke Atas Fasiliti Kajian Luar Negara Bagi Kajian Keselamatan Bukan Klinikal Untuk Tujuan Pendaftaran Produk New Chemical Entity (NCE), Biologik dan Produk Semula Jadi Dengan Tuntutan Terapeutik."*

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Amendment of Appendix 20: Specific Labelling Requirements

3. **Addition of new ingredient No. 102, Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists and safety information on page 103** as follows in accordance with Directive No. 19, 2025: *Direktif Untuk Semua Produk Yang Mengandungi Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Aspiration dan Pneumonia Aspiration Semasa Anestesia Umum (General Anaesthesia) atau Sedasi Penuh (Deep Sedation)* as decided in DCA Meeting No. 412, which takes effect on 1 October 2025 –

"**GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISTS**

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists;

Package Insert

a) Warnings & Precautions:

Aspiration in association with general anaesthesia or deep sedation
Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying should be considered prior to performing procedures with general anaesthesia or deep sedation.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Before you start to use it:

If you know that you are due to have surgery where you will be under anaesthesia (sleeping), please tell your doctor that you are taking [product name].

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Reference: Directive No. 19, 2025. ***NPRA.600-1/9/13 (66)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Aspiration dan Pneumonia Aspiration Semasa Anestesia Umum (General Anaesthesia) atau Sedasi Penuh (Deep Sedation)"*

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(October 2025 Updates)

There are three (3) amendments for the October 2025 DRGD Updates as follows:

Main Body of DRGD Third Edition, Tenth Revision July 2025

Section B: Product Registration Process

1. Amendment of existing information, 7.12 Product Authentication, Page 44

Appendix of DRGD Third Edition, Tenth Revision July 2025

Appendix 20: Specific Labelling Requirements

2. Amendment of existing safety information, No. 13, Amiodarone, Page 21
3. Amendment of existing safety information, No. 16, Antidepressants, Page 22

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DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, ELEVENTH REVISION
JANUARY 2026
(October 2025 Updates)

Amendment of Section B: Product Registration Process

1. Amendment of existing information in 7.12 Product Authentication on page 44 by –

   (a) replacing "Bil. (17) dlm. BPFK/PPP/07/25 Jld. 3 Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 17 Tahun 2019: Penggunaan Label Keselamatan Baharu Dari Pembekal Yang Dilantik Oleh Kementerian Kesihatan Malaysia (KKM) (27 September 2019)" with "NPRA.600-1/9/13 (68) Jld. 1 Arahan Pengarah Perkhidmatan Farmasi Bilangan 21 Tahun 2025: Direktif Berkenaan Penggunaan Label Keselamatan Farmatag® Baharu daripada Syarikat Netsmart Sdn Bhd (7 October 2025)" in c) Circulars and directives pertaining to security label (hologram).

Amendment of Appendix 20: Specific Labelling Requirements

2. **Amendment of existing safety information, No. 13, Amiodarone on page 21** as follows in accordance with Directive No. 22, 2025: *Direktif untuk semua produk yang mengandungi amiodarone: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Penguna (RiMUP) dengan maklumat keselamatan berkaitan risiko primary graft dysfunction (PGD) selepas pemindahan jantung (heart transplantation)* as decided in DCA Meeting No. 413, which takes effect on 7 October 2025 –

"**AMIODARONE**

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

Package Insert

a) Warnings & Precautions:

Transplantation

In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of primary graft dysfunction (PGD).

PGD is a life-threatening complication of heart transplantation that presents as left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see section Adverse Effects). Severe PGD may be irreversible.

For patients who are on the heart transplant waiting list, consideration should be given to use an alternative antiarrhythmic drug as early as possible before transplant.

b) Adverse Effects/ Undesirable Effects:

Injury, poisoning and procedural complications

Frequency 'not known': Potentially fatal primary graft dysfunction post cardiac transplant (See section Warnings and Precautions)

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Before you start to use it:

If you are on a heart transplant waiting list, your doctor may change your treatment. This is because taking amiodarone before heart transplantation has shown an increased risk of a life-threatening complication (primary graft dysfunction) in which the transplanted heart stops working properly within the first 24 hours after surgery.

b) Side effects:

Frequency not known:

- Life-threatening complication after heart transplantation (primary graft dysfunction) in which the transplanted heart stops working properly

  Reference: Directive No. 22, 2025. ***NPRA.600-1/9/13 (69)Jld.1*** *Direktif untuk semua produk yang mengandungi amiodarone: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Penguna (RiMUP) dengan maklumat keselamatan berkaitan risiko primary graft dysfunction (PGD) selepas pemindahan jantung (heart transplantation)"*

3. **Amendment of existing safety information, No. 16, Antidepressants on page 22** as follows in accordance with Directive No. 23, 2025: *Direktif untuk semua produk yang mengandungi Selective Serotonin Reuptake Inhibitor (SSRI) dan Serotonin-Norepinephrine Reuptake Inhibitor (SNRI): Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko sexual dysfunction berterusan* as decided in DCA Meeting No. 413, which takes effect on 7 October 2025 –

"**CITALOPRAM, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VENLAFAXINE, DESVENLAFAXINE AND DULOXETINE**

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, desvenlafaxine and duloxetine;

Package Insert

a) Warnings & Precautions:

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

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Consumer Medication Information Leaflet (RiMUP)

a) While you are using it:

Medicines like [Product name] (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction. In some cases, these symptoms have continued after stopping treatment.

