LIST OF UPDATES FOR

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JULY 2024

(April 2024 Updates)

There are thirteen (13) amendments for the April 2024 DRGD Updates as follows:

Main Body of DRGD Third Edition, Seventh Revision January 2024

1. Addition of information, 7.10 Proposed Package Insert, Page 42

Appendix of DRGD Third Edition, Seventh Revision January 2024

2. Addition of new Appendix 7B: Guideline on Natural Products with Modern Claim

Appendix 20: Specific Labelling Requirements

3. Addition of new ingredient and safety information, No. 51, Ciprofloxacin, Page 50
4. Addition of new ingredient and safety information, No. 142, Moxifloxacin, Page 140
5. Addition of new ingredient and safety information, No. 119, Levofloxacin, Page 118
6. Addition of new ingredient and safety information, No. 151, Ofloxacin, Page 146
7. Addition of new ingredient and safety information, No. 65, Dapagliflozin (including combination products), Page 65
8. Addition of new ingredient and safety information, No. 80, Empagliflozin (including combination products), Page 80
9. Addition of new ingredient and safety information, No. 39, Canagliflozin (including combination products), Page 40
10. Addition of new ingredient and safety information, No. 122, Lithium, Page 120
11. Addition of new ingredient and safety information, No. 125, Mefenamic Acid, Page 124
12. Addition of new ingredient and safety information, No. 152, Olmesartan (including combination products), Page 146
13. Amendment of existing safety information, No. 101, Hydrochlorothiazide (including combination products), Page 101

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Amendment of Main Body of DRGD Third Edition, Seventh Revision January 2024

1. Addition of information in 7.10 Proposed Package Insert on Page 42 by –

   (a) inserting the statement, "(including clinical studies – clinical studies not applicable for generics)" after "d) Pharmacodynamics".

Addition of new Appendix 7B: Guideline on Natural Products with Modern Claim

2. Renumbering of previous Appendix 7B: Guideline on Natural Products with Therapeutic Claim to Appendix 7C.

Amendment of Appendix 20: Specific Labelling Requirements

3. **Addition of new ingredient 51. Ciprofloxacin and safety information on page 50** as follows in accordance with Directive No. 8, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

   "**CIPROFLOXACIN**

   The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing ciprofloxacin for systemic use (oral and injection dosage forms):

   Package Insert

   a) Warnings & Precautions:

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including [Product name]. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, [Product name] should be discontinued and appropriate measures instituted. Caution is recommended if [Product name] is to be used in psychotic patients or in patients with a history of psychiatric disease.

b) Adverse Effects/ Undesirable Effects:

Psychiatric disorders

Rare: Depression (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)

Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)

Consumer Medication Information Leaflet (RiMUP)

a) While you are using it:

You may experience mental health problems even when taking/ using fluoroquinolone antibiotics, including [Product name] for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts. If you develop such reactions, stop taking/ using [Product name] and inform your doctor immediately.

b) Side effects:

Rare: Depression (potentially leading to thoughts of suicide, suicide attempts, or completed suicide), or hallucinations
Very rare: Psychotic reactions potentially leading to thoughts of suicide, suicide attempts, or completed suicide

Reference: Directive No. 8, 2024. *NPRA.600-1/9/13 (39)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin,*

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Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour"

4. **Addition of new ingredient 142. Moxifloxacin and safety information on page 140** as follows in accordance with Directive No. 8, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

"MOXIFLOXACIN

The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing moxifloxacin for systemic use (oral and injection dosage forms):

<u>Package Insert</u>

a) Warnings & Precautions:

<u>Psychiatric reactions</u>

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including [Product name]. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, [Product name] should be discontinued and appropriate measures instituted. Caution is recommended if [Product name] is to be used in psychotic patients or in patients with a history of psychiatric disease.

b) Adverse Effects/ Undesirable Effects:

<u>Psychiatric disorders</u>

Rare: Depression (in very rare cases potentially culminating in self- injurious behaviour, such as suicidal ideation/ thoughts or suicide attempts), Hallucination

Very Rare: Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideation/ thoughts or suicide attempts)

Consumer Medication Information Leaflet (RiMUP)

a) While you are using it:

You may experience mental health problems even when taking/ using fluoroquinolone antibiotics, including [Product name] for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts. If you develop such reactions, stop taking/ using [Product name] and inform your doctor immediately.

b) Side effects:

