<table>
<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>1.</td><td>SECTION A: GENERAL OVERVIEW

1.4
MEDICAL DEVICE - DRUG - COSMETIC INTERPHASE PRODUCTS</td><td>
<u>Addition</u> of the following product as highlighted in Table III: MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) PRODUCT CLASSIFICATION DECISION
<table>
<tr><th>NO</th><th>PRODUCT</th><th>INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)</th><th>CATEGORY</th><th>CUSTODIAN DIVISION</th></tr>
<tr><td>24.</td><td colspan="4"><u>Other topical antiseptics/ disinfectants</u></td></tr>
<tr><td></td><td>i. Swabs/ Wipes containing antiseptics/ disinfectants/ antimicrobial substances (eg. chlorhexidine, iodine, cetrimide)</td><td>For use on human skin and intended to be used for a medical purpose, eg pre/post injection, wound cleaning etc.</td><td>DRUG</td><td>NPRA</td></tr>
</table>
</td><td>20 June 2019</td></tr>
</table>

NO.	UPDATES					EFFECTIVE DATE
	SECTION/ APPENDIX	DETAILS				
			ii. Preparations (including swabs/ wipes) containing antiseptics/ disinfectants/ antimicrobial substances (eg. alcohol, chlorhexidine, iodine, cetrimide)	Intended for the disinfection of medical devices.	**MEDICAL DEVICE**	**MDA**	
			iii. Alcohol wipes/ swab	For use on human skin and intended to be used for a medical purpose, eg; pre/post injection, wound cleaning etc.	**MEDICAL DEVICE**	**MDA**	

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	DETAILS	
2.	**SECTION B: PRODUCT REGISTRATION PROCESS** **8. FLOW OF REGISTRATION PROCESS** **8.1.5 MULTIPLE APPLICATIONS**	**Amendment** (highlighted) of the following information : **8.1.5 MULTIPLE APPLICATIONS** Separate application for product registration shall be required for each product for the following conditions: a) Products containing the same ingredients but made to different specifications, in terms of strength/ content of ingredient(s), dosage form, description, etc.; or b) Different manufacturer. However, different packings (materials) or pack sizes (quantity/ volume) of a product made by the same manufacturer to the same specifications, formulation and dosage form (including parenteral preparations, peritoneal dialysis fluids and haemofiltration solutions which are introduced into human bodies) shall require only one application for product registration. The product registration shall be for the packings and pack sizes stated in the registration documents only.	**27 August 2019**

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	DETAILS	
		Note: ~~Registration of same product in all aspects but with different product name by the same PRH is not allowed by the Authority.~~ Registration application of **a same product in all aspects** with different product names: a) by the **same PRH** is **not allowed** by the Authority b) by **different PRH may be considered** by the Authority with **acceptable justification** Product name must comply to the requirements in Section 9.1.4 of the DRGD.	

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
3.	**SECTION A: GENERAL OVERVIEW** **6. GENERAL CONDITIONS FOR REGISTRATION OF DRUG PRODUCTS UNDER THE CONTROL OF DRUGS AND COSMETICS REGULATIONS 1984** **6.4 PRODUCT AUTHENTICATION**	**Addition** of the **new directive on hologram** (highlighted) and **deletion** of information as below : **6.4 PRODUCT AUTHENTICATION** The registered product shall be affixed with the security device approved by the Authority. The said security device (hologram), which is serialized, shall be used to authenticate and verify that the product is registered with the Authority, and will be affixed to each unit pack of the product, whether locally manufactured or imported. The security device shall be affixed onto the outer packaging of the product, (or, where there is no outer packaging, on the immediate packaging), on the front panel of the product label. None of the product particulars on the label shall be covered over by the security device. Please refer to: a) Appendix 9: Labelling Requirements where the security device/ label may be affixed on the product label; b) FAQ no. 20 on hologram; and c) Circulars and directives pertaining to security label (hologram): i) ~~Bil (32) dlm BPFK/02/5/1.3 Keputusan Mengenai Tarikh Perlaksanaan Penggunaan Label Hologram Meditag (6 August 2004)~~ ii) ~~Bil (36) dlm BPFK/02/5/1.3 Keputusan Pihak Berkuasa Kawalan Dadah Berhubung Penggunaan Label~~	**1 September 2019**

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	DETAILS	
		~~Hologram (Product Authentication) (5 November 2004)~~ ~~iii) Bil (62) dlm BPFK/02/5/1.3~~ ~~Menaiktaraf Ciri-ciri Keselamatan Label Meditag (15 August 2006)~~ iv) (1)dlm.BPFK/PPP/07/25 Jld. 1 Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984. Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 2 Tahun 2013: Direktif Pelaksanaan dan Pengendalian Label Keselamatan (4 April 2013) ~~v) Bil (26) dlm. BPFK/PPP/07/25 Jld. 1~~ ~~Direktif Berhubung Penggunaan Label Keselamatan Hologram Meditag™ 4~~ vi) Bil (17) dlm. BPFK/PPP/07/25 Jld 3 Penggunaan Label Keselamatan Baharu Dari Pembekal Yang Dilantik Oleh Kementerian Kesihatan Malaysia	

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JANUARY 2020 (September 2019 Updates)

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

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

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>180.</td><td>RETINOIDS (ORAL) INDICATED FOR TREATMENT OF SKIN DISEASES
(Please refer <u>Attachment 1</u>)</td></tr></table></td><td>1 October 2019</td></tr>
</table>

Attachment 1

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

RETINOIDS (ORAL) INDICATED FOR TREATMENT OF SKIN DISEASES

The following statements shall be included in the **Label, Package Insert** and **Consumer Medication Information Leaflet (RiMUP)** for products containing oral retinoids indicated for treatment of skin diseases;

Label

A boxed warning should be added to the outer packaging as follows:

WARNING

CAN SERIOUSLY HARM AN UNBORN BABY

Women must use effective contraception

Do not use if you are pregnant or you think you may be pregnant

Package Insert

a) Contraindications:

- Pregnant women
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (See Section Warnings & Precautions)

b) Warnings & Precautions:

Teratogenic effects

[Product name] is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.

[Product name] is strictly contraindicated in:

- Pregnant women
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Pregnancy Prevention Programme

[Product name] is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- [approved indications] (See Section Indications)
- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk.
- She understands the need for frequent follow-up (e.g. on a monthly basis).
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month* [*3 years for acitretin] after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.
- Even if she has amenorrhea she must follow all the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment [for acitretin this statement should be - She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment].
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of [product name].

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month* [*3 years for acitretin] after cessation of treatment.

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

- Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.
  for acitretin this last bullet point should be]
- Negative pregnancy test results have been obtained before, during and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. The dates and results of pregnancy tests should be documented.

If pregnancy occurs in a woman treated with [product name], treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.
If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the fetus. This risk persists until the product has been completely eliminated, which is within one month* following the end of treatment [*3 years for acitretin].

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.

As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month* [*3 years for acitretin] after stopping treatment with [product name], even in patients with amenorrhea.

Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

Pregnancy testing

<u>Prior to starting therapy</u>

At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with [product name].

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Follow-up visits

Follow-up visits should be arranged at regular intervals, ideally monthly. Follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment

1 month after stopping treatment, women should undergo a final pregnancy test.
[for acitretin this last paragraph should be]
Women should undergo pregnancy test periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment.

Prescribing and dispensing restrictions

For women of childbearing potential, the prescription duration of [product name] ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of [product name] should occur on the same day.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication.

Male patients

The available data suggest that the level of maternal exposure from the semen of the patients receiving [product name] is not of a sufficient magnitude to be associated with the teratogenic effects of [product name]. Male patients should be reminded that they must not share their medication with anyone, particularly females.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month* [* 3 years for acitretin] following discontinuation of [product name] because of the potential risk to the foetus of a pregnant transfusion recipient.