Reference: Directive No. 23, 2025. ***NPRA.600-1/9/13 (70)Jld.1*** *Direktif untuk semua produk yang mengandungi Selective Serotonin Reuptake Inhibitor (SSRI) dan Serotonin-Norepinephrine Reuptake Inhibitor (SNRI): Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko sexual dysfunction berterusan"*

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(December 2025 Updates)

There is one (1) amendments for the December 2025 DRGD Updates as follows:

Appendix of DRGD Third Edition, Tenth Revision July 2025

Appendix 7: Guideline on Registration of Natural Products

1. Addition of new information, Table 2: Botanicals (and botanical ingredients) containing scheduled poisons listed under the Poisons Act 1952, Page 11

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(December 2025 Updates)

Amendment of Appendix 7: Guideline on Registration of Natural Products

1. **Amendment of existing information in Table 2: Botanicals (and botanical ingredients) containing scheduled poisons listed under the Poisons Act 1952 on page 11** by –

   (a) <u>adding</u> the following item:

Genus	Species	Common / Local Name	Part of plant prohibited	Constituent of concern
Mucuna	*pruriens*	"*velvet bean*" or "*cowhage*"	*Whole plant*	*Levodopa*

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(January 2026 Updates)

There are nine (9) amendments for the January 2026 DRGD Updates as follows:

Main Body of DRGD Third Edition, Tenth Revision July 2025

Section E: Post-Registration Process

1. Amendment of Information, 20. Amendments to Particulars of a Registered Product, Page 64
2. Amendment of information, 20.4 New/ Additional Indication, Page 66

Appendix of DRGD Third Edition, Tenth Revision July 2025

Appendix 6: Guideline on Registration of Health Supplements

3. Amendment of information, Table 17: Allowable claims for specific active ingredients in HS products, Page 56

Appendix 7: Guideline on Registration of Natural Products

4. Amendment of information, 2.6.2 Specific Labelling Statements/ Warning & Precautions), Page 43
5. Amendment of information, 2.6.1 Statements to Be Stated on Product Label), Page 40

Appendix 20: Specific Labelling Requirements

6. Amendment of existing safety information, No. 55, CLINDAMYCIN, Page 55
7. Amendment of existing safety information, No. 62, CO-TRIMOXAZOLE (SULFAMETHOXAZOLE, TRIMETHOPRIM), Page 65
8. Addition of new ingredient and safety information, No. 127, LINEZOLID, Page 126
9. Addition of new ingredient and safety information, No. 166, PALBOCICLIB, Page 164

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Amendment of Section E: Post-Registration Process

1. Amendment of information in 20. Amendments to Particulars of a Registered Product on page 64 by –

   (a) adding the information in **Attachment 1**.

2. Amendment of information in 20.4 New/ Additional Indication on page 66 by –

   (a) substituting existing information with **Attachment 2**.

Amendment of Appendix 6: Guideline on Registration of Health Supplements

3. Amendment of information, Table 17: Allowable claims for specific active ingredients in HS products on page 56 by –

   (a) adding new functional claim, “Help support skin health” to Collagen Hydrolysate.

   (b) adding new functional claim, “supports bone health” to Manganese.

   (c) adding new functional claim, “supports energy metabolism” to Vitamin B3 (Niacin).

   (d) adding new functional claim, “supports energy metabolism” to Vitamin B5 (Panthothenic Acid).

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Amendment of Appendix 7: Guideline on Registration of Natural Products

4. Amendment of information, 2.6.2 Specific Labelling Statements/ Warning & Precautions) on page 43 by –

   (a) deleting the following item:

No.	Substance	Specific Cautionary Statement
4.	For pack size meant as samples, please state:	**Sample not for sale**

5. Amendment of information, 2.6.1 Statements to Be Stated on Product Label) on page 40 by –

   (a) adding the following information, "For pack size meant as samples, please state: 'Sample Not For Sale'"

Amendment of Appendix 20: Specific Labelling Requirements

6. **Amendment of existing safety information, No. 55, CLINDAMYCIN on page 55** as follows in accordance with Directive No. 4, 2026: *Direktif untuk semua produk yang mengandungi clindamycin dalam sediaan oral kapsul: Pengemaskinian sisip bungkusan dan RiMUP bagi memperkukuhkan maklumat keselamatan berkaitan risiko oesophagitis dan oesophageal ulcer* as decided in DCA Meeting No. 416, which takes effect on 15 January 2026 –