Rare: Depression (in very rare cases leading to self-harm, such as suicidal ideations/ thoughts (desire to kill oneself), or suicide attempts), hallucinations

Very rare: Psychotic reactions (potentially leading to self-harm, such as suicidal ideations/ thoughts (desire to kill oneself), or suicide attempts)

Reference: Directive No. 8, 2024. ***NPRA.600-1/9/13 (39)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour"*

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5. **Addition of new ingredient 119. Levofloxacin and safety information on page 118** as follows in accordance with Directive No. 8, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

*"***LEVOFLOXACIN**

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing levofloxacin for systemic use (oral and injection dosage forms):

Package Insert

a) Warnings & Precautions:

Psychiatric reactions
Psychiatric reactions may occur even after the first administration of fluoroquinolones, including [Product name]. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, [Product name] should be discontinued and appropriate measures instituted. Caution is recommended if [Product name] is to be used in psychotic patients or in patients with a history of psychiatric disease.

b) Adverse Effects/ Undesirable Effects:

Psychiatric disorders
Rare: Psychotic reactions (with e.g. hallucination, paranoia), Depression

Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)

Not known (cannot be estimated from available data): Psychotic disorders with self-endangering behavior including suicidal ideation or suicide attempt

Consumer Medication Information Leaflet (RiMUP)

a) While you are using it:

You may experience mental health problems even when taking/ using fluoroquinolone antibiotics, including [Product name] for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts. If you develop such reactions, stop taking/ using [Product name] and inform your doctor immediately.

b) Side effects:

Rare: Change in your opinion and thoughts (psychotic reactions) with a risk of having suicidal thoughts or actions, hallucination, depression

Very rare: Psychotic behaviour

Not known (frequency cannot be estimated from the available data): Psychotic reactions with a risk of having suicidal thoughts or actions

Reference: Directive No. 8, 2024. ***NPRA.600-1/9/13 (39)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour"*

6. **Addition of new ingredient 151. Ofloxacin and safety information on page 146** as follows in accordance with Directive No. 8, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

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"OFLOXACIN

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing ofloxacin for systemic use (oral and injection dosage forms):

Package Insert

a) Warnings & Precautions:

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including [Product name]. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, [Product name] should be discontinued and appropriate measures instituted. Caution is recommended if [Product name] is to be used in psychotic patients or in patients with a history of psychiatric disease.

b) Adverse Effects/ Undesirable Effects:

Psychiatric disorders

Rare: Psychotic disorder (for e.g.hallucination)

Very Rare: Psychotic behaviour

Frequency not known (cannot be estimated from the available data): Psychotic disorders and depression with self-endangering behavior including suicidal ideation or suicide attempt

Consumer Medication Information Leaflet (RiMUP)

a) While you are using it:

You may experience mental health problems even when taking/ using fluoroquinolone antibiotics, including [Product name] for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts. If you develop such reactions, stop taking/ using [Product name] and inform your doctor immediately.

b) Side effects:

Rare: Psychotic reactions with a risk of having suicidal thoughts or actions, hallucination, depression

Very rare: Psychotic behaviour

Not known (frequency cannot be estimated from the available data): Psychotic reactions with a risk of having suicidal thoughts or actions

Reference: Directive No. 8, 2024. *NPRA.600-1/9/13 (39)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Ciprofloxacin, Moxifloxacin, Levofloxacin dan Ofloxacin Untuk Kegunaan Sistemik (Sediaan Oral dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Suicidal Behaviour"*

7. **Addition of new ingredient 65. Dapagliflozin (including combination products) and safety information on page 65** as follows in accordance with Directive No. 9, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

"**DAPAGLIFLOZIN (INCLUDING COMBINATION PRODUCTS)**

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

Package Insert

a) Interactions:

Concomitant use of dapagliflozin and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]- taking other medicines

Especially tell your doctor:

- if you are taking lithium because [product name] can lower the amount of lithium in your blood.

Reference: Directive No. 9, 2024. *NPRA.600-1/9/13 (40)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat"*

8. **Addition of new ingredient 80. Empagliflozin (including combination products) and safety information on page 80** as follows in accordance with Directive No. 9, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

"**EMPAGLIFLOZIN (INCLUDING COMBINATION PRODUCTS)**

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

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Package Insert

a) Interactions:

Lithium

Concomitant use of SGLT2 inhibitors, including empagliflozin, with lithium may decrease blood lithium levels through increased renal lithium elimination. Therefore, serum lithium concentration should be monitored more frequently with empagliflozin initiation or following dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]- taking other medicines

It is important to tell your doctor:

- if you are taking lithium because [product name] can lower the amount of lithium in your blood.

