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

Ruj. Kami : (24) dlm. BPFK/PPP/07/25
Tarikh : 0 8 JAN 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 17 TAHUN 2014: DIREKTIF UNTUK SEMUA PRODUK METOCLOPRAMIDE: MEMPERKETATKAN INDIKASI DAN MENGEHADKAN DOS PENGGUNAAN BERIKUTAN RISIKO KESAN ADVERS NEUROLOGIK

Adalah saya merujuk kepada Arahan Bilangan 17 tahun 2014 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 17 Tahun 2014 telah bersetuju bagi memperketatkan indikasi dan mengehadkan dos penggunaan berikutan risiko kesan advers neurologik untuk semua produk metoclopramide seperti pada surat arahan Bil. (24) BPFK/PPP/07/25.

3. Pihak pemegang pendaftaran, pemegang lesen mengimport dan pemegang lesen pemborong 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
ra/nb/ppp/bpfk/291214
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BPFK/PPP/07/25 (24)

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

BILANGAN 17 TAHUN 2014

DIREKTIF UNTUK SEMUA PRODUK METOCLOPRAMIDE: MEMPERKETATKAN INDIKASI DAN MENGEHADKAN DOS PENGGUNAAN BERIKUTAN RISIKO KESAN ADVERS NEUROLOGIK

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 metoclopramide bagi memperketatkan indikasi dan mengehadkan dos penggunaan berikutan risiko kesan advers neurologik.

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **283** pada **23 Disember 2014** telah membuat keputusan bagi memperketatkan indikasi dan mengehadkan dos penggunaan berikutan risiko kesan advers neurologik untuk semua produk metoclopramide.

PELAKSANAAN

3.1 Oleh itu arahan – arahan berikut perlu dipatuhi untuk semua produk metoclopramide seperti berikut:-

3.1.1 Pengemaskinian semua sisip bungkusan produk metoclopramide dengan memperketatkan indikasi dan mengehadkan dos penggunaan mengikut bentuk dos seperti berikut:

a) Lampiran 1 (produk parenteral)
b) Lampiran 2 (produk oral- tablet/sirap)
c) Lampiran 3 (produk rektal-supositori)

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

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

(b) Produk berdaftar : **01 Julai 2015**

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

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

"BERKHIDMAT UNTUK NEGARA"

(DATO' EISAH A. RAHMAN)
Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia
ra/nb/ppp/bpfk/241214

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.

5.1 Indication

Adult population

[BRAND NAME] is indicated for use in adults for:
-prevention of post-operative nausea and vomiting,
- symptomatic treatment of nausea and vomiting, including nausea and vomiting induced by migraine attacks,
-prevention of radiotherapy-induced nausea and vomiting.

Pediatric population

[BRAND NAME] is indicated in children aged 1 to 18 years for:
-prevention of delayed chemotherapy-induced nausea and vomiting as a second-line option,
-prevention of post-operative nausea and vomiting as a second-line option.

5.2 Dose and Administration

The solution can be administered by the intravenous or intramuscular route.
The intravenous doses must be administered as a slow bolus (for at least 3 minutes).

All indications (adults)
A single 10 mg dose is recommended for the prevention of post-operative nausea and vomiting.
The recommended dose for the symptomatic treatment of nausea and vomiting, including nausea and vomiting induced by migraine attacks and for the prevention of radiotherapy-induced nausea and vomiting is 10 mg per dose, 1 to 3 times daily. The maximum recommended daily dose is 30 mg or 0.5 mg/kg.
Treatment duration when administering by injection should be as short as possible and a switch to administration via oral or rectal route should be instituted as quickly as possible.

All indications (children from 1 to 18 years of age)
The recommended dosage is 0.1 to 0.15 mg/kg, 1 to 3 times daily, by intravenous route.
The maximum daily dose is 0.5 mg/kg.