   Refer to **Attachment 3**

Reference: Directive No. 4, 2026. *NPRA.600-1/9/13 (75)Jld.1* *Direktif untuk semua produk yang mengandungi clindamycin dalam sediaan oral kapsul: Pengemaskinian sisip bungkusan dan RiMUP bagi memperkukuhkan maklumat keselamatan berkaitan risiko oesophagitis dan oesophageal ulcer*

7. **Amendment of existing safety information, No. 62, CO-TRIMOXAZOLE (SULFAMETHOXAZOLE, TRIMETHOPRIM) on page 65** as follows in accordance with Directive No. 5, 2026: *Direktif untuk semua produk yang mengandungi kombinasi sulfamethoxazole dan trimethoprim (cotrimoxazole): Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko circulatory shock* as decided in DCA Meeting No. 416, which takes effect on 15 January 2026 –

   Refer to **Attachment 4**

   Reference: Directive No. 5, 2026. *NPRA.600-1/9/13 (76)Jld.1* *Direktif untuk semua produk yang mengandungi kombinasi sulfamethoxazole dan trimethoprim (cotrimoxazole): Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko circulatory shock*

8. **Addition of new ingredient and safety information, No. 127, LINEZOLID on page 126** as follows in accordance with Directive No. 3, 2026: *Direktif untuk semua produk yang mengandungi linezolid: Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko rhabdomyolysis* as decided in DCA Meeting No. 416, which takes effect on 15 January 2026 –

   Refer to **Attachment 5**

   Reference: Directive No. 3, 2026. *NPRA.600-1/9/13 (74)Jld.1* *Direktif untuk semua produk yang mengandungi linezolid: Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko rhabdomyolysis*

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9. **Addition of new ingredient and safety information, No. 166, PALBOCICLIB on page 164** as follows in accordance with Directive No. 2, 2026: *Direktif untuk semua produk yang mengandungi palbociclib: Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko venous thromboembolism (VTE)* as decided in DCA Meeting No. 416, which takes effect on 15 January 2026 –

   Refer to **Attachment 6**

   Reference: Directive No. 2, 2026. *NPRA.600-1/9/13 (73)Jld.1* *Direktif untuk semua produk yang mengandungi palbociclib: Pengemaskinian sisip bungkusan dan RiMUP dengan maklumat keselamatan berkaitan risiko venous thromboembolism (VTE)*

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ATTACHMENT 1

DRGD July 2025	DRGD January 2026
20. AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT	**20. AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT**
Throughout the life cycle of a registered product, changes to improve product efficacy, quality and safety are likely to occur. Therefore, the applicant shall inform the Authority of any changes or amendments made to particulars of a registered product.	Throughout the life cycle of a registered product, changes to improve product efficacy, quality and safety are likely to occur. Therefore, the applicant shall inform the Authority of any changes or amendments made to particulars of a registered product.
20.1 Variation	**20.1 Variation**
a) Variation refers to the change of particulars of a registered product. No change of any particulars of a registered product [except for Minor Variation Notification (MiV-N)] shall be made without prior approval from NPRA.	a) Variation refers to the change of particulars of a registered product. No change of any particulars of a registered product [except for Minor Variation Notification (MiV-N)] shall be made without prior approval from NPRA.
b) All supporting documents shall be submitted in accordance with the specified conditions for each type of variation.	b) All supporting documents shall be submitted in accordance with the specified conditions for each type of variation.
c) Variation applications and processing fees shall be made according to specific product categories in the Malaysian Variation Guideline (MVG).	c) Variation applications and processing fees shall be made according to specific product categories in the Malaysian Variation Guideline (MVG).
d) If deemed necessary, NPRA reserves the right to request for additional supporting documents and variation approval letters from	d) If deemed necessary, NPRA reserves the right to request for additional supporting documents and variation approval letters from

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other regulatory bodies for all product categories.	other regulatory bodies for all product categories.
e) The registration of a product shall be reviewed for suspension or cancellation if changes that fall under Major Variation (MaV) and Minor Variation Prior Approval (MiV-PA) are implemented without prior approval of the Authority.	e) The registration of a product shall be reviewed for suspension or cancellation if changes that fall under Major Variation (MaV) and Minor Variation Prior Approval (MiV-PA) are implemented without prior approval of the Authority.
f) Variation application shall be submitted through the online QUEST system.	f) Variation application shall be submitted through the online QUEST system.
	g) Variation applications that have been approved by at least one of DCA's reference countries are eligible for submission via the Reliance pathway. Please refer to <u>Section 20.1.3</u> for further details.
20.1.1 Variation Application for Pharmaceutical Products	**20.1.1 Variation Application for Pharmaceutical Products**
Variation application for pharmaceutical products shall be done according to the Malaysian Variation Guideline (MVG).	Variation application for pharmaceutical products shall be done according to the Malaysian Variation Guideline (MVG).
References:	**References:**
i. *Bil. (2) dlm. BPFK/PPP/07/25*, *Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 3 Tahun 2013: Direktif Untuk*	i. *Bil. (2) dlm. BPFK/PPP/07/25*, *Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 3 Tahun 2013: Direktif Untuk*