Reference: Directive No. 9, 2024. *NPRA.600-1/9/13 (40)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat"*

9. **Addition of new ingredient 39. Canagliflozin (including combination products) and safety information on page 40** as follows in accordance with Directive No. 9, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

"**CANAGLIFLOZIN (INCLUDING COMBINATION PRODUCTS)**

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

Package Insert

a) Interactions:

Lithium

The concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more closely during treatment with canagliflozin, especially during initiation and dosage changes.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]- taking other medicines

In particular, tell your doctor if you are taking any of the following medicines:

- lithium (a medicine used to treat bipolar disorder)

Reference: Directive No. 9, 2024. *NPRA.600-1/9/13 (40)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat"*

10. **Addition of new ingredient 122. Lithium and safety information on page 120** as follows in accordance with Directive No. 9, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium*

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(Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

"**LITHIUM**

The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing lithium (for treatment purpose only):

<u>Package Insert</u>

a) Interactions:

SGLT2 inhibitors may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after initiation and dose changes of SGLT2 inhibitors.

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

a) Before you use [product name]- taking other medicines

The following medication interacts with Lithium Carbonate:

- Medication of the class 'sodium-glucose co-transporter 2 (SGLT2) inhibitors' such as empagliflozin (medication for type 2 diabetes or heart failure), dapagliflozin (medication for type 2 diabetes, heart failure or chronic kidney disease), canagliflozin (medication for type 2 diabetes, heart failure or chronic kidney disease).

Reference: Directive No. 9, 2024. *<u>NPRA.600-1/9/13 (40)Jld.1</u>* *Direktif Untuk Semua Produk Yang Mengandungi Dapagliflozin, Empagliflozin, Canagliflozin (Termasuk Produk Kombinasi) dan Lithium (Untuk Tujuan Rawatan): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Penurunan Paras Serum Lithium Akibat Interaksi Ubat"*

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11. **Addition of new ingredient 125. Mefenamic Acid and safety information on page 124** as follows in accordance with Directive No. 10, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Mefenamic Acid: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Generalised Bullous Fixed Drug Eruption (GBFDE)* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

"**MEFENAMIC ACID**

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

<u>Package Insert</u>

a) Warnings & Precautions:

<u>Skin Reactions</u>
Serious skin reactions such as Generalised bullous fixed drug eruption (GBFDE) have been reported very rarely in association with the use of mefenamic acid. Mefenamic acid should be discontinued at the first appearance of the skin rash, mucosal lesions or any other sign of hypersensitivity.

b) Adverse Effects/ Undesirable Effects:

<u>Skin and subcutaneous tissue disorders:</u>

Generalised bullous fixed drug eruption (GBFDE)

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

a) While you are using it:

If you suffer from skin rash and blisters during your treatment, inform your doctor immediately.

b) Side effects:

Skin rash sometimes with blisters.

Reference: Directive No. 10, 2024. *NPRA.600-1/9/13 (41)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Mefenamic Acid: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Generalised Bullous Fixed Drug Eruption (GBFDE)"*

12. **Addition of new ingredient 152. Olmesartan (including combination products) and safety information on page 146** as follows in accordance with Directive No. 11, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Olmesartan (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hepatitis Autoimun (Autoimmune Hepatitis)* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

"**OLMESARTAN (INCLUDING COMBINATION PRODUCTS)**

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

Package Insert

a) Adverse Effects/ Undesirable Effects:

Hepatobiliary disorders

Frequency 'not known': Autoimmune hepatitis*

*Cases of autoimmune hepatitis with a latency of few months to years have been reported post-marketing, that were reversible after the withdrawal of olmesartan.

Consumer Medication Information Leaflet (RiMUP)

a) Side effects:

Frequency not known:

- If you experience yellowing of the whites of the eyes, dark urine, itching of the skin, even if you started therapy with [product name] longer time ago, contact your doctor immediately who will evaluate your symptoms and decide on how to continue your blood pressure medication.

