Biro Pengawalan Farmaseutikal Kebangsaan
National Pharmaceutical Control Bureau
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA

Ruj. Kami : (28) dlm. BPFK/PPP/07/25
Tarikh : 0 3 JUN 2015

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 4 TAHUN 2015: DIREKTIF UNTUK SEMUA PRODUK DOMPERIDONE UNTUK MENGEHADKAN PENGGUNAAN BERIKUTAN RISIKO KESAN ADVERS JANTUNG.

Adalah saya merujuk kepada Arahan Bilangan 4 tahun 2015 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 4 Tahun 2015 telah bersetuju untuk mengehadkan penggunaan berikutan risiko kesan advers jantung bagi semua produk domperidone seperti pada surat arahan Bil. (28) BPFK/PPP/07/25.

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

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,

TAN ANN LING
Pengarah Regulatori Farmasi
Biro Pengawalan Farmaseutikal Kebangsaan
Kementerian Kesihatan Malaysia
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BPFK/PPP/07/25 (28)

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

BILANGAN 4 TAHUN 2015

DIREKTIF UNTUK SEMUA PRODUK DOMPERIDONE UNTUK MENGEHADKAN PENGGUNAAN BERIKUTAN RISIKO KESAN ADVERS JANTUNG

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 produk domperidone bagi mengehadkan penggunaan semua produk domperidone berikutan risiko kesan advers jantung.

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **287** pada **30 April 2014** telah membuat keputusan bagi mengehadkan penggunaan semua produk domperidone berikutan risiko kesan advers jantung.

PELAKSANAAN

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

3.1.1 Pada bahagian ***Therapeutic Indications***

Domperidone is indicated for the relief of the symptoms of nausea and vomiting.

This includes:

- *Nausea and vomiting of functional, organic, infectious or dietary origin.*
- *Nausea and vomiting induced by:*
  - *radiotherapy or drug therapy.*
  - *dopamine agonists (such as L-dopa and bromocriptine) used in the treatment of Parkinson's disease.*

3.1.2 Pada bahagian ***Dosage and Administration***

It is recommended to take [product name] *15-30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed.*

Adults and adolescents ≥ 12 years and weighing ≥35 kg and children weighing ≥ 35 kg

The dose of [product name] *should be the lowest effective dose for the individual situation (typically 30 mg/day) and can be increased if necessary to a maximum daily oral dose of 40 mg.*

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. If nausea and vomiting persists for longer than one week, patients should consult their physician. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed.

Formulation (domperidone per unit)	***Dosage***	***Maximum dose per day***
Film-coated tablets (10 mg/tablet)	*1 tablet three to four times per day*	*40 mg (4×10 mg tablet)*
Oral suspension (1 mg/ml)	*10 mL three to four times per day*	*40 mg (40 mL of 1 mg/mL oral suspension)*

Neonates, Infants and children < 12 years of age and weighing < 35 kg, and adults and adolescents weighing < 35 kg

The dose of [product name] *should be the lowest effective dose. The total daily dose is dependent on weight (see table below). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life, the risk of neurological side effects is higher in young children. Overdosing may cause nervous system disorders in children. The*

dose should be determined accurately based on body weight and not exceed the recommended maximum individual and daily dose in neonates, infants, toddlers and children.

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed. Film-coated tablets and orodispersible tablets are unsuitable for use in children, adults and adolescents weighing less than 35 kg. Suppositories are unsuitable for use in children.

Formulation (domperidone per unit)	***Dosage***	***Maximum dose per day***
Oral suspension (1 mg/mL)	*0.25 mg/kg three to four times per day*	*1 mg/kg but no more than 35 mL (35mg)*

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L), the dosing frequency of [product name] *should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Patients with severe renal impairment should be reviewed regularly.*

Hepatic impairment

[Product name] *is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh >9) hepatic impairment. Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment.*

3.1.3 Pada bahagian ***Contraindications***

[Product name] *is contraindicated in the following situations:*

- *Known hypersensitivity to domperidone or any of the excipients.*
- *Prolactin-releasing pituitary tumour (prolactinoma).*
- *In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see Warnings and Precautions).*
- *co-administration with QT-prolonging drugs*
- *co-administration with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects).*

- *Whenever stimulation of gastric motility might be dangerous, e.g., in the presence of gastro-intestinal haemorrhage, mechanical obstruction or perforation.*
- *In patients with moderate or severe hepatic impairment.*

3.1.4 Pada bahagian ***Warnings and Precautions***

Cardiovascular effects

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT-prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see Adverse Reactions).

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see Adverse Reactions). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and children.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see Contraindications).

Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

3.1.5 Pada bahagian ***Adverse Reactions***

{information to be included}

Postmarketing:
Cardiac Disorders
Frequency: Very rare
Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, Sudden cardiac death (see Warnings and Precautions)

4. Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada sisip bungkusan semua produk domperidone bagi:

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **15 Jun 2015**

(b) Produk berdaftar : **15 Disember 2015**

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

6. Tarikh kuat kuasa arahan ini ialah mulai **15 Jun 2015.**

"BERKHIDMAT UNTUK NEGARA"

(DATO' EISAH A. RAHMAN)
Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia
ra/nb/ppp/bpfk/060515

s.k. 1. Pengarah Penguatkuasa Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia.

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

3. Pengarah Regulatori Farmasi
Biro Pengawalan Farmaseutikal Kebangsaan
Kementerian Kesihatan Malaysia.