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Melaksanakan Malaysian Variation Guideline (MVG) (29 April 2013) ii. *Bil (7) dlm. NPRA/PPPK/01/04*, *Pekeliling Berkenaan Pengemaskinian Garis Panduan Malaysian Variation Guideline for Pharmaceutical Products* (14 July 2022)	*Melaksanakan* Malaysian Variation Guideline (MVG) (29 April 2013) ii. *Bil (7) dlm. NPRA/PPPK/01/04*, *Pekeliling Berkenaan Pengemaskinian Garis Panduan Malaysian Variation Guideline for Pharmaceutical Products* (14 July 2022)
For unregulated drug substances, kindly note that only the following sections are required and will depend on the type of variation being applied. This is applicable until further notice:	For unregulated drug substances, kindly note that only the following sections are required and will depend on the type of variation being applied. This is applicable until further notice:
i. General Information (Nomenclature, Structure, General Properties)	i. General Information (Nomenclature, Structure, General Properties)
ii. Manufacturer Details	ii. Manufacturer Details
iii. Specification of API	iii. Specification of API
iv. Batch Analysis	iv. Batch Analysis
v. Certificate of Analysis (COA) from API manufacturer	v. Certificate of Analysis (COA) from API manufacturer
vi. Certificate of Analysis (COA) from finished product manufacturer	vi. Certificate of Analysis (COA) from finished product manufacturer
vii. Justification of Specification	vii. Justification of Specification
viii. Certificates of Suitability (CEP) and its related sections	viii. Certificates of Suitability (CEP) and its related sections
ix. Drug Master File (DMF) and its related sections	ix. Drug Master File (DMF) and its related sections
x. Certificate of GMP for API Manufacturer	x. Certificate of GMP for API Manufacturer

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xi. Other Supporting Documents	xi. Other Supporting Documents
20.1.2 Variation Application for Health Supplement and Natural Products	**20.1.2 Variation Application for Biological Products**
Variation application for Health Supplement Products and Natural Products shall be done according to the Malaysian Variation Guideline (MVG) for Natural (Traditional Medicine & Homeopathy) and Health Supplement Products (Abridged Evaluation).	Variation application for biologics shall be done according to the Malaysian Variation Guidelines for Biologics (MVGB).
Reference: Directive No. 14, 2016. *BPFK/PPP/07/25(45)*: *Direktif Untuk Melaksanakan* Malaysian Variation Guideline (MVG) for Natural (Traditional Medicine & Homeopathy) and Health Supplement Products (Abridged Evaluation) (26 July 2016)	**Reference:** Directive No. 2, 2017. *BPFK/PPP/07/25(7)Jld.1*: *Direktif Untuk Melaksanakan* Malaysian Variation Guideline for Biologics (MVGB) (15 February 2017)
20.1.3 Variation Application for Biological Products	**20.1.3 Variation reliance (for pharmaceutical & biological products only)**
Variation application for biologics shall be done according to the Malaysian Variation Guidelines for Biologics (MVGB).	**1. A Letter of Intent (LOI) or cover letter needs to be submitted to request the use of reliance for the application and should**

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Reference: Directive No. 2, 2017. *BPFK/PPP/07/25(7)Jld.1*: *Direktif Untuk Melaksanakan* Malaysian Variation Guideline for Biologics (MVGB) (15 February 2017)	**clearly list all relevant variation categories.** **2. Official approval letter or notification of the post-approval changes from the chosen reference agency/ WHO.** **3. An assessment report from the chosen reference agency/WHO may be required as the approval letter may not include details of the approved changes. For variations accompanied by an assessment report, it is strongly recommended to provide the report at the time of submission to facilitate early verification of sameness.** **4. Q&A documentation will be requested during evaluation (if required).** **5. An overall summary of changes, presented in a comparative tabulated format showing both the approved and proposed changes (where applicable), should be provided. Please specify the file name of each submitted document and indicate its location in the QUEST3+ system.**

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	NOTES: • **Please ensure that the variations submitted are in accordance with those submitted in the reference agency.** • **It is not advisable to bundle them with other variations that are not part of the reliance submission. The timeline will not be applicable if the submission includes other variations that are not part of the reliance submission.** • **Variation applications submitted under the reliance pathway may be switched to the standard variation evaluation timeline if deemed ineligible for reliance. This may occur in situations such as:** **i. When the approval letter contains limited information, for example when the details of the approved changes are not clearly described.** **ii. When additional evaluation is warranted, such as when the proposed changes cannot be verified against the approval letter or the assessment report.** **20.1.4 Variation Application for Health Supplement and Natural Products**

<table>
<tr><th>DRGD July 2025</th><th>DRGD January 2026</th></tr>
<tr><td></td><td>

Variation application for Health Supplement Products and Natural Products shall be done according to the Malaysian Variation Guideline (MVG) for Natural (Traditional Medicine & Homeopathy) and Health Supplement Products (Abridged Evaluation).