Reference: Directive No. 11, 2024. *NPRA.600-1/9/13 (42)Jld.1* *Direktif Untuk Semua Produk Yang Mengandungi Olmesartan (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hepatitis Autoimun (Autoimmune Hepatitis)"*

13. **The specific labelling requirements for existing ingredient, No. 101, Hydrochlorothiazide on page 101** is amended as follows in accordance with Directive No. 12, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Hydrochlorothiazide (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Acute Respiratory Distress Syndrome (ARDS)* as decided in DCA Meeting No. 395, which takes effect on 1 May 2024 –

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"HYDROCHLOROTHIAZIDE (INCLUDING COMBINATION PRODUCTS)

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

Package Insert

a) Warnings & Precautions:

Hydrochlorothiazide

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, [product name] should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

b) Adverse Effects/ Undesirable Effects:

Respiratory, thoracic and mediastinal disorders
Frequency 'very rare': Acute respiratory distress syndrome (ARDS)

Consumer Medication Information Leaflet (RiMUP)

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

Before taking [product name], tell your doctor:

- if you experience breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking [product name], seek medical attention immediately.

b) Side effects:

Very Rare:

- Acute respiratory distress (signs include severe shortness of breath, fever, weakness and confusion).

Reference: Directive No. 12, 2024. ***NPRA.600-1/9/13 (43)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Hydrochlorothiazide (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Acute Respiratory Distress Syndrome (ARDS)"*

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(May 2024 Updates)

There are six (6) amendments for the May 2024 DRGD Updates as follows:

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Appendix 19: General Labelling Requirements

1. Amendment of information, Table 1, Page 2

Appendix 29: Certificate

2. Amendment of information, 1. Certificate of Pharmaceutical Product (CPP), Page 1

Appendix 32: Explanatory Notes for Repackers

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4. Amendment of information, 4. Types of Repacking Activity, Page 3
5. Amendment of information, 5. Additional Notes, Page 6
6. Amendment of information, 6. References, Page 6

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Amendment of Appendix 19: General Labelling Requirements

1. Amendment of information in Table 1 on Page 2 by –

   (a) substituting "✓" with "✓*" for "Immediate Labels" under items, No. 15. Name & content of preservative(s) where present, No. 16. Name & content of alcohol, where present, and No. 17. To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine.

Amendment of Appendix 29: Certificate

2. Amendment of information in 1. Certificate of Pharmaceutical Product (CPP) on Page 1 by –

   (a) substituting the following content,

"1. CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP)

A CPP in the format recommended by WHO for a registered product can be applied by the PRH where such certificate is required by any country importing such product.

To apply a CPP, the PRH shall fill up completely and submit the online application form via the QUEST system.

A fee, as stated in Appendix 9: **Fees**, is payable on the issue of such certification.

Upon receipt of complete application, the certificate shall be issued within fifteen (15) working days.

For imported products, the following requirements shall be furnished, either a:

i) CPP from the competent authority in the country of origin; OR
*(**Note:** In the event a CPP is not available from the country manufacture, e.g. where a product is not licensed for sale in said country because its manufacturer is manufacturing under contract only for product owner from another country, the following alternatives may be considered: GMP Certification/ Manufacturing License for the manufacturer from the relevant competent authority, together with CPP from the country of the product owner; or CPP from country of release, if CPP from the country of the product owner is not available)*

ii) CFS and GMP from the relevant competent authorities is deemed acceptable by the Authority for health supplements and natural products only.

CPP shall be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce & be issued by the Health Authorities listed in the WHO Certification Scheme (*list is available from WHO website*: *http://www.who.int*).

CPP which is issued by EMA for products registered through the centralized procedure in EU will be accepted.

CPP issued by the manufacturer or other authorities are not acceptable.

If more than one manufacturer is involved in the manufacture of a product, GMP certification shall be available for all the manufacturers.

The Authority reserves the right to conduct an inspection on any manufacturing site.

Unless otherwise supported by justifications acceptable to the Authority, the following products are unlikely to be registered:

i) products not licensed/ certified for sale in the country of manufacture/ product owner;
ii) products manufactured for export only (imported products)."

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with the following content,

"1. CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP)

The Certificate of Pharmaceutical Product (CPP) is a document issued by a competent authority for establishing the status of a pharmaceutical product under a national drug product licensing system. Competent authority refers to any local or national regulatory authority responsible for regulating the quality, efficacy, and safety of medicine. The CPP issued by other organizations or bodies, that the competent authority has appointed is also acceptable. The competent authority may issue a CPP for any product that has been registered locally if such a certificate is required by the Product Registration Holder (PRH) for the purpose of export.

