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

(August 2018 Updates)

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

NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
1.	**SECTION A: GENERAL OVERVIEW** **1.4 MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE PRODUCTS** **1.4.1 Introduction**	Additional of below**:** Please refer : **(iii) Pekeliling Lanjutan Tarikh Pelaksanaan Pemakaian *Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products* (22 Dec 2017)** **Circular (3) dlm. BPFK/PPP/01/103 Jld 4**	**22 December 2017**
2.	**SECTION A: GENERAL OVERVIEW** **1.4 MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE PRODUCTS** **1.4.2 CLASSIFICATION CRITERIA**	Amendments in Table III: Summary of Medical Device-Drug-Cosmetic Interphase (MDDCI) Product Classification Decision (Please refer Attachment 1) (changes as highlighted in yellow)	**27 June 2018**

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

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>safety information/ statements</u> regarding Severe Cutaneous Adverse Reactions (SCARs);

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>23.</td><td>AZITHROMYCIN

(Please refer Attachment 2)
(changes as highlighted in yellow)</td></tr></table></td><td>1 August 2018</td></tr>
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<tr><th>NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th></tr>
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<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> regarding Severe Cutaneous Adverse Reactions (SCARs);

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

(Please refer Attachment 3 - highlighted in yellow)</td></tr></table></td><td>1 August 2018</td></tr>
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<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>71.</td><td>ERYTHROMYCIN

(Please refer Attachment 4)
(changes as highlighted in yellow)</td></tr></table></td><td>1 August 2018</td></tr>
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<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td></td><td>ROXITHROMYCIN

(Please refer Attachment 5 - highlighted in yellow)</td></tr></table></td><td>1 August 2018</td></tr>
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<tr><td>7.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td>Addition of the following substance and safety information/ statements on the risk of fungaemia;

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

(Please refer Attachment 6 - highlighted in yellow)</td></tr></table></td><td>1 August 2018</td></tr>
<tr><td>8.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

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(Please refer Attachment 7 - highlighted in yellow)</td></tr></table></td><td>1 August 2018</td></tr>
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NO.	UPDATES		EFFECTIVE DATE
	SECTION/ APPENDIX	**DETAILS**	
9.	**APPENDIX 8 : LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES**	Addition of the ingredient Cetrimide as a restricted excipient; **8.2.2 LIST OF RESTRICTED EXCIPIENTS** (Please refer Attachment 8- highlighted in yellow)	**1 September 2018**
10.	**APPENDIX 1 : FEES**	Updating/ Amendment to**:** **1.4 CHARGES FOR AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT** (Please refer Attachment 9 – changes as highlighted in yellow)	**1 July 2016**
11.	**SECTION E : POST-REGISTRATION PROCESS** **14. MAINTENANCE OF REGISTRATION**	Additional requirement for re-registration: 14.1 REQUIREMENT The requirements for product re-registration as aforementioned are as follows: **i) Products previously registered as "Pendaftaran Hak" or "Not Commercially Viable Medicine (NVCM)".** **Reference:** **Circular Bil (20) dlm. BPFK/PPP/07/25 Jld. 2** **Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 20 Tahun 2018: Direktif Permohonan Pendaftaran Semula Produk Yang Pernah Didaftarkan secara "Pendaftaran Hak" dan Produk "Not Commercially Viable Medicine (NCVM)" (26 June 2018)**	**1 July 2018**

Attachment 1

Table III: ~~SUMMARY OF~~ 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 (e.g. toothpaste, tooth powder, mouthwash, dental varnish/ suspension)	b. To maintain oral hygiene and prevent oral diseases based on pharmacological, immunological or metabolic action	**DRUG** ~~(If concentration of fluoride is >1500ppm)~~	**NPRA**
	iii. Oral wound dressing, non - animal/ microbial derived (e.g. gel, paste, fluid, spray solution of water/oil).	A compound intended as a protective cover for the oral mucosa to manage wounds and sores in the mouth. It may also be used to treat mucosal irritations/ inflammation, dryness and gingivitis.	**MEDICAL DEVICE** (If it contains an active substance with pharmacological, immunological or metabolic primary mode of action, it will be classified as **DRUG**)	**MDA**
6.	**Dialysis Products**			
	i. Peritoneal dialysis dialysate	It is used for the exchange of solutes across the peritoneum of the patient (in this case, used as a semi-permeable membrane)	**DRUG** For continuous ambulatory peritoneal dialysis (CAPD) products with CAPD system (e.g. dialysate bag, drainage bag, transfer tubing, linking connector, disc, injection	**NPRA**