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Educational material

In order to assist healthcare professionals and patients in avoiding fetal exposure to [product name] the Product Registration Holder will provide educational material to reinforce the warnings about the teratogenicity of [product name], to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Please refer to Appendix 7 : SPECIAL CONDITIONS FOR REGISTRATION FOR A PARTICULAR PRODUCT OR GROUP OF PRODUCTS

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

WARNING
CAN SERIOUSLY HARM AN UNBORN BABY
Women must use effective contraception
Do not use if you are pregnant or you think you may be pregnant

When you must not use it:

- If you are pregnant or breast-feeding
- If there is any chance you could become pregnant

Women must use effective contraception before, during and after taking [product name]:

- You must agree to use at least one very reliable method of contraception (for example an intra uterine device or contraceptive implant) or, two effective methods that work in different ways (for example a hormonal contraceptive pill and a condom). Discuss with your doctor which methods would be suitable for you.
- You must use contraception for a month before taking [product name], during treatment and for a month* afterwards [*for acitretin should be 3 years].
- You must use contraception even if you do not have periods or you are not sexually active (unless your doctor decides this is not necessary).

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Women must agree to pregnancy testing before, during and after taking [product name]:

- You must agree to regular follow-up visits, ideally every month.
- You must agree to have regular pregnancy tests, ideally every month during treatment and, because some medicine may still be left in your body, 1 month* after stopping [product name] (unless your doctor decides this is not necessary in your case). {*for acitretin: 'every 1 to 3 months for 3 years after stopping [product name]'}.
- You must agree to extra pregnancy tests if your doctor asks you.
- You must not get pregnant during treatment or for a month afterwards because some medicine may still be left in your body.
  for acitretin this last bullet point should be:
- You must not get pregnant during treatment or for 3 years afterwards because some medicine may still be left in your body.

If you get pregnant while taking [product name], stop taking the medicine straight away, and contact your doctor.

Also, if you become pregnant within one month* [* 3 years for acitretin] after you stop taking [product name], you should contact your doctor.

Advice for men

The levels of oral retinoid in the semen of men taking [product name] are too low to harm their partners' unborn baby. However, you must never share your medication with anyone, especially females.

Additional precautions

You should never give this medicinal product to another person. Please take any unused capsules to your pharmacist at the end of treatment.

You should not donate blood during treatment with this medicine and for 1 month* [*3 years for acitretin] after stopping [product name] because an unborn baby could be harmed if a pregnant patient receives your blood.

Reference: Directive No.16 Year 2019. Ref : BPFK/PPP/07/25 (16). *Direktif Untuk Semua Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik*

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

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

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>181.</td><td>RETINOIDS (TOPICAL)
(Please refer <u>Attachment 2</u>)</td></tr></table></td><td>1 October 2019</td></tr>
</table>

Attachment 2

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

RETINOIDS (TOPICAL)

The following statements shall be included in the **Package Insert** and **Consumer Medication Information Leaflet (RiMUP)** for topical products containing retinoids;

Package Insert

a) Contraindications:

- Pregnancy (see Section Pregnancy and Lactation)
- Women planning a pregnancy

b) Pregnancy and Lactation [replacing specific labeling requirements - Tretinoin Topical]:

Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

[Product name] is contraindicated (see Section Contraindications) in pregnancy, or in women planning a pregnancy.

If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Do not use [product name] if you are pregnant or thinking of becoming pregnant. Your doctor can give you more information.

Reference: Directive No.16 Year 2019. Ref : BPFK/PPP/07/25 (16). *Direktif Untuk Semua Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik*

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JANUARY 2020 (October 2019 Updates)

<table>
<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>1.</td><td>APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS

2. GENERAL REQUIREMENTS FOR REGISTRATION OF NATURAL PRODUCTS

2.4 PRODUCT NAME</td><td><u>Addition</u> of the following name as highlighted in Table 7: Product names which are not permitted to be registered are as specified :

<table><tr><th>No.</th><th>None-Permissible Product Names</th><th>Example</th></tr><tr><td>12</td><td>Prohibited use of product names which represent weight loss/ slimming properties/ names that can be associated with weight loss/ slim</td><td>Example:

Slim, Langsing, Trim, Trimnfit, Sleen, Kurus, Susut perut,Xlim, Weight watcher, Burn</td></tr></table></td><td>26 September 2019</td></tr>
</table>

<table>
<tr><th>NO.</th><th colspan="4">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th></th><th>SECTION/ APPENDIX</th><th colspan="3">DETAILS</th></tr>
<tr><td>2.</td><td>16.2
CHANGE OF MANUFACTURING SITE

16.2.3
TYPES OF MANUFACTURING SITE CHANGES (COS)

Table XVIII:</td><td colspan="3"><u>Amendment</u> of the following as highlighted in Table XVIII: Types of Manufacturing Site Changes

<table>
<tr><th>No</th><th colspan="2">Types of COS</th><th>Description</th></tr>
<tr><td>5</td><td>Type V</td><td>Change of manufacturing site in crisis situation</td><td>i) Change of location of the site of manufacture that is deemed necessary due to certain circumstances such as natural disasters, closure or suspension of premise (revocation of manufacturing license), bankruptcy and matters related to breach of product quality, safety and efficacy ONLY.

ii) Prior to submission of Type V COS, approval letter issued by the secretariat of the Authority shall be obtained.

iii) Application for Type V COS must be made within ~~three (3) months~~ six (6) months from the date of the crisis.

iv) Type V COS applications for natural products and health supplements are only applicable for local manufacturers.</td></tr>
</table></td><td>17 October 2019</td></tr>
</table>

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JANUARY 2020 (October 2019 Updates)

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
3.	**SECTION D: INSPECTION & LICENSING** **12.2 MANAGING CHANGES OF MANUFACTURER S FACILITY**	**12.2 MANAGING CHANGES OF MANUFACTURERS FACILITY** **Addition** and **Amendment** of information as highlighted in Attachment 1.	**1 November 2019**

Attachment 1

12.2 MANAGING CHANGES OF MANUFACTURERS FACILITY

This section only focuses on manufacturing and its storage / warehouse facilities. Changes on products particulars should be addressed under the Section E of Post Registration Process whereby it discusses on Amendments to Particulars of a Registered Products.

Changes at manufacturer's facility can potentially have a quality and safety impact. It is the responsibility of the site to assess information on the changes occurs through formal change control system and risk management, where applicable. Manufacturers, Importers and Wholesalers are recommended to have a system for categorizing types of changes. All changes to the facility are required to be notified to the Centre for Compliance & Licensing (CCL) ~~prior to implementation~~.

Notification of changes will be review to assess the significance and it may be verified during scheduled GMP inspection. The CCL will communicate further and arrange for an investigative/ for-cause inspection focusing on these changes, if deemed necessary.

Additional Information:

1. This section is applicable to local manufacturer only. Read further on change of importer or wholesaler particulars under Section E of Post Registration Process.

2. For further details, please refer to Table of Example Immediate and Periodical Notification.

Type of notification are as follow:

12.2.1 Immediate notification

This notification is applicable to manufacturers who plan/ undergo a major/ significant/ substantial change that could have an impact on the product quality and safety. The Immediate Notification shall be made to or approved by the Centre for Compliance and Licensing (CCL) prior to implementation. The Immediate Notification can be submitted as follows:

a) Completing 'Borang Permohonan Penilaian Pelan Susun Atur Premis Pengilang, (BPFK 503) for changes related to manufacturing layout and process flow

OR

b) Official writing which may include at least information such as;
   - Description of changes to the facility
   - Plan of changes (For example: Gantt Chart, Validation Master Plan, etc)
   - Details of the products affected, where applicable

Types of changes are listed in **Table A. Example of Immediate Notification**

12.2.2 Periodical Notification

This notification is applicable to manufacturer that plan/ undergo a minor change that would not give any impact to the product quality and safety. The Periodical Notification can be submitted in the form of official writing which may include at least information such as;

- Description of changes
- Plan of changes (For example: Gantt Chart, Validation Master Plan, etc)

Example of changes that required Periodical Notification are as per **Table B. Example of Periodical Notification**

Disclaimer: Both **Table A. Example of Immediate Notification** and **Table B. Example of Periodical Notification** is just for example and as guidance for both regulator and industries. The further action is still subjected to the evaluation by CCL based on the risk of the changes that proposed/ implemented by the manufacturer.