On the other hand, a CPP from an exporting country may be required to support product registration in Malaysia. The CPP plays a crucial role in supporting the registration of imported medicinal products in Malaysia. The CPP serves as official documentation issued by the regulatory authority of the exporting country, confirming that the pharmaceutical product meets regulatory requirements and is authorized for sale in that country. The submission of CPP during the product registration application provides assurance to NPRA that the product has undergone evaluation and approval processes consistent with international standards, including confirmation that the product is manufactured in a facility compliant with Good Manufacturing Practice (GMP).

A. <u>How to apply for a CPP</u>

PRH may apply for a CPP in the format recommended by WHO for a registered product in Malaysia when such a certificate is required by any country importing the product.

To apply for a CPP, the PRH shall complete the online application form and submit it via the QUEST system.

A fee, as stated in **Appendix 9: Fees**, is payable on the issue of such certification.

The certificate shall be issued within fifteen (15) working days upon receipt of a complete application.

B. Submission of a CPP to support registration applications for imported products

A CPP is required at the point of submission for imported products. A CPP may serve as a reliance tool to confirm the quality, safety, and efficacy of a product hence this could facilitate the review process of such product and its registration approval in Malaysia.

If the CPP is to be provided, the following are applicable:

a) CPP from the competent authority in the country of origin (country of manufacture) in the format of the *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* or by the authorized body.
b) CPP issued by the manufacturer is not acceptable.
c) CPP that is valid at the time of submission. If the expiration date is not stated on the CPP, the CPP validity should not exceed 2 years from the date of issuance.
d) Both original and electronic CPPs issued by the NRAs are acceptable.
e) All information except for brand name/trade name reflected in the CPP must be applicable and consistent with the proposed product for the Malaysian market.
f) CPPs indicating that the product is solely for export only (not registered and not marketed in the exporting country) are not acceptable.
g) If more than one manufacturer is involved in the manufacture of a product and are intended to be registered in Malaysia but not stated in the CPP, GMP certification should be submitted for all the manufacturers. NPRA reserves the right to conduct an inspection on any manufacturing site when deemed necessary.
h) In the event a CPP from the country of origin is not available, for example when the product is manufactured under contract for a product owner from another country and the product is not licensed for sale in the manufacturing country, the following alternatives may be considered:
    i. CPP from the country of the product owner; OR
    ii. CPP from the country of release or CPP from DCA reference country, if CPP from the country of the product owner is not available.
i) CPPs with a declaration that the product is not marketed may be acceptable if:
    i. The CPP is issued by a competent authority; AND
    ii. Manufacturer declares in the declaration letter the reason for not marketing the product in the country. The acceptance of the reason for not marketing the product in the country is subject to NPRA's discretion

Note: Point i) is not applicable for non-scheduled poison (OTC), health supplements and natural products (excluding natural product with therapeutic claim and health supplement with disease risk reduction)

C. Alternative documents in lieu of CPP to support registration applications for imported products

a) If a CPP cannot be provided at the point of submission, the following documents can be considered as alternatives
   i. An official approval letter or document by the competent authority that states the registration status of the product; AND
   ii. Certificate of Free Sale (CFS) or proof that the product is marketed in the exporting country. If the product is not marketed in the exporting country, the manufacturer declares in the declaration letter the reason for not marketing the product in the country. The acceptance of the reason for not marketing the product in the country is subject to NPRA's discretion; AND
   iii. The Summary of Product Characteristics (SmPC) or Package Insert (PI) approved by the competent authority

b) For non-scheduled poison (OTC), health supplements and natural products (excluding natural product with therapeutic claim and health supplement with disease risk reduction), a Certificate of Free Sale (CFS) and Good Manufacturing Practice (GMP) certificate from the relevant competent authorities are required as alternative documents.

D. The submission of a CPP for product not registered in any other country

a) Submission of a product registration without a CPP due to the fact that the product has not been previously approved in any country can be considered on a case- by-case basis depending on the country's need.
b) Prior to submitting the dossier, the applicant should submit an exemption request letter with justifications to the Director of NPRA. Subsequently, the applicant may request a pre-submission meeting to provide an overview of the product and regulatory submission plan in other countries (if any).
c) This requirement is not applicable for non-scheduled poison (OTC) products, health supplements and natural products."