Dosing table

Age	Body Weight	Dose	Frequency
1-3 years	10-14kg	1mg	Up to 3 times daily
3-5 years	15-19kg	2mg	Up to 3 times daily
5-9 years	20-29kg	2.5mg	Up to 3 times daily
9-18 years	30-60kg	5mg	Up to 3 times daily
15-18 years	Over 60kg	10mg	Up to 3 times daily

For the prevention of delayed chemotherapy-induced nausea and vomiting, the maximum treatment duration is 5 days.
For the prevention of post-operative nausea and vomiting, the maximum treatment duration is 48 hours.

Frequency of administration:
A minimum interval of 6 hours between two administrations is to be respected, even if vomiting or rejection of the dose occurs.

	Special populations *Elderly subjects* In elderly subjects, a dose reduction should be considered, based on kidney and liver function, and overall frailty. *Kidney failure* In patients with end-stage kidney failure (creatinine clearance ≤ 15 ml/min), the daily dose should be reduced by 75%. In patients with moderate to severe kidney failure (creatinine clearance between 15 and 60 ml/min), the dose should be reduced by 50%. *Liver failure* In patients with severe liver failure, the dose should be reduced by 50%. Other pharmaceutical forms may be more suitable for these patient populations. *Pediatric population* Metoclopramide is contraindicated in children aged less than one year.
5.3	**Contraindication**
	- Hypersensitivity to the active substance or to any of the excipients listed - Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk - Confirmed or suspected pheochromocytoma, due to the risk of severe hypertension episodes - History of neuroleptic or metoclopramide-induced tardive dyskinesia - Epilepsy (increased crises frequency and intensity) - Parkinson's disease - Combination with levodopa or dopaminergic agonists - Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency - Use in children less than 1 year of age
5.4	**Special Warnings and Precautions For Use**
	Neurological disorders Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions generally occur at the beginning of treatment, and can occur after a single dose. If extrapyramidal symptoms occur, metoclopramide should be discontinued immediately. These effects are generally completely reversible after treatment discontinuation; however, symptomatic treatment may be required (benzodiazepines in children, and/or anticholinergic antiparkinsonian medicinal products in adults). An interval of at least six hours should be respected between each dose even if vomiting or rejection of the dose occurs, in order to avoid overdose.

	Long-term treatment with metoclopramide may cause potentially irreversible tardive dyskinesia, particularly in elderly subjects. Treatment should not exceed 3 months because of the risk of tardive dyskinesia. Treatment must be discontinued if clinical signs of tardive dyskinesia occur. Neuroleptic malignant syndrome has been described with metoclopramide in combination with neuroleptics and with metoclopramide monotherapy. Metoclopramide must be immediately discontinued if symptoms of neuroleptic malignant syndrome develop, and appropriate treatment should be initiated. Particular caution should be exercised in patients with underlying neurological disorders, and in patients receiving other centrally-acting drugs. Symptoms of Parkinson's disease may also be exacerbated by metoclopramide. **Methemoglobinemia** Methemoglobinemia, which could be related to NADH-cytochrome b5 reductase deficiency, has been reported. If this occurs, treatment must be immediately and permanently discontinued, and appropriate measures initiated (such as treatment with methylene blue). **Cardiac disorders** Serious cardiovascular undesirable effects, including cases of severe bradycardia, circulatory collapse, cardiac arrest and QT prolongation have been reported during administration of metoclopramide by injection, particularly via the intravenous route. Particular caution should be exercised when administering metoclopramide, particularly via the intravenous route, in elderly subjects, patients with cardiac conduction disorders (including QT prolongation), patients with electrolyte imbalance, bradycardia, and patients taking other drugs known to prolong QT interval. The intravenous injection must be given as a slow bolus (of at least 3 minutes' duration) in order to reduce the risk of undesirable effects (e.g. hypotension, akathisia). **Kidney or liver failure** In patients with kidney failure or severe liver failure, a dose reduction is recommended.

5.1 Indication

Adult population
[BRAND NAME] is indicated in adults for:
- Prevention of delayed chemotherapy induced nausea and vomiting (CINV)
- Prevention of radiotherapy induced nausea and vomiting (RINV).
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting.

Paediatric population
[BRAND NAME] is indicated in children (aged 1-18 years) for:
- Prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a second line option

5.2 Dose and Administration

Adults:
The recommended single dose is 10 mg, repeated up to three times daily.