Table A. Example of Immediate Notification

Items	Example	Description	Requirement for application of BPFK 503	Type of Application	Documentation required	Remarks (if any)
1	Change of Manufacturing site (including drug substance if any)	Require submission of new layout plan Eg. New lot	YES	New premise layout (Processing Fee= RM1000.00)	As per BPFK-503 requirement	Verification of information by GMP inspection if necessary. Please refer further to Section E.
2	~~Change or addition of warehouse facility~~	~~Renovation or addition of new warehouse or alternative warehouse~~	~~NO~~	~~Not applicable~~	~~Notification to CCL, NPRA~~	~~Verification of information by GMP inspection if necessary.~~ ~~The new warehouse need to be licensed by NPRA before operation.~~

Items	Example	Description	Requirement for application of BPFK 503	Type of Application	Documentation required	Remarks (if any)
3	Introduction new line/ upgrading clean room	a. Addition of new manufacturing/ packaging line	YES	Revision for existing premise layout (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information by GMP inspection if necessary. Please refer further to Section E.
		b. New Production Block	YES	Revision for existing premise layout ~~or addition new production block in the sam licensed premise layout~~ (no changes of premise address) (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information by GMP inspection if necessary. Please refer further to Section E.

Items	Example	Description	Requirement for application of BPFK 503	Type of Application	Documentation required	Remarks (if any)
		c. Upgrading to clean room Eg. Renovate the production floor according to clean room requirement	YES	Revision for existing premise layout (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information by GMP inspection if necessary.
4	Change of Manufacturing/ Packaging Rooms (including manufacturing/packaging room that located in warehouse facility eg. Centralized dispensing room in warehouse)	a. Relocate or addition of manufacturing rooms which affecting the process flow ~~Rename or relocate of manufacturing rooms without affecting process flow~~ ~~Eg. Tableting Room to Compression~~ Room	YES	Revision for existing premise layout (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information by GMP inspection if necessary.

Items	Example	Description	Requirement for application of BPFK 503	Type of Application	Documentation required	Remarks (if any)
		b. Change of the function of the room	YES	Revision for existing premise layout (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information by GMP inspection if necessary.
		c. Resize the room (without affecting existing process flow)	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary.
5	Change of equipment, or manufacturing process or utility	a. Addition of critical equipment.	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary.
		b. Changes/ addition of critical steps in manufacturing (including packaging) process.	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary. May involve product variation.

Items	Example	Description	Requirement for application of BPFK 503	Type of Application	Documentation required	Remarks (if any)
		c. Changes/ addition of critical utility such as water system, pharmaceutical gases and HVAC etc.	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary.

TABLE B. Example of Periodical Notification

Items	Example	Description	Requirement for application of BPFK 503	Type of Application	Documentation required	Remarks (if any)
1	Change or addition of warehouse facility	Renovation or addition of new warehouse or alternative warehouse	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary. The new warehouse need to be licensed by NPRA before operation.
2	Change or addition of QC facility	Renovation or addition of QC facility Eg. Retention sample, microbiological laboratory, stability chamber etc.	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary.
3	Other renovation (without affecting existing manufacturing layout)	Other renovation eg. change of flooring, ceiling, door and wall	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary.

Items	Example	Description	Requirement for application of BPFK 503	Type of Application	Documentation required	Remarks (if any)
4	Change of key personnel	Applicable to QA/QC Manager, Head of production, Production Pharmacist	NO	Not applicable	Notification to CCL, NPRA	May involved change of holder of manufacturing license.
5	Addition or replacement of manufacturing equipments without affecting existing manufacturing layout	a. Replacement of old equipment with new equipment in existing designated room eg. Replace the old tableting machine with new tableting machine in existing tableting room. ~~New Capsulation or tabletting machine in the available room.~~	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary.

Items	Example	Description	Requirement for application of BPFK 503	Type of Application	Documentation required	Remarks (if any)
		b. Installation of new equipment in existing designated room (vacant room)	NO	Not applicable	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary.
6	Change of company name or address	Changes of company name, building number, postal code, street name, etc. due to changes in ownership or other reason.	NO	Not applicable	Notification to CCL, NPRA & Form 9 Companies Act 1965 (SSM Certificate) & Business License from local authority	Pre-licensing GMP inspection to be conducted at the site if the SSM no. is different. New Manufacturer's License application is required if involved changes of SSM number. Please refer to Section E. May involve variation application to update the company details.

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JANUARY 2020 (December 2019 Updates)

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
1.	**SECTION A: GENERAL OVERVIEW** **5. Types of Application**	**5.1.5 REGISTRATION OF ORPHAN PRODUCT** To replace the whole Section 5.1.5 with statement: *under revision	**12 December 2019**

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JANUARY 2020 (December 2019 Updates)

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

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

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>39.</td><td>CARBIMAZOLE OR METHIMAZOLE (THIAMAZOLE)

(Please refer Attachment 1)</td></tr></table></td><td>15 December 2019</td></tr>
</table>

Attachment 1

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

CARBIMAZOLE OR METHIMAZOLE (THIAMAZOLE)

The following statements shall be included in the **Package Insert** and **Consumer Medication Information Leaflet (RiMUP)** for products containing carbimazole or methimazole (thiamazole);

Package Insert

a) Contraindications:

Patients with a history of acute pancreatitis after administration of carbimazole or active metabolite, methimazole (thiamazole).

b) Warnings and Precautions:

Carbimazole may cause white cell disorders such as neutropenia and agranulocytosis, which may be fatal if treatment with carbimazole is not stopped promptly. These reactions usually occur during the first 3 months of therapy, and in most cases, are reversible on stopping treatment. Since agranulocytosis can develop very rapidly, periodic leucocyte counts alone may not be effective in the early detection of these reactions.

There have been post-marketing reports of acute pancreatitis in patients receiving carbimazole or its active metabolite, methimazole (thiamazole). In case of acute pancreatitis, carbimazole or methimazole (thiamazole) should be discontinued immediately. Carbimazole or methimazole (thiamazole) must not be given to patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite methimazole (thiamazole). Re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset.

Women of childbearing potential and pregnancy
Women of childbearing potential have to use effective contraceptive measures during treatment.

The use of carbimazole or methimazole (thiamazole) in pregnant women must be based on the individual benefit/risk assessment. If carbimazole or methimazole (thiamazole) is used during pregnancy, the lowest effective dose without additional administration of thyroid hormones should be administered. Close maternal, foetal and neonatal monitoring is warranted.

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
c) Fertility, Pregnancy and Lactation: Women of childbearing potential and pregnancy Women of childbearing potential have to use effective contraceptive measures during treatment (see Section Warnings and Precautions). Pregnancy Carbimazole or methimazole (thiamazole) crosses the placenta but, provided the mother's dose is within the standard range and her thyroid status is monitored; there is no evidence of neonatal thyroid abnormalities. Studies have shown that the incidence of congenital malformations is greater in the children of mothers whose hyperthyroidism has remained untreated than in those who have been treated with carbimazole or methimazole (thiamazole). However, cases of congenital malformations have been observed following the use of carbimazole or its active metabolite, methimazole (thiamazole) during pregnancy. A causal relationship of these malformations, especially choanal atresia and aplasia cutis congenita (congenital scalp defects), to transplacental exposure to carbimazole and methimazole (thiamazole) cannot be excluded. Therefore the use of carbimazole or methimazole (thiamazole) in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section Warnings and Precautions). Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported. Therefore, carbimazole or methimazole (thiamazole) should be used in pregnancy only when propylthiouracil is not suitable. If carbimazole or methimazole (thiamazole) is used in pregnancy, the dose must be regulated by the patient's clinical condition. The lowest dose possible should be used, and this can often be discontinued three or four weeks before term, in order to reduce the risk of neonatal complications. The blocking-replacement regimen should not be used during pregnancy since very little thyroxine crosses the placenta in the last trimester. Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications. Carbimazole or methimazole (thiamazole) is able to cross the human placenta.