Reference: Directive No. 14, 2016. *BPFK/PPP/07/25(45)*: *Direktif Untuk Melaksanakan* Malaysian Variation Guideline (MVG) for Natural (Traditional Medicine & Homeopathy) and Health Supplement Products (Abridged Evaluation) (26 July 2016)

20.1.5 Variation Timeline

<table>
<tr><th colspan="2">Variation (Pharmaceutical & biological products)</th><th>Timeline : (working days)</th></tr>
<tr><td>MiV-N or MiVB-N</td><td>Maximum of 5*
*PRH may submit up to a maximum of 5 concurrent MiV-N/MiVN-B categories per</td><td>30</td></tr>
</table>

</td></tr>
</table>

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		registered product. **The review timeline may be extended if more than 5 concurrent MiV-N/MiVN-B categories are submitted.**	
	MiV-PA or MiVB-PA	**Maximum of 3*** ***PRH may submit up to a maximum of 3 concurrent MiV- PA/MiVB-PA categories per registered product.** **The review timeline may be extended if more than 3 concurrent MiV- PA/MiVB-PA categories are submitted** ***Inclusion of a MiV-PA2* under MiV-PA/MiVB-PA for safety-related changes – Tell & do** **"Tell & Do" If the application fulfills the requirements as per MVG/MVGB Guideline, NPRA shall approve the proposed change. Changes can be implemented immediately after submission**	**90**
	MaV or MaVB	**Maximum of 3*** ***PRH may submit up to a maximum of 3 concurrent MaV/MaVB categories per registered product.** **The review timeline may be extended if more than 3 concurrent MaV/MaVB categories are submitted.**	**120**
	Grouping (bundle applications)	**Maximum of 5 variation categories including a maximum of 3 MaV/MaVB categories *** ***PRH may submit up to a maximum of 5 variation categories concurrently including**	**150**

<table>
<tr><th>DRGD July 2025</th><th>DRGD January 2026</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>a maximum of 3 MaV/MaVB categories per registered product.
The review timeline may be extended if more than 3 concurrent MaV/MaVB categories are submitted.</td><td></td></tr>
<tr><td></td><td>Other than the grouping/bundle above</td><td>180</td></tr>
</table>

<u>Variation timelines for reliance (pharmaceutical & biological products only)</u>

<table>
<tr><th>Type of variation groupings</th><th>Timeline (wd)</th></tr>
<tr><td>Including MaV/MaVB (maximum of 10 categories*)</td><td>Not more than 100</td></tr>
<tr><td>Including MaV/MaVB (more than 10 categories*)</td><td>Not more than 150</td></tr>
<tr><td>Excluding MaV/MaVB</td><td>Not more than 80</td></tr>
</table>
*Inclusive of MiV-N Post-approval Changes Reliance

<table>
<tr><th>Variations (TMHS)</th><th>Timeline (working days)</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>DRGD July 2025</th><th>DRGD January 2026</th></tr>
<tr><td></td><td>
<table>
<tr><td>MiV-N</td><td>Maximum of 5*
*PRH may submit up to a maximum of 5 concurrent MiV-N categories per registered product.
The review timeline may be extended if more than 5 concurrent MiV-N categories are submitted.</td><td>10</td></tr>
<tr><td>MiV-PA</td><td>Maximum of 3*
*PRH may submit up to a maximum of 3 concurrent MiV- PA categories per registered product.
The review timeline may be extended if more than 3 concurrent MiV- PA categories are submitted</td><td>70</td></tr>
<tr><td>MaV</td><td>Maximum of 3*
*PRH may submit up to a maximum of 3 concurrent MaV categories per registered product.
The review timeline may be extended if more than 3 concurrent MaV applications are submitted.</td><td>100</td></tr>
<tr><td>Grouping (bundle applications)</td><td>Maximum of 5 variation applications including a maximum of 3 MaV applications*
*PRH may submit up to a maximum of 5 variation categories concurrently including a maximum of 3 MaV categories per registered product.
The review timeline may be extended if more than 3 concurrent MaV categories are submitted</td><td>120</td></tr>
</table>
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</table>

<table>
<tr><th>DRGD July 2025</th><th>DRGD January 2026</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>Other than the grouping/bundle above</td><td>150</td></tr>
</table>