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Amendment of Appendix 32: Explanatory Notes for Repackers

3. Addition of information in 3. Definitions on Page 1 by –

   (a) adding the following definitions,

Terms	Definitions
Importer	Any person who, whether as owner, consignee, agent or broker, is in possession of, or in anywise entitled to the custody, or control, of the imported article.
Wholesaler	A person who sell to other person who intends to sell again.

4. Amendment of information in 4. Types of Repacking Activity on Page 3 by –

   (a) deleting "for Immediate Labels" from the Remark, "Refer to **Appendix 19: General Labelling Requirements** for Immediate Labels" for item no. 4.

   (b) deleting "for Unit Outer Carton" from the Remark, "Refer to **Appendix 19: General Labelling Requirements** for Unit Outer Carton" for item no. 5.

(c) adding "Wholesaler" to Responsibility, and substituting the Remark, "The importer/ repacker shall maintain the relevant documents (e.g. hologram records, stock card)" with "Refer to **Appendix 19: General Labelling Requirements.** Relevant documents (e.g. hologram records, stock card, etc.) shall be maintained." for item no. 6.

(d) inserting "product's" in front of "secondary packaging product (unit box)" in Description of Repacking Activity and "Primary Repacker" to Responsibility for item no. 7.

(e) inserting "product's" in front of "secondary packaging product (unit box)" in Description of Repacking Activity and "Primary Repacker" to Responsibility for item no. 8.

(f) deleting "etc." from Description of Repacking Activity and inserting "Primary Repacker" and "Wholesaler" to Responsibility and "Refer to **Appendix 19: General Labelling Requirements"** in Remarks for item no. 12.

(g) inserting "Wholesaler" to Responsibility and "Refer to **Appendix 19: General Labelling Requirements"** in Remarks for item no. 13.

(h) inserting "Wholesaler" to Responsibility and "Refer to **Appendix 19: General Labelling Requirements"** in Remarks for item no. 14.

(i) inserting "Wholesaler" to Responsibility for item no. 15.

(j) inserting "Wholesaler" to Responsibility for item no. 16.

(k) substituting "product immediate" with "immediate product" in Description of Repacking Activity and inserting "Wholesaler" to Responsibility for item no. 17.

(l) inserting "Wholesaler" to Responsibility and "Refer to **Appendix 19: General Labelling Requirements"** in Remarks for item no. 18.

(m) substituting "Refer to Guideline on Electronic Labelling (E-Labelling) for Pharmaceutical Products in Malaysia" with "Refer to **Appendix 19: General Labelling Requirements"** in Remarks for item no. 19.

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5. Amendment of information in 5. Additional Notes on Page 6 by –

   (a) inserting “Good Manufacturing Practice (GMP)/” in front of “Good Distribution Practice (GDP) controlled or licensed facility.” in 5.1.

   (b) inserting “etc.” into (batch packaging records/logbooks/inventory records/ procedures) in 5.2.

   (c) substituting “Good Distribution Practice Guideline” with “Guideline on Good Distribution Practice” and “National Pharmaceutical Regulatory Division (NPRA)” with “National Pharmaceutical Regulatory Agency (NPRA)” in 5.3.

6. Amendment of information in 6. References on Page 6 by –

   (a) substituting “Good Distribution Practice Guideline” with “Guideline on Good Distribution Practice” in 6.1.

   (b) substituting “Control of Cosmetic Products” with “Guideline for Control of Cosmetic Products in Malaysia” in 6.2.

   (c) substituting “WHO GMP: Main Principles for Pharmaceutical Products” with “WHO Good Manufacturing Practice for Pharmaceutical Products: Main Principles” in 6.6.

   (d) adding “6.7 Sale of Drugs Act 1952” and “6.8 Poisons Act 1952”.

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There are seven (7) amendments for the July 2024 DRGD Updates as follows:

Main Body of DRGD Third Edition, Seventh Revision January 2024

1. Amendment of 10.3 Evaluation Timeline for Product Registration, Page 50
2. Second amendment of 10.3 Evaluation Timeline for Product Registration, Page 50

Appendix of DRGD Third Edition, Seventh Revision January 2024

Appendix 6: Guideline on Registration of Health Supplements

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

Appendix 9: Fees

4. Amendment of information, 2. Processing and Analysis Fees for Product Registration, Page 3

Appendix 12: Priority Review

5. Amendment of Paragraph 1, Page 1

Appendix 20: Specific Labelling Requirements

6. Amendment of existing safety information, No. 23, Azacitidine, Page 28
7. Amendment of existing safety information, No. 47, Hydroxychloroquine, Page 47