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
Based on human experience from epidemiological studies and spontaneous reporting, carbimazole or methimazole (thiamazole) is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses. Reported malformations include aplasia cutis congenita, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly, and ventricular septal defect. Carbimazole or methimazole (thiamazole) must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. If carbimazole or methimazole (thiamazole) is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended (see section Warnings and Precautions). **d) Undesirable Effects/ Side Effects:** SOC Gastrointestinal disorders Frequency “Not Known” : Acute pancreatitis **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [Product Name]:** When you must not use it: - Do not use <Product name> if you had inflammation of the pancreas (acute pancreatitis) after administration of carbimazole or thiamazole in the past. Before you start to use it: - <Product name> can cause harm to an unborn baby. If you can get pregnant, use reliable contraception from the time you start treatment and during treatment. - If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor straight away. Your treatment with <product name> may need to be continued during pregnancy if the potential benefit outweighs the potential risk to you and your unborn baby. **b) While you are using [Product Name]:** Things to be careful of: - Tell your doctor straight away if you develop fever or abdominal pain, which may be signs of inflammation of the pancreas (acute pancreatitis). <Product name> may need to be discontinued.

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
c) Side Effects: - Inflammation of the pancreas (acute pancreatitis) **Reference: Directive No.19 Year 2019. Ref : BPFK/PPP/07/25 (19) Jld. 3.** *Direktif untuk semua produk yang mengandungi carbimazole atau methimazole (thiamazole):Pengemaskinian sisip bungkusan dan risalah maklumat ubat untuk pengguna (RIMUP) dengan maklumat keselamatan berkaitan risiko pankreatitis akut (acute pancreatitis) dan pengukuhan maklumat keselamatan berkaitan risiko kecacatan kongenital (congenital malformation).*

<table>
<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
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9.2 : SPECIFIC LABELLING REQUIREMENTS</td><td><u>Amendment</u> (as highlighted) of the <u>safety information/ statements</u> as below :

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>121.</td><td>LOPERAMIDE
(Please refer Attachment 2)</td></tr></table></td><td>15 December 2019</td></tr>
</table>

Attachment 2

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

LOPERAMIDE

1. The following boxed warning shall be included on the **labels** of products containing Loperamide:

NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE

1. The following statement shall be included in the **package inserts** of products containing Loperamide:

a) WARNING

Not recommended for children under 6 years of age. Its use has been associated with fatal episodes of paralytic ileus in infants and young children.

b) PRECAUTION

Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes. If severe dehydration or electrolyte imbalance is present Loperamide should be withheld until appropriate corrective therapy has been initiated.

c) Warnings and Precautions

The use of higher than the recommended doses for control of the diarrhea may cause abnormal heart rhythms and serious cardiac events leading to death. However, in adult patients receiving the recommended dosage of loperamide, cases of syncope and ventricular tachycardia have been reported. Some of these patients were taking other drugs or had other risk factors that may have increased their risk of cardiac adverse reactions.

Abuse and misuse of loperamide, as an opioid substitute, have been described in individuals with opioid addiction (see Overdose).

d) Adverse Reactions

Post-marketing Experience

Cardiac Disorders: QT/QTc interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death (see Warning and Precautions)>

e) Overdose

In individuals who have intentionally ingested overdoses (reported in doses from 40 mg up to 792 mg per day) of loperamide HCL, prolongation of the QT/QTc interval, Torsades de Pointed, other ventricular arrhythmias and cardiac arrest, have been observed (see Warnings and Precautions). Fatal cases have also been reported.

Abuse, misuse and/or overdose with excessively large doses of loperamide, may unmask Brugada syndrome.

3. The following statement shall be included in the **RiMUP** of products containing Loperamide:

a) If you use too much (overdose)

If you have taken more than the recommended dose of [product name], immediately contact your doctor or go to the Emergency Department of your nearest hospital for advice.

Symptoms may include :

- changes to your heartbeat such as increased heart rate and irregular heart rhythm (these symptoms can have potentially serious, life-threatening consequences)
- muscle stiffness
- uncoordinated movements
- drowsiness
- difficulty urinating
- weak breathing

References :

a) Directive No. 14 Year 2017. Ref. BPFK/PPP/07/25 (19) Jld 1. *Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Loperamide : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Pada Jantung Yang Serius Susulan Pengambilan Loperamide Melebihi Dos Yang Disyorkan Dan Isu Penyalahgunaan*

b) Directive No.18 Year 2019 . Ref. BPFK/PPP/07/25 (18) Jld. 3. *Direktif untuk semua produk yang mengandungi loperamide: Pengemaskinian sisip bungkusan dengan maklumat keselamatan berkaitan unmasking brugada syndrome dengan pengambilan dos berlebihan*

LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JANUARY 2020 (January 2020 Updates)

NO.	UPDATES		EFFECTIVE DATE	REFERENCE
	SECTION/ APPENDIX	**DETAILS**		
1.	**APPENDIX 7 : SPECIAL CONDITIONS FOR REGISTRATION FOR A PARTICULAR PRODUCT OR GROUP OF PRODUCTS**	**Addition** of the following substance and information as in Attachment 1.	**1 October 2019**	**Directive No.16 Year 2019 BPFK/PPP/07/25 (16)Jld.3.** *Direktif Untuk Semua Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik*

Attachment 1

5. ORAL RETINOIDS INDICATED FOR TREATMENT OF SKIN DISEASES

Oral retinoid products are required to have the following educational materials :

a) Patient Reminder Card
b) Prescriber Checklist/ Acknowledgement Form
c) Pharmacist Checklist

PATIENT REMINDER CARD

Important information to know:

- [Product name] must not be taken during pregnancy. [Product name] can seriously harm an unborn baby if a pregnant woman takes it.
- If you become pregnant or think you might be pregnant, stop taking [product name] immediately and contact your doctor.
- If you have any questions or concerns about taking [product name], talk to your doctor or pharmacist.

What you must do:

- You must use effective contraception before, during and for 1 month* [*for acitretin: 3 years] after stopping treatment with [product name].
- You must not become pregnant while taking [product name], or for 1 month* [*for acitretin: 3 years] after stopping treatment.
- You must attend regular follow-up visits and have regular pregnancy testing.

Reminder for Men and Women

Do not share this medication with anybody and return any unused capsules back to the pharmacy. You should not donate blood during treatment with this medicine and for 1 month* [*for acitretin: 3 years] after stopping treatment.

PRESCRIBER CHECKLIST/ ACKNOWLEDGEMENT FORM FOR PRESCRIBING [PRODUCT NAME] TO FEMALE PATIENTS

The potential for pregnancy must be assessed for all female patients prescribed [product name].

A woman has a potential for pregnancy if one of the following applies:

Is a sexually mature woman who:

1. has not had a hysterectomy or bilateral oophorectomy
2. is not in a natural postmenopause for a minimum of 24 consecutive months (i.e., menstruated at a certain point in the last 24 consecutive months).

Before initiating [product name] in a female patient, the following checklist is to be completed by the prescriber and kept with the patient notes to document compliance with the [product name] Pregnancy Prevention Programme. After completion, a copy of this document should be given to the patient.

[Product name] belongs to the retinoid class of drugs that cause severe birth defects. Foetal exposure to [product name], even for short periods, presents a high risk of congenital malformations. [Product name] is therefore strictly contraindicated in women of childbearing potential, unless all conditions in the [product name] Pregnancy Prevention Programme are fulfilled.

As the prescriber, you must make sure that the risk of serious harm from drug exposed pregnancy is fully understood by all female patients before treating them with [product name].

This checklist should also be used in all follow-up visits with women of childbearing potential.

Please use the patient reminder card to support your discussion with the patient.

Is the patient a woman of childbearing potential? If No, go to Section 4.

Women of childbearing potential: Review the below statements, explain them to the patient and record confirmation of this and acknowledgment from the patient in this form. If the answer to any of these questions is NO, [product name] must not be prescribed.