			port, overpouch etc), it will be classified as **Drug-device combination product regulated as DRUG** **(refer to No.9. Drug - Delivery Products Regulated as Drug Products)**	
9.	**Drug - Delivery Products Regulated as Drug Products** (e.g. insulin prefilled pen/ syringes, asthma inhalers, intrauterine with hormone action ~~contraceptives whose primary purpose is to release progestogens~~), CAPD products with CAPD system (e.g. dialysate bag, drainage bag, transfer tubing, linking connector, disc, injection port, overpouch etc)	To administer pharmacologically active substance	**Drug-device combination product regulated as DRUG** **~~NOTE:~~** ~~The device component will be regulated on a case to case basis.~~	**NPRA**
14.	**Head lice products**	a. Acts solely by coating and/ or suffocating the lice and/ or its eggs	**MEDICAL DEVICE**	**MDA**
		b. Disrupting the water balance mechanism of the lice by dissolving and emulsifying off their protective cuticular lipid layer, alters physical	**MEDICAL DEVICE**	**MDA**

		characteristics of the egg so that the nymph develops to maturity but cannot hatch.		
		c. To coat the hair in a film that deters lice from transferring from an infected head to the one treated	**MEDICAL DEVICE**	**MDA**
16.	**In vivo diagnostic agents**	a. For diagnostic purposes, e.g. - X-ray / MRI contrast media - NMR enhancing agents - Ophthalmic diagnostic agents, e.g. staining agent such as fluorescent ophthalmic strips for diagnostic purposes - Carrier solutions to stabilize microbubbles for ultrasound imaging - Radiopharmaceuticals for diagnostic use e.g. ^{14}C- Urea Capsule for H pylori test - Hapten preparation for the diagnosis of contact allergy	**DRUG**	**NPRA**
18.	**Local refrigeration anaesthesia**	Used as local anaesthetic due to intense cold produced by instant evaporation e.g. in minor operative procedures or to alleviate pain associated muscle injuries etc; of which results in insensitivity of peripheral nerve endings and a local anaesthesia. Its principal mode of action is not pharmacological, immunological or metabolic	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it will be classified as **DRUG**)	**MDA**
22.	**Nasal inhaler/ spray**	~~A hand-held device designed to administer substances directly into the nares of a patient~~, To act ~~serve~~ as a barrier against external influences by formation	**MEDICAL DEVICE** (If it contains a pharmacologically	**MDA**

		of a moisturizing film on the nasal mucosa.	active substance, it will be classified as **DRUG**)	
28.	**Product for synovial joint ~~fluid replacement fluid (Joint lubricant)~~**	~~To help cushion the joint, especially in cases of reduced endogenous synovial fluid viscosity from degenerative disease.~~ a. Used as synovial fluid replacements where viscosupplementation provides support and lubrication to help cushion the joint, especially in cases of reduced endogenous synovial fluid viscosity from degenerative disease.	**MEDICAL DEVICE**	**MDA**
		b. Elicits pain relief and improvement in osteoarthritis via several complex biochemical actions resulting modulation of cell activity	**DRUG**	**NPRA**
30.	**Wound care/ treatment products**			
	v. Silver-containing topical preparations for application to a skin wound ~~(e.g. silver nitrate/ silver sulfadiazine/ colloidal silver gel, cream)~~	~~a.~~ To administer/ apply an antiseptic/ antimicrobial to wounds for the purpose of treating infection ~~with mild to moderate exudates such as:~~ ~~- First and second degree burns~~ ~~- Traumatic wounds~~ ~~- Surgical wounds~~ ~~- Partial full thickness wounds~~ ~~- Grafted wounds and donor sites~~ ~~- Lacerations and abrasions~~	**DRUG**	**NPRA**
		b. Treatment of ~~non infected~~ wounds by creating a viscoelastic and lubricated environment and providing a protective barrier at the level of the lesion, for natural wound healing, of which the silver acts as ancillary medicinal substance	**MEDICAL DEVICE**	**MDA**

Attachment 2

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
23.	**AZITHROMYCIN** 1. The following statement shall be included in the package insert and RiMUP of **all products containing Azithromycin:** **Package Insert** ~~**Special**~~ **a) Warnings and Precautions** ~~**for Use**~~ ~~**Hypersensitivity**~~ ~~As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.~~ ~~If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.~~ In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. ~~**Prolongation of the QT interval**~~ ~~Prolonged cardiac repolarization and QT interval, imparting a risk of~~

~~developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see section 4.8). Prescribers should consider the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including:~~

- ~~Patients with congenital or documented QT prolongation~~
- ~~Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones~~
- ~~Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia~~
- ~~Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency~~
- ~~Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval~~

b) Adverse ~~Drug Reactions~~ Effects/Undesirable Effects

Skin and Subcutaneous Tissue Disorders:
Frequency not known : severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP).

~~**Post-marketing experience:**~~

~~Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see **Special Warnings and Precautions for Use)**.~~

~~Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, SJS, TEN and DRESS have been reported.~~

Consumer Medication Information Leaflet (RiMUP)

Side Effects

[Product name] may cause severe allergy and serious skin reactions.

Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms:

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

2. The following statement shall be included in the package insert and RiMUP of **products containing azithromycin (except topical/ external and ophthalmic preparations);**

Package Insert

a) Warnings and Precautions:

Prolongation of the QT interval

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see section 4.8). Prescribers should consider the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including:

- Patients with congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in infants (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs.

b) Adverse Effects/Undesirable Effects:

Postmarketing Experience:

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see **~~Special~~ Warnings and Precautions ~~for Use~~)**.

Gastrointestinal Disorders : infantile hypertrophic pyloric stenosis.

Consumer Medication Information Leaflet (RiMUP)

Side Effects

If you notice that the child vomits and/or irritability with feeding occurs, contact doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS).

References:

1. Circular Bil (34) dlm BPFK/PPP/07/25**. Directive Bil 3 Year 2016.**
   Direktif Untuk Semua Produk Yang Mengandungi Azithromycin (Formulasi Sistemik): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Kesan Advers *QT Prolongation* Dan *Drug Reaction With Eosinophilia And Systemic Symptoms (DRESS)*
2. Circular Bil (33) dlm BPFK/PPP/07/25 Jld.1 **Directive No. 28 Year 2017.**
   Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin Dan Erythromycin Kecuali Persediaan Topikal/ Eksternal Dan Ubat Untuk Kegunaan Mata : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan *Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)*
3. Circular Bil (22) dlm BPFK/PPP/07/25 Jld.2 **Directive Bil 22 Year 2018.**
   Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin Dan Roxithromycin: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Severe Cutaneous Adverse Reactions (SCARs)*

Attachment 3

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	CLARITHROMYCIN The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Clarithromycin; **Package Insert** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known : severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms:

	• skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference:** Circular Bil (22) dlm BPFK/PPP/07/25 Jld.2 **Directive Bil 22 Year 2018.** Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin Dan Roxithromycin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Severe Cutaneous Adverse Reactions (SCARs)*

Attachment 4

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
71.	**ERYTHROMYCIN** 1. The following statement shall be included in the package insert and RiMUP of products containing erythromycin; **Package Insert** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known : severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **Consumer Medication Information Leaflet (RiMUP)** **Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if

you experience any of the following symptoms:

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

Reference: Circular Bil (22) dlm BPFK/PPP/07/25 Jld.2**. Directive Bil 22 Year 2018.** Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin Dan Roxithromycin: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Severe Cutaneous Adverse Reactions (SCARs)*

2. The following statement shall be included in the package insert and RiMUP of products containing erythromycin (except topical/ external and ophthalmic preparations);

Package Insert

a) Warnings and Precautions:

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs.

b) Adverse Effects/Undesirable Effects:

Postmarketing Experience:

Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis.

	Consumer Medication Information Leaflet (RiMUP) **Side Effects** If you notice that the child vomits and/or irritability with feeding occurs, contact doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS). **Reference:** Circular Bil (33) dlm BPFK/PPP/07/25 Jld.1 **Directive No. 28 Year 2017.** Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin Dan Erythromycin Kecuali Persediaan Topikal/ Eksternal Dan Ubat Untuk Kegunaan Mata : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan *Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)*

Attachment 5

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	ROXITHROMYCIN The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Roxithromycin; **Package Insert** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms:

	• skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference:** Circular Bil (22) dlm BPFK/PPP/07/25 Jld.2**. Directive Bil 22 Year 2018.** Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin Dan Roxithromycin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Severe Cutaneous Adverse Reactions (SCARs)*

Attachment 6

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	SACCHAROMYCES BOULARDII The following statements shall be included in the package insert, Consumer Medication Information Leaflet (RiMUP) and Label for products containing *Saccharomyces boulardii*; **Package Insert** **a) Contraindications:** • Patients having a central venous catheter • Critically ill patients or immunocompromised patients due to a risk of fungaemia(See Section Warnings & Precautions) **b) Warnings and Precautions:** There have been very rare cases of fungaemia reported mostly in patients with central venous catheter, critically ill or immuno-compromised patients, most often resulting in pyrexia. In most cases, the outcome has been satisfactory after cessation of treatment by *Saccharomyces boulardii*, administration of antifungal treatment and removal of the catheter when necessary. However, the outcome was fatal in some critically ill patients (see Section Contraindications & Section Adverse Effects/Undesirable Effects). **c) Adverse Effects/Undesirable Effects:** Infections and Infestations Very rare: Fungaemia in patients with a central venous catheter and in critically ill or immunocompromised patients (see Section Warnings & Precautions).

