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Tarikh : 24 AUG 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 16 TAHUN 2017: DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI *PROTON PUMP INHIBITORS* (PPI): PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RIMUP) DENGAN MAKLUMAT BERKAITAN RISIKO KESAN ADVERS AKIBAT PENGGUNAAN JANGKA PANJANG.

Adalah saya merujuk kepada Arahan Bilangan 16 Tahun 2017 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 16 Tahun 2017 telah bersetuju untuk menambah maklumat berkaitan risiko kesan advers akibat penggunaan jangka panjang bagi semua produk yang mengandungi *proton pump inhibitors* (PPI) seperti pada surat arahan Bil. (21) 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
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BPFK/PPP/07/25 (21) Jld 1

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

BILANGAN 16 TAHUN 2017

DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI *PROTON PUMP INHIBITORS* (PPI): PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT BERKAITAN RISIKO KESAN ADVERS AKIBAT PENGGUNAAN JANGKA PANJANG

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 *proton pump inhibitors* (PPI) bagi mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat berkaitan risiko kesan advers akibat penggunaan jangka panjang.

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **314** pada **3 Ogos 2017** telah membuat keputusan bagi semua produk yang mengandungi *proton pump inhibitors* (PPI) untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat berkaitan risiko kesan advers akibat penggunaan jangka panjang.

PELAKSANAAN

3.1 Oleh itu arahan – arahan berikut perlu dipatuhi untuk semua produk yang mengandungi *proton pump inhibitors* (PPI) seperti berikut:-

3.1.1 Sisip bungkusan

Pada Bahagian *Warnings and Precautions*

Regular Surveillance
Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

Subacute Cutaneous Lupus Erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping {product name}. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPI like {product name} for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Fracture
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Clostridium Difficile Diarrhea
Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be

considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Vitamin B12 Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Pada Bahagian *Undesirable Effects/Side Effects*

Subacute Cutaneous Lupus Erythematosus (SCLE)
Skin and subcutaneous tissue disorders
Frequency 'not known': Subacute cutaneous lupus erythematosus

Interstitial Nephritis
Renal and urinary disorders: Interstitial nephritis

Hypomagnesaemia
Metabolism and nutritional disorders
Frequency "not known": hypomagnesaemia.

Fracture
Musculoskeletal disorders
Frequency "uncommon": Fracture of the hip, wrist or spine.

Clostridium Difficile Diarrhea
Infections & infestations: Clostridium difficile associated diarrhea.

Fundic Gland Polyps (Benign)
Gastrointestinal disorders
Frequency "common": Fundic gland polyps (benign)

Vitamin B12 Deficiency
Metabolic/Nutritional: Vitamin B12 deficiency

3.1.2 Risalah Maklumat Ubat Untuk Pengguna (RiMUP)

Pada Bahagian *Side Effects*

When you are taking this medicine, your doctor will want to monitor you (especially if you are taking it for long term). Hence, you should report any new and exceptional symptoms and circumstances whenever you see your doctor. Please tell your doctor promptly if you get any of the symptoms below:

- *Rash (especially in areas exposed to the sun), possibly with pain in the joints.(Subacute Cutaneous Lupus Erythematosus ,SCLE)*
- *Fever, extreme tiredness, pus/blood in urine.*
- *Involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate*
- *Fracture in the hip, wrist or spine.*
- *Watery stool, stomach pain and fever that do not go away*
- *Anemic (pale skin, weakness, tiredness or lightheadedness), shortness of breath, a smooth tongue, nerver problems (numbness or tingling, muscle weakness and problems walking), vision loss and mental problems (depression, memory loss or behavioral changes).*

a) *Subacute Cutaneous Lupus Erythematosus (SCLE)*
Frequency "not known"

b) *Interstitial Nephritis*
Kidney problems (interstitial nephritis)

c) *Hypomagnesaemia*
Frequency "not known": Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood.

d) *Fracture*
Frequency "uncommon": Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can ncrease the risk of osteoporosis).

e) *Clostridium Difficile Diarrhea*
Severe diarrhoea which may be caused by an infection (Clostridium difficile) in your intestines.

f) *Fundic Gland Polyps (Benign)*

Frequency "Common": Benign polyps in the stomach

g) *Vitamin B12 Deficiency*
Proton pump inhibitors may cause vitamin B12 deficiency.

4. Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk yang mengandungi *proton pump inhibitors* (PPI) bagi:

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

(b) Produk berdaftar : **1 Mac 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 September 2017.**

"BERKHIDMAT UNTUK NEGARA"

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