	Prescriber confirm: I have explained this to my patient		**Patient confirm: I have understood this**	
Is the patient suffering from a severe form of acne, which is resistant to standard therapies? [for acitretin: Is the patient suffering from a severe form of psoriasis or severe disorder of keratinization ?]	Yes ☐	No ☐	Yes ☐	No ☐
1. Teratogenicity				
The patient understands that [product name] belongs to a class of drugs (retinoids) known to cause severe birth defects and that they must not get pregnant whilst taking it. [Product name] also increases the risk of miscarriage when taken during pregnancy.	Yes ☐	No ☐	Yes ☐	No ☐
2. Contraception				
The patient understands that she must consistently and correctly use at least 1 highly effective method of contraception (i.e. a user-independent form such as an intra-uterine device or implant) or 2 complementary methods of birth control (i.e. user-dependent forms such as oral contraceptive and barrier method) before and during treatment.	Yes ☐	No ☐	Yes ☐	No ☐
The patient understands that the risk persists even after the medication is stopped and that she must not get pregnant within 1 month* [*for acitretin: 3 years] after stopping treatment.	Yes ☐	No ☐	Yes ☐	No ☐
The patient has received advice on contraception which is appropriate for her and has committed to using it throughout the risk period.	Yes ☐	No ☐	Yes ☐	No ☐

	Prescriber confirm : I have explained this to my patient		**Patient Confirm: I have understood this**	
The patient is aware of the risk of contraceptive failure.	Yes ☐	No ☐	Yes ☐	No ☐
3. Pregnancy Testing & Ideally Monthly Prescriptions				
The first prescription for [product name] can only be given after the patient has had one negative medically supervised pregnancy test. This is to make sure she is not already pregnant before starting treatment.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands that in order to support regular follow up, including pregnancy testing and monitoring, ideally the prescription be limited to 30 days.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands the need for and agrees to pregnancy testing before, during and after treatment.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands the need to do a pregnancy test 1 month* after stopping treatment [*for acitretin: 1-3 monthly intervals throughout treatment and also for a period of 3 years after stopping treatment] because the drug stays in the body for 1 month* [*for acitretin: 3 years] after the last dose and can damage an unborn baby if pregnancy occurs.	Yes ☐	No ☐	Yes ☐	No ☐
The contraceptive methods and pregnancy test results were recorded in the patient's medical records.	Yes ☐	No ☐	Yes ☐	No ☐
The patient knows to contact their doctor if they have unprotected sex, miss their period, become pregnant, or suspect that they have become pregnant during the risk period.	Yes ☐	No ☐	Yes ☐	No ☐

	Prescriber confirm : I have explained this to my patient		**Patient Confirm: I have understood this**	
If pregnancy occurs, treatment must be stopped and the patient should be referred to an expert physician specialised or experienced in teratology for advice.	Yes ☐	No ☐	Yes ☐	No ☐
The patient has received a reminder card and copy of this form.	Yes ☐	No ☐	Yes ☐	No ☐
4. Other Precautions				
Patient understands that [product name] has been prescribed to her only and must not be shared with others.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands that she must not donate blood during treatment with [product name] and for one month* [*for acitretin: 3 years] after discontinuation due to the potential risk to the foetus of a pregnant transfusion recipient.	Yes ☐	No ☐	Yes ☐	No ☐

Prescriber's signature: Patient's signature: Date:

PHARMACIST CHECKLIST - GUIDANCE FOR DISPENSING [PRODUCT NAME]

[Product name] belongs to the retinoid class of drugs that cause severe birth defects. Foetal exposure to [product name], even for short periods of time, presents a high risk of congenital malformations and miscarriage.

[Product name] is therefore strictly contraindicated during pregnancy and in women of childbearing potential, unless all conditions in the Pregnancy Prevention Programme are fulfilled.

Female patient must use effective contraception before, during and for 1 month* [*for acitretin: 3 years] after stopping treatment with [product name].

A negative pregnancy test, issuing a prescription and dispensing [product name] should ideally occur on the same day.

If you are aware that a pregnancy has occurred in a woman treated with [product name], treatment should be stopped immediately and the woman should be promptly referred to the prescribing doctor.

If you are aware that a female patient has become pregnant within 1 month* [*for acitretin: 3 years] of stopping [product name], she should be referred to her prescribing doctor.

As the pharmacist, you should only dispense [product name] after checking the following information:

For women of child-bearing potential:	
In order to support regular follow up, including pregnancy testing and monitoring, the prescription for [product name] ideally be limited to a 30-day supply.	
All patients should be instructed:	
Never to give the [product name] to another person.	
To return any unused capsules to their pharmacist at the end of treatment.	
Not to donate blood during [product name] therapy and for 1 month* [*for acitretin: 3 years] after discontinuation due to the potential risk to the foetus of a pregnant transfusion recipient.	

NO.	UPDATES		EFFECTIVE DATE	REFERENCE
	SECTION/ APPENDIX	DETAILS		
2.	**SECTION A: GENERAL OVERVIEW** **1.4 MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE PRODUCTS**	**Amendments** as highlighted in Attachment 2.	**28 November 2019**	**MDDCI Steering Committee Meeting** **No. 02/2019** **(28 November 2019)**

Attachment 2

Table III: MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) PRODUCT CLASSIFICATION DECISION

NO	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
5.	**Dental Products**			
	i. Fluoride dental preparations (eg. toothpaste, tooth powder, mouthwash, dental varnish/ suspension)	a. To maintain oral hygiene.	**COSMETIC** (If concentration of fluoride ≤1500ppm)	**NPRA**
		b. To maintain oral hygiene and prevent oral diseases based on pharmacological, immunological or metabolic action.	**DRUG**	**NPRA**
		c. A liquid substance used for the protection of pulpal tissue and to provide a marginal seal to newly placed amalgam restorations. A thin coating of this solution is applied over the tooth's surfaces before placement of restorations. It is used as a protective agent for the tooth against constituents of restorative materials. After application, this device cannot be reused.	**MEDICAL DEVICE**	**MDA**

NO	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
		d. As a desensitizing agent for the treatment of hypersensitive teeth, for sealing the dentinal tubules for cavity preparations or on sensitive root surfaces or to line cavity preparations under amalgam restorations.	**MEDICAL DEVICE**	**MDA**
13.	**General-body orifice lubricant**	Lubricant intended to facilitate entry of a diagnostic or therapeutic device into a body orifice by reducing friction between the device and the body; Lubricant during catherisation, probing, endoscopy, changing fistula catheters, intubation, and prevention of iatrogenic injuries to the rectum and colon. E.g ancillary local anaesthetic: lidocaine	**MEDICAL DEVICE** (If it incorporates an ancillary pharmacologically active substance, it will be classified as a **Device-Drug combination product** and shall be regulated as **MEDICAL DEVICE**	**MDA**
24.	**Other topical antiseptics/ disinfectants**			
	i. **Swabs/ Wipes containing antiseptics/ disinfectants/ antimicrobial substances** (eg. chlorhexidine, iodine, cetrimide)	For use on human skin and intended to be used for a medical purpose, eg pre/post injection, wound cleaning etc.	**DRUG**	**NPRA**

NO	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
	ii. Preparations (including swabs/ wipes) containing antiseptics/ disinfectants/ antimicrobial substances (eg. alcohol, chlorhexidine, iodine, cetrimide)	Intended for the disinfection of medical devices.	**MEDICAL DEVICE**	**MDA**
	iii. Alcohol wipes/ swab	To be used for a medical purpose to wipe intact skin for needles access.	**MEDICAL DEVICE**	**MDA**
26.	**<u>Personal Care Products</u>**			
	i. Personal Intimate Hygiene	a. For female/ male intimate hygiene **NOTE :** The product should be rinsed off.	**COSMETIC**	**NPRA**
		b. For symptomatic relief of vaginal irritation/ infections by changing the vaginal pH	~~**DRUG**~~ **MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG**)	~~**NPRA**~~ **MDA**

NO	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
27.	**Skin Barrier Product** (eg. lotion, emulsion, ointment, cream)	a. To form a physical barrier between the skin and the environment to seal out moisture in order to promote healing and relief to the symptoms of skin dryness, impaired barrier function, skin problems/ diseases.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG**)	**MDA**
		b. Soothe and prevent diaper rash discomfort.	**DRUG**	**NPRA**
		c. To maintain/ improve normal skin condition without any therapeutic claims.	**COSMETIC**	**NPRA**
28.	**Soft tissue filler/ Dermal filler**	To correct cutaneous contour deformities of the skin (e.g., moderate to severe facial wrinkles and folds such as nasolabial folds, scars), particularly in cases of aging or degenerative lesions.	**MEDICAL DEVICE** (If it incorporates an ancillary local anaesthetic, eg., lidocaine, it will be classified as a **Device-Drug combination product** and shall be regulated as **MEDICAL DEVICE)**	**MDA**