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Amendment of Main Body of DRGD Third Edition, Seventh Revision January 2024

1. Amendment of 10.3 Evaluation Timeline for Product Registration on Page 50 by –

(a) inserting the following into Full Evaluation:

NO.	PRODUCT CATEGORY	* EVALUATION TIMELINE
(A)	**FULL EVALUATION**	
6.	Health Supplement with Disease Risk Reduction Claim	245 working days

(b) replacing the details for Natural Products and Health Supplements with the following:

(B)	ABRIDGED EVALUATION	* EVALUATION TIMELINE
8.	Natural Products** a) Single active ingredient b) Two (2) or more active ingredients ** *Applicable for:* *i) Traditional Claims; and* *ii) Modern Claims*	a) 116 working days b) 136 working days

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(B)	ABRIDGED EVALUATION	* EVALUATION TIMELINE
9.	Health Supplements*** a) Single active ingredient b) Two (2) or more active ingredients *** *Applicable for:* *i) General or Nutritional Claims; and* *ii) Functional Claims (Medium Claims)*	a) 116 working days b) 136 working days

2. Second amendment of 10.3 Evaluation Timeline for Product Registration on Page 50 by –

(a) inserting the following note,

"^The timeline stated may not apply to situations below:

1. For products with new data (involving major supporting documents) submitted during product evaluation that require a comprehensive review
2. For products submitted with more than three indications and/ or products that require an extensive review (for example, products with three or more pivotal trials/studies)

The final timeline will be determined by the Drug Evaluation Committee."

to the respective Evaluation Timeline for New Drug Products (NCE), New Drug Products (Hybrid), Biologics and Generics (Scheduled Poison).

Amendment of Appendix 6: Guideline on Registration of Health Supplements

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

(a) adding a new functional claim, "Support healthy hair, skin and nails" to Biotin.

(b) adding new functional claims, "Antioxidant" and "Promote energy production" to Coenzyme Q10.

(c) adding new functional claims, "Antioxidant" and "Supports in immune health" to Copper.

(d) adding a new functional claim, "Supports joint health" to Docosahexaenoic acid (DHA).

(e) adding new functional claims, "Supports eye health" and "Supports joint health" to Eicosapentaenoic acid (EPA).

(f) adding a new functional claim, "Support healthy cell division" to Folic Acid.

(g) adding a new functional claim, "Supports skin moisture" to Hyaluronic Acid.

(h) adding a new functional claim, "Antioxidant" to Lutein.

(i) adding new functional claims, "Helps in the development and maintenance of bones and teeth", "Helps to maintain muscle function", "Helps in energy metabolism", "Helps to maintain heart muscle function", "Support nerve function" and "Maintain normal electrolyte balance" to Magnesium.

(j) adding a new functional claim, "Support healthy immune function" to Vitamin A.

(k) adding new functional claims, "Helps in carbohydrate metabolism", "Helps in energy metabolism" and "Helps maintain healthy heart" to Vitamin B1 (Thiamine).

(l) adding new functional claims, "Support healthy nervous system" and "Helps in energy metabolism" to Vitamin B6 (Pyridoxine).

(m) adding new functional claims, "Antioxidant" and "Helps in collagen formation to maintain healthy bones" to Vitamin C.

(n) adding new functional claims, "Supports in immune health" and "Supports maintenance of normal muscle function" to Vitamin D.

(o) adding new functional claims, "Antioxidant" and "Supports in immune health" to Vitamin E.

(p) adding new functional claims, "Supports in immune health", "Helps in connective tissue formation", "Antioxidant", "Helps maintain healthy male reproduction system" and "Helps to maintain healthy skin" to Zinc.

(q) adding the following new ingredients and claims:

Ingredients	**Claims**		
	General	**Functional**	**Reduced Risk Reduction Claim**
Alpha Linolenic Acid	- Helps in maintenance ofgood health	- Supports heart health	
Alpha Lipoic Acid	- Helps in	- Antioxidant	