The maximum recommended daily dose is 30 mg or 0.5mg/kg body weight.
The maximum recommended treatment duration is 5 days.

Prevention of delayed chemotherapy induced nausea and vomiting (CINV) (paediatric patients aged 1-18 years)
The recommended dose is 0.1 to 0.15 mg/kg body weight, repeated up to three times daily by oral route. The maximum dose in 24 hours is 0.5 mg/kg body weight.

Dosing table

Age	Body Weight	Dose	Frequency
1-3 years	10-14kg	1mg	Up to 3 times daily
3-5 years	15-19kg	2mg	Up to 3 times daily
5-9 years	20-29kg	2.5mg	Up to 3 times daily
9-18 years	30-60kg	5mg	Up to 3 times daily
15-18 years	Over 60kg	10mg	Up to 3 times daily

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

Tablets are not suitable for use in children weighing less than 30kg. Other pharmaceutical forms may be more appropriate for administration to this population.

Frequency of administration:
A minimum interval of 6 hours between two administrations is to be respected, even if vomiting or rejection of the dose occurs.

Special population

Elderly

In elderly patients a dose reduction should be considered, based on renal and hepatic function and overall frailty.

	Renal impairment: In patients with end stage renal disease (Creatinine clearance ≤ 15 ml/min), the daily dose should be reduced by 75%. In patients with moderate to severe renal impairment (Creatinine clearance 15-60 ml/min), the dose should be reduced by 50% (see section 5.2). *Hepatic impairment:* In patients with severe hepatic impairment, the dose should be reduced by 50%
5.3	**Contraindication**
	- Hypersensitivity to the active substance or to any of the excipients listed - Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk - Confirmed or suspected pheochromocytoma, due to the risk of severe hypertension episodes - History of neuroleptic or metoclopramide-induced tardive dyskinesia - Epilepsy (increased crises frequency and intensity) - Parkinson's disease - Combination with levodopa or dopaminergic agonists - Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency - Use in children less than 1 year of age
5.4	**Special Warnings and Precautions For Use**
	Neurological disorders Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions generally occur at the beginning of treatment, and can occur after a single dose. If extrapyramidal symptoms occur, metoclopramide should be discontinued immediately. These effects are generally completely reversible after treatment discontinuation; however, symptomatic treatment may be required (benzodiazepines in children, and/or anticholinergic antiparkinsonian medicinal products in adults). An interval of at least six hours should be respected between each dose even if vomiting or rejection of the dose occurs, in order to avoid overdose. Long-term treatment with metoclopramide may cause potentially irreversible tardive dyskinesia, particularly in elderly subjects. Treatment should not exceed 3 months because of the risk of tardive dyskinesia. Treatment must be discontinued if clinical signs of tardive dyskinesia occur. Neuroleptic malignant syndrome has been described with metoclopramide in combination with neuroleptics and with metoclopramide monotherapy. Metoclopramide must be immediately discontinued if symptoms of neuroleptic malignant syndrome develop, and appropriate treatment should be initiated.

	Particular caution should be exercised in patients with underlying neurological disorders, and in patients receiving other centrally-acting drugs. Symptoms of Parkinson's disease may also be exacerbated by metoclopramide. **Methemoglobinemia** Methemoglobinemia, which could be related to NADH-cytochrome b5 reductase deficiency, has been reported. If this occurs, treatment must be immediately and permanently discontinued, and appropriate measures initiated (such as treatment with methylene blue). **Cardiac disorders** Serious cardiovascular undesirable effects, including cases of severe bradycardia, circulatory collapse, cardiac arrest and QT prolongation have been reported during administration of metoclopramide by injection, particularly via the intravenous route. Particular caution should be exercised when administering metoclopramide, particularly via the intravenous route, in elderly subjects, patients with cardiac conduction disorders (including QT prolongation), patients with electrolyte imbalance, bradycardia, and patients taking other drugs known to prolong QT interval. The intravenous injection must be given as a slow bolus (of at least 3 minutes' duration) in order to reduce the risk of undesirable effects (e.g. hypotension, akathisia). **Kidney or liver failure** In patients with kidney failure or severe liver failure, a dose reduction is recommended.