<u>Notes to PRHs:</u>

1. Timelines for PRH to reply to each correspondence according to the category of products and variation types are as follows: failure to meet these timelines may result in application rejection.
a) For pharmaceutical products: 45 wd (for MiV-PA and MiVB-PA) and 60 wd (for MaV, MaVB, Grouping/Bundle applications)
b) For TMHS products: 20 wd (for MiV-PA) and 30 wd (for MaV, Grouping/Bundle applications)

2. For pharmaceutical and biological products only: To ensure a smooth process, all PRHs must attach a cover letter/summary of changes for the intended variation application via Quest3+. The cover letter/summary of changes should include the following:
a) Proposed variation category
b) A brief description of the proposed variation with justification
c) A declaration confirming the fulfilment of all requirements within the suggested category
d) Approvals from the country of origin's National Regulatory Agency or reference agencies (if any)
e) Current and proposed changes to the dossier's tabulated format information. Please specify the file name of each
</td></tr>
</table>

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	document submitted and indicate its location in QUEST3+ system. **f) A declaration that there is no change except for the proposed change** **3. Natural products with therapeutic claims and health supplements with disease risk reduction claims shall follow the revised variation timelines for pharmaceutical products, excluding the variation timelines for reliance.**

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ATTACHMENT 2

20.4 NEW/ ADDITIONAL INDICATION

1. Definition and scope

New/ additional indication (AI) is defined as an indication not initially approved for a registered innovator product. This may include, but not limited to, the following:

i) new therapeutic indication
ii) new route(s) of administration (parenteral)
iii) indication for new age group, such as usage in children
iv) new dosing regimen (different cumulative dose over the dosing interval)
v) additional bacterial strains to expand the indications for antimicrobial products
vi) additional viral serotypes or genotypes to expand the indications for antiviral products, etc.

This application does not include changing/ rephrasing of sentences.

2. AI Category

There are two (2) categories of AI applications: AI Full Evaluation and AI Verification.

a) **AI Full Evaluation**

Main criteria

This category applies to a new indication that has been approved in any one (1) of the DCA's reference agencies (EMA, UK MHRA, Swedish Medical Products Agency, ANSM France, US FDA, TGA Australia, Health Canada, PMDA Japan and Swissmedic).

This application may require comments from relevant specialists

Notes:

- EMA centralised approval is considered as ONE approval
- An application to add a new indication without prior approval by a DCA's reference agency may be considered for evaluation by NPRA for the following conditions:
  i) new indication deemed not feasible for submission to DCA's reference agencies

ii) new indication for a product that has not been registered with any DCA reference agency

AI Full Evaluation is divided into two (2) types:

i) **Standard Full Evaluation**

Standard Full Evaluation applies to applications for a new indication where NPRA is unable to rely fully on a reference agency's assessment (e.g. when assessment reports are not available) or when no reference agency approval available. In such cases, NPRA will conduct an independent assessment of the indication's suitability under local conditions and regulatory requirements to support its decision.

ii) **Reliance Full Evaluation**

Reliance Full Evaluation applies to a new indication where NPRA relies on prior assessments conducted by one of DCA's reference agencies to inform its local decision, leveraging regulatory tools such as the agency's assessment report. NPRA may conduct (where necessary) a targeted review to address any gaps, adapt the assessment to local regulatory requirements, and ensure the indication's suitability in the Malaysian context.

The eligibility criteria for a new indication via Reliance Full Evaluation are as follows:

- The new indication has been approved within **three years** from the date of approval by the chosen primary reference agency
- The new indication, dosing regimen(s), patient population(s), and/or directions for use must be similar as those approved by the chosen reference agency. However, NPRA reserves the right to propose revisions where necessary to ensure alignment with local clinical practice and to provide clearer indication for safe and effective use in Malaysia.
- The new indication may require an assessment by NPRA to review the benefit-risk profile due to local disease epidemiology, medical practice, and/or public health considerations. Examples of products that may require more stringent assessment due to differences in local disease patterns and/or medical practices include some anti-infectives and vaccines for endemic pathogens.

- The new indication has not been rejected, withdrawn or approved via appeal process or pending deferral by a national regulatory agency for safety or efficacy reasons.

b) **AI Verification**

Main criteria

This applies to a new indication that has been registered **in at least two (2)** DCA's reference agencies (EMA, UK MHRA, Swedish Medical Products Agency, ANSM France, US FDA, TGA Australia, Health Canada, PMDA Japan and Swissmedic).

Note:

EMA centralised approval is considered as ONE approval

This application will not require comments from relevant specialists.

AI Verification is divided into two (2) types:

i)Standard Verification

Standard Verification applies to applications for a new indication where NPRA is unable to rely fully on the reference agency's assessment (e.g. in cases where assessment reports are not available). In such situations, NPRA will conduct a limited independent assessment to support its local decision.

ii) Reliance Verification

Reliance Verification applies to a new indication where NPRA relies on prior assessments conducted by the DCA's reference agencies to inform its local decision, leveraging regulatory tools such as the agencies' assessment report.