NO	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
29.	**Synthetic fluid tissue reconstructive material**	As a submucosal implant in the urinary tract for urinary incontinence or vesicoureteral reflux. It may also be injected into the vocal cords to treat the effects of paralysis, atrophy, or scarring. After application, this device cannot be reused.	**MEDICAL DEVICE** (If it incorporates an ancillary pharmacologically active substance, eg., local anaesthetic such as lidocaine, it will be classified as a **Device-Drug combination product** and shall be regulated as **MEDICAL DEVICE)**	**MDA**

NO.	UPDATES		EFFECTIVE DATE	REFERENCE
	SECTION/ APPENDIX	**DETAILS**		
3.	**SECTION A: GENERAL OVERVIEW** **5.1.4 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)**	**Deletion** of information as below: **5.1.3 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)** a) Refers to locally manufactured products for exporting purpose only and not marketed locally. This does not apply to imported products meant to be packed/repacked locally and to be re-export (the application falls under Regulation 7(2)(b), Control of Drugs and Cosmetic Regulations 1984. A separate application form may be obtained from the NPRA website). b) Applications for registration of FEO products are only accepted in the following condition(s) and to be supported with evidence issued by the competent Authority of the importing countries (self-declaration is not accepted): (i) Countries which do not impose specific regulatory requirements as Malaysia (e.g. formulation with banned/ prohibited ingredients, zone IVB stability study, bioavailability/ bioequivalence study, API evaluation etc.); OR (ii) Countries which have different requirements such as different formulation (e.g. colour or strength of ingredients), shape or manufacturing process, etc. as compared to a registered product; OR (iii) Difference in classification category of the products (e.g. as food in	**8 January 2020**	**Drug Evaluation Committee Meeting** **No. 01/2020** **(8 January 2020)**

NO.	UPDATES		EFFECTIVE DATE	REFERENCE
	SECTION/ APPENDIX	DETAILS		
		the importing country) for health supplements and traditional products. c) Applicant may apply for a Certificate of Pharmaceutical Product (CPP) for the registered FEO products. d) For a registered product intended for exportation as well as to be sold in Malaysia: • New application for registration for export only will NOT be required if there is no change in the formulation and appearance of the registered product. • Applicant may apply a CPP for the registered product and together with an explanation/ declaration letter of any difference(s) to the importing country (e.g. a product exported with a different product name). ~~e) For a registered product, now intended to be for export only and no longer for sale in Malaysia:~~ ~~• Application for registration as a FEO product is required.~~ ~~• The existing registration number (i.e. MAL number) will remain the same but with the addition of the administrative code E (For Export Only)~~ f) Applications for registration of FEO products are processed based on abridged evaluation. However, the additional following requirements must be filled for pharmaceutical products (not applicable to health supplements and traditional products):		

NO.	UPDATES		EFFECTIVE DATE	REFERENCE
	SECTION/ APPENDIX	DETAILS		
		(i) Certificate of Analysis (COA) of finished product for at least 1 pilot batch; AND (ii) Minimum 6 months stability data (real time and accelerated stability study) for at least 1 pilot batch. g) Application is via online submission in QUEST system. **Reference:** Bil (11)dlm.BPFK/07/25 Jld.2 *Direktif Kaji Semula Pendaftaran Produk Untuk Tujuan Eksport Sahaja (FEO)*		

<table>
<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th><th rowspan="2">REFERENCE</th></tr>
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<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>197.</td><td>SODIUM VALPROATE

(Please refer Attachment 3)</td></tr></table></td><td>15 January 2020</td><td>Directive No.21 Year 2019
BPFK/PPP/07/25 (21)
Jld. 3
Direktif Untuk Semua Produk Yang Mengandungi Sodium Valproate: Pengukuhan Maklumat Keselamatan Pada Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Berkaitan Risiko Kecacatan Kongenital Dan Masalah Perkembangan Dalam Kalangan Bayi Dan Kanak-Kanak Yang Terdedah Kepada Penggunaan Sodium Valproate Semasa Dalam Kandungan</td></tr>
</table>

Attachment 3

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

SODIUM VALPROATE

1. ~~The following boxed warning shall be included in the package insert of products containing Sodium valproate:~~

> ~~**PANCREATITIS:**~~
>
> ~~CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.~~

2. ~~The following statement shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Sodium Valproate:~~

The following statements shall be included in the **Label, Package Insert** and **Consumer Medication Information Leaflet (RiMUP)** for products containing sodium valproate :

Label

A boxed warning should be added to the outer packaging as follows:

> ***WARNING FOR WOMEN AND GIRLS***
>
> *This medicine can seriously harm an unborn baby*
>
> *Always use effective contraception during treatment with sodium valproate*
>
> *If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.*
>
> *You must CONTINUE taking sodium valproate unless your doctor tells you to stop*

Package Insert

PANCREATITIS:

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.

a) Posology and Method of administration:

Female children and women of childbearing potential
Sodium valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, Warnings and precautions and Fertility, pregnancy and lactation sections). The benefit and risk should be carefully reconsidered at regular treatment reviews. Sodium valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses.

b) Contraindications:

Sodium valproate is contraindicated in the following situations:

- In epilepsy
  - sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
  - sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Warnings and precautions and Fertility, pregnancy and lactation sections)
- In bipolar disorder
  - sodium valproate is contraindicated in pregnancy
  - sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section)

c) Warnings and Precautions:

Female children, Women of childbearing potential, and pregnant women:
Sodium valproate has a high teratogenic potential and children exposed in utero to sodium valproate have a high risk for congenital malformations and neurodevelopmental disorders.

Sodium valproate is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment for epilepsy indication.
- In pregnancy for bipolar disorder indication.
- In women of childbearing potential unless below conditions are fulfilled.

Conditions of Pregnancy Prevention Programme:
The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see Fertility, Pregnancy and Lactation).

Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a physician experienced in the management of epilepsy.

- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with sodium valproate.
- The patient understands the need for regular (at least annual) review of treatment by a prescriber experienced in the management of epilepsy.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary

precautions associated with sodium valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the doctor once the female child using sodium valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.

In patients who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the prescriber to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with sodium valproate. Treatment with sodium valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed sodium valproate must use effective contraception without interruption during the entire duration of treatment with sodium valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by the prescriber

The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

If a woman is planning to become pregnant, a prescriber experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment with sodium valproate and consider alternative treatment options. The patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

- The Patient Card is provided with every sodium valproate dispensation and that patients understand its content.
- Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to sodium valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of sodium valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using sodium valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber. at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant

Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a doctor experienced in the

management of epilepsy.

Please refer to Appendix 7 : SPECIAL CONDITIONS FOR REGISTRATION FOR A PARTICULAR PRODUCT OR GROUP OF PRODUCTS

d) Fertility, Pregnancy and Lactation:

- Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Sodium valproate is contraindicated as treatment for bipolar disorder during pregnancy.
- Sodium valproate is contraindicated for use in women of childbearing potential unless the above mentioned conditions of Pregnancy Prevention Programme are fulfilled (see Contraindications and Warnings and precautions sections)

Pregnancy Exposure Risk related to sodium valproate

Both sodium valproate monotherapy and sodium valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a greater risk of congenital malformations than sodium valproate monotherapy.

Teratogenicity and developmental effects

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to sodium valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders

Data have shown that exposure to sodium valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to sodium valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of sodium valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to sodium valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to sodium valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to sodium valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see **Contraindications and Warnings and precautions sections**)

If a Woman plans a Pregnancy

If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women

Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy.

It is recommended to:
Use the lowest effective dose and divide the daily dose sodium valproate into several small doses to be taken throughout the day.
The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations.

All patients with sodium valproate-exposed pregnancy and their partners should be referred to a

doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to sodium valproate exposure.