5.1	**Indication**
	Adult population *[BRAND NAME]* is indicated in adults for: - Prevention of delayed chemotherapy induced nausea and vomiting (CINV) - Prevention of radiotherapy induced nausea and vomiting (RINV)
5.2	**Dose and Administration**
	All indications (adults) The recommended dosage is 10 mg per dose, 1 to 3 times daily. The maximum recommended daily dose is 30 mg or 0.5 mg/kg. The maximum recommended treatment duration is 5 days. **Method of administration:** A minimum interval of 6 hours between two administrations is to be respected, even if vomiting or rejection of the dose occurs. **Special populations** *Elderly subjects* In elderly subjects, a dose reduction should be considered, based on kidney and liver function, and overall frailty. *Kidney failure* In patients with end-stage kidney failure (creatinine clearance ≤ 15 ml/min), the daily dose should be reduced by 75%. In patients with moderate to severe kidney failure (creatinine clearance between 15 and 60 ml/min), the dose should be reduced by 50%. *Liver failure* In patients with severe liver failure, the dose should be reduced by 50%. Other pharmaceutical forms and dosage strengths may be more suitable for this patient population.
5.3	**Contraindication**
	• Hypersensitivity to the active substance or to any of the excipients listed. • Gastrointestinal hemorrhage, mechanical obstruction or gastrointestinal perforation, in which the stimulation of gastrointestinal motility is a risk. • Confirmed or suspected pheochromocytoma, due to the risk of episodes of severe hypertension. • Known history of neuroleptic- or metoclopramide-induced tardive dyskinesia. • Epilepsy (increase in the frequency and intensity of seizures). • Parkinson's disease. • In combination with levodopa or dopamine agonists. • Known history of methemoglobinemia with metoclopramide or NADH-cytochrome b5 reductase deficiency. • Recent history of proctitis or rectal bleeding. • In children less than 18 years of age.

5.4	Special Warnings and Precautions For Use

Neurological disorders
Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions generally occur at the beginning of treatment, and can occur after a single dose. If extrapyramidal symptoms occur, metoclopramide should be discontinued immediately. These effects are generally completely reversible after treatment discontinuation; however, symptomatic treatment may be required (benzodiazepines in children, and/or anticholinergic antiparkinsonian medicinal products in adults).

An interval of at least six hours should be respected between each dose even if vomiting or rejection of the dose occurs, in order to avoid overdose.

Long-term treatment with metoclopramide may cause potentially irreversible tardive dyskinesia, particularly in elderly subjects. Treatment should not exceed 3 months because of the risk of tardive dyskinesia. Treatment must be discontinued if clinical signs of tardive dyskinesia occur.

Neuroleptic malignant syndrome has been described with metoclopramide in combination with neuroleptics and with metoclopramide monotherapy. Metoclopramide must be immediately discontinued if symptoms of neuroleptic malignant syndrome develop, and appropriate treatment should be initiated.

Particular caution should be exercised in patients with underlying neurological disorders, and in patients receiving other centrally-acting drugs.

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

Methemoglobinemia
Methemoglobinemia, which could be related to NADH-cytochrome b5 reductase deficiency, has been reported. If this occurs, treatment must be immediately and permanently discontinued, and appropriate measures initiated (such as treatment with methylene blue).

Cardiac disorders
Serious cardiovascular undesirable effects, including cases of severe bradycardia, circulatory collapse, cardiac arrest and QT prolongation have been reported during administration of metoclopramide by injection, particularly via the intravenous route.

Particular caution should be exercised when administering metoclopramide, particularly via the intravenous route, in elderly subjects, patients with cardiac conduction disorders (including QT prolongation), patients with electrolyte imbalance, bradycardia, and patients taking other drugs known to prolong QT interval.

The intravenous injection must be given as a slow bolus (of at least 3 minutes' duration) in order to reduce the risk of undesirable effects (e.g. hypotension, akathisia).

Kidney or liver failure
In patients with kidney failure or severe liver failure, a dose reduction is recommended.