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Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
	maintenance ofgood health	- Helps to promote glucose metabolism - Supports healthy nervous system	
Astaxanthin	- Helps in maintenance of good health	- Antioxidant	
Chromium	- Helps in maintenance of good health	- Contributes to normal macronutrient metabolism - Helps to support healthy blood sugar level	
Inulin	- Helps in maintenance of good health	- Helps to stimulate the growth of healthy bacteria (such as bifidobacteria) in the intestine	
L-Glutathione	- Helps in maintenance of good health	- Antioxidant	
L-Lysine	- Helps in maintenance of good health	- Source of essential amino acid for protein synthesis in the body	
Lecithin	- Helps in maintenance of good health	- Supports liver health	
Lycopene	- Helps in maintenance of good health	- Antioxidant - Helps to support prostate health	

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Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Oenothera biennis (Evening primrose oil)	- Helps in maintenance of good health	- Helps in management of premenstrual syndrome (PMS)	
Potassium	- Helps in maintenance of good health	- Supports healthy muscle function	
Pyrroloquinoline quinone (PQQ)	- Helps in maintenance of good health	- Antioxidant	
Saw Palmetto Berry	- Helps in maintenance of good health	- Support healthy urinary flow	
Selenium	- Helps in maintenance of good health	- Antioxidant - Helps to maintain healthy thyroid function - Supports immune system	
Vitis vinifera (Grape seed)	- Helps in maintenance of good health	- Antioxidant	

Amendment of Appendix 9: Fees

4. Amendment of information in 2. Processing and Analysis Fees for Product Registration on Page 3 by –

(a) Replacing the details for Natural Product with the following:

No.	Category of Product	* Processing Fees (RM)	Analysis Fees (RM)	Total Fees (RM)
3.	Natural products with traditional claim	500.00	700.00	1,200.00
4.	Natural products with modern claim	1,000.00	Single active ingredient: 1,200.00	2,200.00
			Two or more active ingredients: 2,000.00	3,000.00

Amendment of Appendix 12: Priority Review

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

(a) adding item, “(vi) Population’s specific needs (e.g., religious purpose)” to “(a) Product which is intended for:”

(b) inserting “three” before “locally manufactured generic/ biosimilar product.” for statement (d).

(c) replacing the statement, "**The priority review status granted based on condition c) shall be cancelled during the duration of product application evaluation, in the event that a same/ similar first generic/ biosimilar product or first locally manufactured generic/ biosimilar product has been approved for registration."* with, "**During product evaluation, the priority review status granted can be cancelled in the event that the condition (d) is no longer fulfilled."*

(d) replacing "phase III pivotal clinical trial" with "a phase III global, multicentre pivotal clinical trial" and "10%" with "5%" for statement (e).

(e) replacing statement 2. with "An application for Priority Review should be submitted via a formal letter to the Director of NPRA within one month after the payment has been confirmed."

Amendment of Appendix 20: Specific Labelling Requirements

6. **The specific labelling requirements for existing ingredient, No. 23, Azacitidine on page 28** is amended as follows in accordance with Directive No. 13, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Azacitidine (Sediaan Injeksi Sahaja) : Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Cutaneous Vasculitis* as decided in DCA Meeting No. 398, which takes effect on 1 August 2024 –

"AZACITIDINE

The following statements shall be included in the package insert for products containing azacitidine;

Package Insert

a) Adverse Effects/ Undesirable Effects:

Skin & subcutaneous tissue disorders
Frequency 'not known': Cutaneous vasculitis

Reference: Directive No. 13, 2024. ***NPRA.600-1/9/13 (44)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Azacitidine (Sediaan Injeksi Sahaja) : Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Cutaneous Vasculitis"*

7. **The specific labelling requirements for existing ingredient, No. 47,** Hydroxychloroquine **on page 47** is amended as follows in accordance with Directive No. 14, 2024: *Direktif Untuk Semua Produk Yang Mengandungi Hydroxychloroquine : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Acute Febrile Neutrophilic Dermatosis (Sweet's Syndrome)* as decided in DCA Meeting No. 398, which takes effect on 1 August 2024 –

"HYDROXYCHLOROQUINE

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

Package Insert

a) Adverse Effects/ Undesirable Effects:
Skin and subcutaneous tissue disorders

Frequency 'not known': Sweet's syndrome

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Consumer Medication Information Leaflet (RiMUP)

a) Side Effects:

Skin reaction including plum-colored, raised, painful sores, particularly on your arms, hands, fingers, face and neck, which may also be accompanied by fever. This could be a condition called Sweet's syndrome

Reference: Directive No. 14, 2024. ***NPRA.600-1/9/13 (45)Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Hydroxychloroquine : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Acute Febrile Neutrophilic Dermatosis (Sweet's Syndrome)"*