The eligibility criteria for a new indication via Reliance Verification are as follows:

a) The new indication has been approved within **three years** from the date of approval by the chosen primary reference agency
b) The new indication, dosing regimen(s), patient population(s), and/or directions for use must be similar to those approved by the chosen reference agency.

c) The new indication does not require an assessment by NPRA to review the benefit-risk profile due to local disease epidemiology, medical practice, and/or public health considerations (e.g. some anti-infectives, vaccines for endemic pathogens, etc.).
d) The new indication has not been rejected, withdrawn or approved via appeal process or pending deferral by a national regulatory agency for safety or efficacy reasons.

ADDITIONAL NOTES FOR ALL NEW/ADDITIONAL INDICATION SUBMISSION

- AI application submissions other than those listed above will be considered on a case-by-case basis. The applicant is advised to consult the respective section prior to submission.
- NPRA reserves the right to reclassify an application from the reliance pathway to the standard pathway, if additional review is deemed necessary during the evaluation process.
- Concurrent manual submissions may be considered based on unmet medical needs.
- For reliance submissions, multiple indications can be submitted if they are all approved by the chosen reference agencies and covered within one assessment report.

3. Priority Review for Additional Indications

Priority Review may be requested and granted for Additional Indications which fulfils the following conditions:

- Additional indication specifically for oncology, supported by a Phase III global, multicentre pivotal clinical trial conducted in Malaysia, in which at least 5% of the total randomised subjects are Malaysian.

Applicants seeking Priority Review for an additional indication shall submit a formal request, in the form of a cover letter, through the QUEST3+ system concurrently with the application. This request must be accompanied by a justification and clinical evidence demonstrating compliance with the specified eligibility requirement. Following submission, the NPRA will assess the request and determine its qualification for Priority Review. After the screening

stage, applicants will be notified of the outcome via remarks in the system; applications that do not meet the criteria will be evaluated under the standard review pathway.

4. Supporting documents for all AI categories

The supporting documents include, but are not limited to the following:

a. Approval of AI(s) in country of origin (if applicable);
b. Approval status in the reference countries, together with the corresponding approval letter and approved package insert;
c. Approval indication status in ASEAN Member States, and the corresponding approved package insert (if applicable)
d. Revised Package Insert (annotated and clean);
e. World Wide Approval status
f. Consumer Medication Information Leaflet (RiMUP), if applicable;
g. Clinical Expert Reports;
h. Synopsis of Individual Studies;
i. Clinical Studies Report/ In-House Clinical Trials;
j. Published Clinical Papers (if applicable);
k. Latest available Periodic Benefit-Risk Evaluation Report (PBRER)

NOTES

- The relevant updates (e.g new adverse event(s), warnings and precaution(s), drug interaction(s), contraindication, pharmacodynamics, pharmacokinetics identified in clinical trials supporting the new indication) must be included in the Package Insert.
- Editorial changes including rewording of sentences (without changing the content) is allowed.
- Any other changes to the Package Insert that are not related to the new indication shall not be included and must be filed as a separate variation application.

Additional documents - for Reliance Full Evaluation and Reliance Verification only

The following additional documents will need to be submitted for AI Reliance:

a) **Full assessment report -** Unredacted and unedited assessment reports and supporting documents from the chosen primary reference agency only [complete clinical assessment reports, including assessment on the question and answer (Q & A) documents between the applicant and agency]

Notes: NPRA may also consider accepting a Public Assessment Report from the **EMA and US FDA** to be submitted with a Q & A document. However, the acceptance of Public Assessment Report from other DCA reference agencies may be considered on a case-to-case basis. Please consult the respective section prior to the submission.

NPRA may also consider unredacted and unedited assessment reports without the necessity of accompanying Q&A documents, where PMDA is selected as the reference agency.

b) Declaration statement to indicate that the assessment report, list of Q & A and all other relevant documents provided are authentic.

c) Checklist for AI (Reliance) - refer Appendix I

5. Timelines

AI category	**Screening timeline** (working days)	**Evaluation timeline** (working days)	**Evaluation timeline - Priority Review** (working days)
AI Standard Full Evaluation	30	180	120
AI Standard Verification		150	100
AI Reliance Full Evaluation		90	Not applicable
AI Reliance Verification			

Note: Evaluation timeline stated excludes screening and stop clock.