~~Package Insert~~

~~a) Posology and Method of Administration:~~

~~Female children, female adolescents, women of childbearing potential and pregnant women~~

~~[Product Name] should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably [Product Name] should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.~~

~~b) Special Warnings and Precautions for Use:~~

~~1.1.1. Female children/Female adolescents/ Women of childbearing potential/Pregnancy~~

~~[Product Name] should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate.~~

~~The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with [Product Name] plans a pregnancy or if she becomes pregnant.~~

~~Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of [Product Name] during pregnancy (see Fertility, Pregnancy and Lactation).~~

~~The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.~~

~~In particular the prescriber must ensure the patient understands:~~

- ~~The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.~~
- ~~The need to use effective contraception.~~
- ~~The need for regular review of treatment.~~
- ~~The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.~~

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible:

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.

c) Fertility, Pregnancy and Lactation:

[Product Name] should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Pregnancy Exposure Risk related to valproate

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders

Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence

~~in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.~~

~~There are limited data on the long term outcomes.~~

~~Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.~~

~~Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).~~

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

~~If a Woman wants to plan a Pregnancy~~

- ~~During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child.~~
- ~~In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed~~
- ~~In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.~~

~~Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:~~

- ~~Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day.~~
- ~~The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.~~
- ~~Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.~~
- ~~To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.~~

~~d) Interactions:~~

~~Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.~~

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

WARNING FOR WOMEN AND GIRLS

This medicine can seriously harm an unborn baby

Always use effective contraception during treatment with sodium valproate

If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.

You must CONTINUE taking sodium valproate unless your doctor tells you to stop

Before you start to use it:

- Tell your healthcare professionals if you are pregnant.
- If you are a woman able to have a baby you must not take sodium valproate unless you use an effective method of birth control (contraception) at all times during your treatment with sodium valproate.

b) While you are using it:

Things you must do:

- Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.
- If you are a parent or a caregiver of a female child treated with sodium valproate, you should contact their doctor once your child experiences their first period (menarche).

Things you must not do:

- Continue taking sodium valproate or using your birth control (contraception) until you have discussed your pregnancy or your plan to get pregnant with your doctor.

Things to be careful of:

- Sodium valproate can seriously harm an unborn baby when taken during pregnancy.
- The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take sodium valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because sodium valproate has been used for many years it is known that in women who take sodium valproate around

10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.

- It is estimated that up to 30-40% of preschool children whose mothers took sodium valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to sodium valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).

c) Taking other medicines

Some medicines and sodium valproate may interfere with each other, these include propofol (a medicine used before and during general anaesthesia). Tell your doctor that you are taking [product name] if you are going for an operation.

References :

1. **Directive No. 17 Year 2016. Rujukan BPFK/PPP/07/25 (3) Jld 1.** *Direktif Bagi Semua Produk Yang Mengandungi Sodium Valproate Bagi Memperkukuhkan Amaran Berkaitan Risiko Abnormal Pregnancy Outcomes*
2. **Directive No. 7 Year 2018. Ref. BPFK/PPP/07/25 (7) Jld 2.** *Direktif Untuk Semua Produk Yang Mengandungi Propofol Dan Sodium Valproate : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat*
3. **Directive No. 21 Year 2019. Ref : BPFK/PPP/07/25 (21) Jld. 3** *Direktif Untuk Semua Produk Yang Mengandungi Sodium Valproate: Pengukuhan Maklumat Keselamatan Pada Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Berkaitan Risiko Kecacatan Kongenital Dan Masalah Perkembangan Dalam Kalangan Bayi Dan Kanak-Kanak Yang Terdedah Kepada Penggunaan Sodium Valproate Semasa Dalam Kandungan*

NO.	UPDATES		EFFECTIVE DATE	REFERENCE
	SECTION/ APPENDIX	DETAILS		
5.	**APPENDIX 7 : SPECIAL CONDITIONS FOR REGISTRATION FOR A PARTICULAR PRODUCT OR GROUP OF PRODUCTS**	**Addition** of the following substance and information as in Attachment 4.	**15 January 2020**	**Directive No.21 Year 2019 BPFK/PPP/07/25 (21) Jld. 3** *Direktif Untuk Semua Produk Yang Mengandungi Sodium Valproate: Pengukuhan Maklumat Keselamatan Pada Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Berkaitan Risiko Kecacatan Kongenital Dan Masalah Perkembangan Dalam Kalangan Bayi Dan Kanak-Kanak Yang Terdedah Kepada Penggunaan Sodium Valproate Semasa Dalam Kandungan*

Attachment 4

10. SODIUM VALPROATE

The following education materials shall be prepared for products containing sodium valproate (as below);

a) Patient Card
b) Annual Risk Acknowledgement Form
c) Guide for Healthcare Professionals
d) Guide for Female Patients/ Caregivers

PATIENT CARD

Muka Hadapan Kad

Patient Card for Sodium valproate [Product Name]: Contraception and Pregnancy

What You Must Know

- Sodium valproate is an effective medicine to treat epilepsy or bipolar disorder
- Sodium valproate can cause serious harm to your baby when taken during pregnancy
- Always use effective contraception throughout the entire duration of treatment

Note:
- This also applies to all girls and women taking sodium valproate who could become pregnant
- Keep this card safe so you always know what to do

Muka Belakang Kad

Patient Card for Sodium valproate [Product Name]: Contraception and Pregnancy

What You Must Do

- Read the package leaflet carefully before use
- Never stop taking sodium valproate unless your doctor tells you as your condition may become worse
- If you are thinking of getting pregnant, CONTINUE taking your sodium valproate and contraception until you talk to your doctor.
- If you think you are pregnant, CONTINUE taking sodium valproate. Make an urgent appointment with your doctor.

Note:
- This also applies to all girls and women taking sodium valproate who could become pregnant
- Keep this card safe so you always know what to do

ANNUAL RISK ACKNOWLEDGEMENT FORM

PART A. TO BE COMPLETED AND SIGNED BY THE PRESCRIBER

Patient name : _____
MRN / ICNo. : _____
Address : _____

For girls and women of childbearing age treated with sodium valproate <Product Name>
Read, complete and sign this form during a visit with the prescriber: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

Name of patient or care-giver: _____
I confirm that the above-named patient needs sodium valproate because:

- □ this patient does not respond adequately to other treatments or
- □ this patient does not tolerate other treatments
- □ that this patient is already stable on …… dose and she is reluctant to change to other medication.
- □ Other reason……..(to specify)

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

- □ The overall risk to fetus and children whose mothers are exposed to sodium valproate during pregnancy are:
  - an approximately 10% chance of birth defects and
  - up to 30 to 40% chance of a wide range of early developmental problems that can lead to learning difficulties.
- □ Sodium valproate should not be used during pregnancy (except in rare situations for epileptic patients that are resistant or intolerant to other treatments)
- □ The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber.
- □ The need for negative pregnancy test at treatment initiation and as required thereafter (if child bearing age).
- □ The need for an effective contraception without interruption during the entire duration of treatment with sodium valproate (if childbearing age).
- □ The need to arrange an appointment with her doctor as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- □ The need to contact her doctor immediately for an urgent review of the treatment in case of suspected or inadvertent pregnancy.
- □ In case of pregnancy, I confirm that this pregnant patient:
  - received the lowest possible effective dose of sodium valproate to minimise the possible harmful effect on the unborn
  - is informed about the possibilities of pregnancy support or counselling and appropriate monitoring of her baby if she is pregnant.