	Consumer Medication Information Leaflet (RiMUP) **a) Before you use [product name]:** When you must not take it Do not take this product if you are immunocompromised (altered/weakened immune system) or have central venous catheter. **b) Side Effects:** Very rare side effects: Penetration of yeast into blood (fungaemia) **Label** Please consult your doctor/pharmacist before using this product. Do not take this product if you are immunocompromised (altered/ weakened immune system) or have central venous catheter. **Reference: Circular Bil (23) BPFK/PPP/07/25 Jld.2. Directive No. 23 Year 2018.** Direktif Untuk Semua Produk Yang Mengandungi *Saccharomyces Boulardii* : Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko *Fungaemia*

Attachment 7

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	IODINATED CONTRAST MEDIA The following statements shall be included in the package insertfor products containing Iodinated Contrast Media; **Package Insert** **a) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Severe cutaneous adverse reactions {e.g. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP)} have been reported in post-marketing experience of iodinated contrast media. **Reference: Circular Bil (24) dlm. BPFK/PPP/07/25 (24) Jld 2. Directive No. 24 Year 2018.** Direktif Untuk Semua Produk Yang Mengandungi *Iodinated Contrast Media* : Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan *Severe Cutaneous Adverse Reactions (SCARs)*

Attachment 8

8.2 LIST OF PROHIBITED AND RESTRICTED EXCIPIENTS

8.2.2 LIST OF RESTRICTED EXCIPIENTS		
Excipients	**Restrictions**	
1. Colouring Agents (Including in Capsule Shells)		
a) Tartrazine (CI= 19140, FD & C Yellow No.5, E102)	Not allowed in the following preparations: – Oral; – Rectal; – Vaginal or – Nasal Preparations	
b) Red 2G	Not allowed in the following preparations: – Oral Preparations; and – Preparations Used for Mucosa Membrane	
2. Sweeteners/ Flavouring Agent		
a) Menthol	0.4mg/kg body weight/day (dosage and use in children should be clearly stated).	
b) Saccharin and Salts	Limited to not more than 5mg/kg/day	
c) Cyclamates	Limited to not more than 1.5mg/kg body weight/day	
3. Preservatives		
a) Chloroform	Limited to not more than 0.5% in Pharmaceuticals for Internal Use	
b) Thiomersal *	Not allowed in ophthalmic Preparations	
4. Others		
a) Phthalates	Variant	Maximum Limit of Daily Exposures (mg/kg body weight/day)
	Dibutyl Phthalate (DBP)	0.01mg/ kg/ day
	Diethyl Phthalate (DEP)	4mg/ kg/ day
	Polyvinyl Acetate Phthalate (PVAP)	2mg/ kg/ day
b) Cetrimide	Limited to less than 0.1% w/v (topical preparations for Natural Products)	

Attachment 9

1.4 CHARGES FOR AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

1.4.1 CHANGE OF MANUFACTURING SITE & CHANGE OF PRODUCT REGISTRATION HOLDER

Types of Amendment	Processing fee	
	Pharmaceutical	Natural Product
1. Change of Manufacturing Site (Type I)	RM 1,000.00	RM 100.00
2. Change of Manufacturing Site (Type II, III, IV, V)	RM 1,000.00	RM 500.00
3. Change of Product Registration Holder	RM 1,000.00	RM 500.00
~~4. Minor Variation Prior Approval (MiV-PA)~~	~~RM 150.00~~	~~RM 50.00~~
~~5. Major Variation (MaV)~~	~~RM 300.00~~	~~RM 100.00~~
~~6. Additional Indication~~	~~RM 1000.00~~	~~Not applicable~~

1.4.2 VARIATION & ADDITIONAL INDICATION

Types of Amendment	Processing fee	
	Full Evaluation	Abridged Evaluation
1. Minor Variation Prior Approval (MiV-PA)	RM 150.00	RM 50.00
2. Major Variation (MaV)	RM 300.00	RM 100.00
3. Additional Indication	RM 1000.00	Not applicable