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Appendix I

CHECKLIST FOR NEW/ADDITIONAL INDICATION (AI Reliance - to be filled by the applicant

PRODUCT NAME :

REGISTRATION NO. (MAL) :

PRODUCT REGISTRATION HOLDER (PRH) :

CHOSEN REFERENCE AGENCY :

ADDITIONAL INDICATION	**MALAYSIA**	**CHOSEN REFERENCE AGENCY**	**COMMENTS**
Proposed Indication			
Proposed Posology			

APPROVAL BY OTHER REFERENCE AGENCIES			
Reference agency	**Date of AI approval**	**Approved Indication / Posology (specific to new indication only)**	**Comment**
EMA			
US FDA			
UK MHRA			
TGA Australia			
PMDA Japan			

Health Canada			
ANSM France			
Swedish Medical Products Agency			
Swissmedic			

DOCUMENTS SUBMITTED	**Yes/ No**	**COMMENT**
- complete clinical assessment reports (unredacted/unedited)		
- question and answer documents between the applicant and agency and all annexes		
- declaration statement to indicate that the assessment report, list of Q & A and all other relevant documents provided are authentic		
- Other supporting document/clinical guidelines (to support the new indication) – *if any*		

CLINICAL STUDIES SUBMITTED			
Clinical study (s)	**Malaysia**	**Chosen reference agency**	**Comments**
Clinical Study 1	− Study name		
	− Study design − Primary objective − Primary endpoints		
	Results (brief)		
	Clinical efficacy & safety conclusion		
Clinical Study 2 **(*if any)***	− Study name		
	− Study design − Primary Objective − Primary endpoints		
	Results (brief)		

	Clinical efficacy/ safety conclusion		
PACKAGE INSERT (SUMMARY OF CHANGES) *summary of other changes must be those consequential to the Additional Indication (e.g., Summary of other changes resulting from the new indication and posology)*			
Section	**Malaysia**	**Chosen reference agency**	**Comments**

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ATTACHMENT 3

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
CLINDAMYCIN (ORAL CAPSULE FORM) The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing clindamycin (oral capsule form); **<u>Package Insert</u>** **a) Route of Administration** To avoid the possibility of oesophageal irritation, clindamycin hydrochloride capsules should be taken with a full glass of water and no less than 30 minutes before lying down. **b) Warnings & Precautions:** Due to the risk of oesophagitis and oesophageal ulcer, it is important to ensure compliance with administration guidance (see Sections Route of administration and Adverse Effects/ Undesirable Effects). **c) Adverse Effects/ Undesirable Effects:** <u>Gastrointestinal disorders</u> Frequency 'not known': Oesophageal ulcer, oesophagitis **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) How to use [product name]:** [Product name] should be taken with a full glass of water and no less than 30 minutes before lying down. **b) While you are using it:** Due to the risk of stomach and throat irritation, it is important to ensure compliance with administration guidance (see How to use [product name]). **c) Side effects:** Inflammation/ ulcer from the throat to the stomach tube lining

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ATTACHMENT 4

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
CO-TRIMOXAZOLE (SULFAMETHOXAZOLE, TRIMETHOPRIM) The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing co-trimoxazole (sulfamethoxazole, trimethoprim); **<u>Package Insert</u>** **a) Warnings & Precautions:** Circulatory shock Cases of circulatory shock, often accompanied by fever and not responding to standard treatment for hypersensitivity, have been reported with sulfamethoxazole + trimethoprim, mainly in immunocompromised patients. **b) Adverse Effects/ Undesirable Effects:** <u>Vascular disorders</u> Frequency 'not known': circulatory shock **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side effects:** Serious side effects Seek immediate medical attention if you experience fever, dizziness, fainting, or a rapid heartbeat (palpitations) after taking this medication. These symptoms may indicate very low blood pressure or an increased heart rate, which can be signs of shock.

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ATTACHMENT 5

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
LINEZOLID The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing linezolid; **<u>Package Insert</u>** **a) Warnings & Precautions:** Rhabdomyolysis has been reported with the use of linezolid. If signs or symptoms of rhabdomyolysis are observed, linezolid should be discontinued and appropriate therapy initiated. b) Adverse Effects/ Undesirable Effects: System Organ Class (SOC): <u>Musculoskeletal and connective tissue disorders</u> Frequency 'rare': Rhabdomyolysis* *ADR identified post-marketing **<u>Consumer Medication Information Leaflet (RiMUP) (for oral dosage form only)</u>** **a) While you are using it:** If signs or symptoms of rhabdomyolysis (breakdown of damaged muscle) are observed, you should stop using [Product name] and tell your doctor immediately. **b) Side effects:** Rhabdomyolysis (breakdown of damaged muscle) - muscle pain, tenderness or weakness and dark urine

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ATTACHMENT 6

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

PALBOCICLIB

The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing palbociclib;

<u>Package Insert</u>

a) Warnings & Precautions:

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with [Product name] [see Adverse Effects/Undesirable Effects]. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.

b) Adverse Effects/ Undesirable Effects:

<u>Other Clinical Trials Experience</u>

The following adverse reaction has been reported following administration of [Product name]:

Venous thromboembolism

<u>Consumer Medication Information Leaflet (RiMUP)</u>

a) Side effects:

- signs of blood clots in the vein (venous thromboembolism) such as pain or stiffness, swelling and redness in the affected leg (or arm), chest pain, shortness of breath, light-headedness, rapid breathing or rapid heart rate