Name of Prescriber: _____ Signature: _____ Date: _____

Part A and B shall be completed: all boxes shall be ticked, and the form signed by the prescriber. This is to make sure all the risks and information related to the use of sodium valproate during pregnancy have been understood. Part A – to be kept by the prescriber

ANNUAL RISK ACKNOWLEDGEMENT FORM

PART B. TO BE COMPLETED BY PRESCRIBER AND SIGNED BY THE PATIENT OR CAREGIVER

Patient name : _____
MRN / ICNo. : _____
Address : _____

For girls and women of childbearing age treated with sodium valproate <Product Name>
Read, complete and sign this form during a visit with the prescriber: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

I have discussed the following with my doctor and understand:

- ☐ Why I need sodium sodium valproate rather than other medicine
- ☐ I have decided to continue with the treatment after being advised on the risk
- ☐ That I should visit the prescriber regularly (at least annually) to review whether sodium valproate treatment remains the best option for me
- ☐ The overall risk to fetus and children whose mothers took sodium sodium valproate during pregnancy are:
  - an approximately 10% chance of birth defects and
  - up to 30 to 40% chance of a wide range of early developmental problems that can lead to significant learning difficulties
- ☐ Why I need a negative pregnancy test at treatment initiation and if needed thereafter (if child bearing age)
- ☐ That I must use an effective contraception without interruption during the entire duration of my treatment with sodium valproate (if childbearing age).
- ☐ We discussed the possibilities of effective contraception or we planned a consultation with a professional who is experienced in advising on effective contraception.
- ☐ The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber.
- ☐ The need to consult my doctor as soon as I am planning to become pregnant to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- ☐ That I should request an **urgent** appointment if I think I am pregnant
- ☐ In case of a pregnancy, I have discussed the following with my doctor and understand:
  - The possibilities of pregnancy support or counselling
  - The need to appropriate monitoring of my baby if I am pregnant

Name of Patient/Caregiver: _____Signature: _____ Date: _____

Name of Prescriber: _____ Signature: _____ Date: _____

Part B shall be completed: all boxes shall be ticked, and the form signed by prescriber and the patient. This is to make sure all the risks and information related to the use of sodium valproate during pregnancy have been understood.
Part B - to be given to patient
- a copy to be kept by the prescriber

GUIDE FOR HEALTHCARE PROFESSIONALS

RISK OF CONGENITAL MALFORMATIONS AND NEURODEVELOPMENTAL DISORDERS FOLLOWING USE OF SODIUM VALPROATE

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

BACKGROUND INFORMATION: SAFETY DATA

1. Congenital Malformations

Data derived from two meta-analysis (including registries and cohort studies) have shown that 10.73% (95% Confidence Interval: 8.16-13.29%)[1] to 10.93% (95% Confidence Interval: 8.91-13.13%) of children of epileptic women exposed to sodium valproate monotherapy during pregnancy suffer from congenital malformations)[2]. This represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%[1]. Available data show that the risk is dose dependent.The risk is greatest at higher doses (above 1g daily). A threshold dose below which no risk exists cannot be established based on available data.

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body system.

2. Developmental Disorders

Exposure to sodium valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk regardless of when during the pregnancy exposure occurs cannot be excluded.

Studies[3-6] in preschool children show that up to 30-40% of children with a history of sodium valproate exposure in utero experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Available data show that children with a history of sodium valproate exposure in utero are at increased risk of autistic spectrum disorder (an approximately three-fold) and childhood autism (an approximately fivefold) compared with the general study population[6].

Limited data suggests that children with a history of sodium valproate exposure in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)[7].

RECOMMENDATIONS

1. The use of sodium valproate had been restricted in pregnancy as such:
   - In epilepsy
     - sodium valproate is contraindicated unless there is no suitable alternative treatment.
   - In bipolar disorder
     - sodium valproate is contraindicated in pregnancy.
2. The use of sodium valproate in women of childbearing potential is contraindicated unless patient had been assessed and counselled appropriately on the risks associated with sodium valproate.
3. Treatment should only be initiated if other treatments ineffective or not tolerated.
4. Treatment should only be initiated after pregnancy has been excluded (negative pregnancy test).

5. The benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably, sodium valproate should be prescribed as monotherapy and at the lowest effective dose. A prolonged release formulation is preferred to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses
6. Carry out annual review and ad-hoc treatment review when required. The benefit and risk should be carefully reconsidered during every treatment review.
7. In the case where sodium valproate must be used during pregnancy, prenatal monitoring is recommended to detect any malformations.

COUNSELLING POINT

- advise patient/ caretaker on the risk of congenital malformations and neurodevelopmental disorders associated with sodium valproate. Inform patient also about the risks of untreated seizure or bipolar disorder.

- advise patient to use effective contraception without interruption throughout the entire duration of sodium valproate treatment

- advise patient not to stop treatment abruptly and to urgently contact the doctor when planning for pregnancy or in the case of suspected pregnancy.

- ensure that patient has received educational materials such as patient card and patient guide that has been provided by the supplier of sodium valproate.

References

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3. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010 October; 51(10):2058-65.
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7. Christensen J et al. Prenatal Sodium valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013; 309(16):1696-1703
8. Cohen M.J et al. Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years.Epilepsy Behav. 2011; 22(2):240-246

GUIDE FOR FEMALE PATIENTS/ CAREGIVERS

RISK OF BIRTH DEFECT & DEVELOPMENTAL PROBLEM FOLLOWING USE OF SODIUM VALPROATE

This information in this leaflet is for women and girls who are prescribed with sodium valproate and are able to get pregnant (child-bearing age). Please read this leaflet carefully and talk to your doctor of pharmacist if you have any question

KEY POINTS:

- Sodium valproate is an effective medicine used to treat seizure (epilepsy) and bipolar disorder.
- Sodium valproate can seriously harm an unborn child when taken during pregnancy and should not be taken by women and girls unless no other medicine works.
- Never stop taking sodium valproate unless your doctor tells you to stop.
- Always use contraception and do not stop using as long as you are taking sodium valproate.
- See your doctor at once if you are planning pregnancy or if you suspect that you are pregnant. Do not stop taking sodium valproate.
- Please make sure that you receive the patient educational materials such as patient card and patient guide from your healthcare provider.

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

- For women who are able to get pregnant (of child-bearing age):
  - When taking sodium valproate, always use **reliable contraception** and never stop using it so you do not have unplanned pregnancy as long as you are taking sodium valproate
  - Tell your doctor at once if you think you may be pregnant or know you are pregnant.
  - Never stop taking sodium valproate unless your doctor tells you to as your condition may become worse
- If you are thinking to get pregnant:
  - Arrange urgent appointment with your doctor if you plan to get pregnant or if you suspect that you are pregnant. Do not stop taking sodium valproate and contraception until you have seen your doctor.

You can help by reporting any side effects that you may get directly to the National Pharmaceutical Regulatory Agency (NPRA) through the website http://npra.gov.my (Consumer→Consumer Reporting of Side effects To Medicines Or Vaccines→ConSERF).

INFORMATION ON THE RISKS TO THE UNBORN CHILD

- Sodium valproate can be harmful to unborn children when taken by a woman during pregnancy.

- Sodium valproate can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; and limb defects.
- Because sodium valproate has been used for many years, we know that in women who take sodium valproate, around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born in the general population.
- It is estimated that up to 30-40% of preschool children whose mothers took sodium valproate during pregnancy may have problems with **early childhood development**. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory. In addition, disorders which affect the way a child communicates and interacts with others, for example autism, are more often diagnosed in children exposed to sodium valproate.

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

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

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>202.</td><td>SULFASALAZINE

(Please refer Attachment 5)</td></tr></table></td><td>15 January 2020</td><td>Directive No.20 Year 2019
BPFK/PPP/07/25 (20) Jld. 3
Direktif Untuk Semua Produk Yang Mengandungi Sulfasalazine: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Gangguan Terhadap Ujian Makmal Yang Menggunakan Reaksi Dihydronicotinamide-Adenine Dinucleotide/ Dihydronicotinamide-Adenine Dinucleotide Phosphate (NADH/NADPH)</td></tr>
</table>

Attachment 5

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

SULFASALAZINE

The following statements shall be included in the Package Insert and Consumer Medication Information Leaflet (RiMUP) for products containing sulfasalazine;

Package Insert

a) Warnings and Precautions:

Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use nicotinamide adenine dinucleotide [NAD(H)] or nicotinamide adenine dinucleotide phosphate [NADP(H)]. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine (see Section Interactions with Other Medicaments).

b) Interactions with Other Medicaments:

Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), ammonia, thyroxine, or glucose. Consult with the testing laboratory regarding the methodology used.

Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings (see Section Warnings and Precautions).

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [Product Name]:

Before you start to use it

Tell your doctor if you are taking or have recently taken [product name], or any other sulfasalazine containing products, because they may affect results of blood and urine tests.

SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Reference : Directive No.20 Year 2019 . Ref : BPFK/PPP/07/25 (20) Jld. 3 *Direktif Untuk Semua Produk Yang Mengandungi Sulfasalazine: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Gangguan Terhadap Ujian Makmal Yang Menggunakan Reaksi Dihydronicotinamide-Adenine Dinucleotide/ Dihydronicotinamide-Adenine Dinucleotide Phosphate (NADH/NADPH)*