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Tarikh : 17 OCT 2017

SEMUA PEMEGANG PENDAFTARAN

SEMUA PERSATUAN BERKENAAN
(SEPERTI DI SENARAI EDARAN)

Tuan/ Puan,

PERATURAN-PERATURAN KAWALAN DADAH DAN KOSMETIK 1984

ARAHAN PENGARAH KANAN PERKHIDMATAN FARMASI BILANGAN 25 TAHUN 2017: DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI METFORMIN: PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT BERKAITAN PENGGUNAAN DALAM KALANGAN PESAKIT YANG MEMPUNYAI *MODERATELY REDUCED KIDNEY FUNCTION* DAN PENGUKUHAN AMARAN *LACTIC ACIDOSIS*

Adalah saya merujuk kepada Arahan Bilangan 25 Tahun 2017 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 25 Tahun 2017 telah bersetuju untuk menambah maklumat berkaitan penggunaan dalam kalangan pesakit yang mempunyai *moderately reduced kidney* function dan pengukuhan amaran *lactic acidosis* bagi semua produk yang mengandungi metformin seperti pada surat arahan Bil. (30)BPFK/PPP/07/25 Jld. 1.

3. Pihak pemegang pendaftaran adalah diarahkan untuk mematuhi keperluan tersebut.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,

DR RAMLI ZAINAL (RPh 1045)
Pengarah Regulatori Farmasi
Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia

SITI AIDA ABDULLAH
Timbalan Pengarah
Pusat Pembangunan Organisasi
Biro Pengawalan Farmaseutikal Kebangsaan
Kementerian Kesihatan Malaysia

ra/nb/ppp/NPRA/091017

BPFK/PPP/07/25 (30) Jld 1

ARAHAN DI BAWAH PERATURAN 29 PERATURAN – PERATURAN KAWALAN DADAH DAN KOSMETIK 1984

BILANGAN 25 TAHUN 2017

DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI METFORMIN: PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT BERKAITAN PENGGUNAAN DALAM KALANGAN PESAKIT YANG MEMPUNYAI *MODERATELY REDUCED KIDNEY FUNCTION* DAN PENGUKUHAN AMARAN *LACTIC ACIDOSIS*

TUJUAN

1.1 Arahan ini dikeluarkan oleh Pengarah Kanan Perkhidmatan Farmasi di bawah Peraturan 29 (1) Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984.

1.2 Arahan ini ditujukan kepada semua pemegang pendaftaran semua produk yang mengandungi metformin bagi mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat berkaitan penggunaan dalam kalangan pesakit yang mempunyai *moderately reduced kidney function* dan pengukuhan amaran *lactic acidosis.*

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **316** pada **3 Oktober 2017** telah membuat keputusan bagi semua produk yang mengandungi metformin untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat berkaitan penggunaan dalam kalangan pesakit yang mempunyai *moderately reduced kidney function* dan pengukuhan amaran *lactic acidosis.*

PELAKSANAAN

3.1 Oleh itu arahan – arahan berikut perlu dipatuhi untuk semua produk yang mengandungi metformin seperti berikut:-

3.1.1 Sisip bungkusan

Pada bahagian *Recommended Dosage:*

a) Produk bahan aktif tunggal yang mengandungi metformin sahaja

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR mL/min	*Total maximum daily dose (to be divided into 2-3 daily doses)**	*Additional considerations*
60-89	*3000 mg*	*Dose reduction may be considered in relation to declining renal function.*
45-59	*2000 mg*	*Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.*
30-44	*1000 mg*	
<30	*-*	*Metformin is contraindicated.*

** The text "to be divided into 2-3 daily doses" should be omitted for extended release products containing metformin as single agent.*

b) Produk kombinasi yang mengandungi metformin

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR <60 ml/min.

If no adequate strength of <Product name> is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	*Metformin*	*[other monocomponent]*
60-89	*Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.*	
45-59	*Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.*	
30-44	*Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.*	
<30	*Metformin is contraindicated.*	

Pada bahagian *Contraindications:*

- *Severely reduced kidney function (GFR <30 mL/min)*
- *Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)*

Pada bahagian *Warnings and Precautions:*

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly there after [See Section Recommended Dosage]. Metformin is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function [See Section Contraindications].

3.1.2 Risalah Maklumat Ubat Untuk Pengguna (RiMUP)

Pada bahagian *Before you use <product name>:*

Do not take <product name>:

- *If you have severely reduced kidney function.*
- *If you have lactic acidosis [too much lactic acid in the blood (see "Risk of lactic acidosis" below)] or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms of acidosis may include stomach pain, abnormal breathing and drowsiness (if severe).*

Pada bahagian *Before you start to use it:*

Risk of lactic acidosis

<Product name> may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration, liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). If any of the above apply to you, talk to your doctor for further instructions.

Stop taking <product name> for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking <product name> and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.

Symptoms of lactic acidosis include:

- *vomiting*
- *stomach ache (abdominal pain)*
- *muscle cramps*
- *a general feeling of not being well with severe tiredness*
- *difficulty in breathing*

Lactic acidosis is a medical emergency and must be treated in a hospital.

During treatment with <product name>, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

4. Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk yang mengandungi metformin bagi:

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **1 November 2017**

(b) Produk berdaftar : **1 Mei 2018**

5. Permohonan pindaan pada sisip bungkusan dan RiMUP bagi produk berdaftar perlu dikemukakan sebagai permohonan variasi.

6. Tarikh kuat kuasa arahan ini ialah mulai **1 November 2017.**

"BERKHIDMAT UNTUK NEGARA"

MOHD YUNOS BIN SHAARI, RPh 1079
Pengarah
Lembaga Farmasi Malaysia
Kementerian Kesihatan Malaysia

(DR. SALMAH BT. BAHRI) RPh. 783
Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia

ra/nb/ppp/NPRA/091017

s.k. 1. Pengarah Regulatori Farmasi
Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia.

2. Pengarah Amalan dan Perkembangan Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia.

3. Pengarah Penguatkuasa Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia