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MADRAC

Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia

SAFETY ISSUES OF CURRENT INTEREST

NEW RESTRICTIONS OF USE FOR METOCLOPRAMIDE AND DOMPERIDONE
by Vidhya Hariraj and Rema Panickar

The NPCB recently distributed safety advisories *[Bil.(4)dlm.BPFK/PASCA/FV/16]* to public and private healthcare facilities regarding new restrictions of use for metoclopramide and domperidone, to minimise the risk of neurological and cardiovascular adverse effects respectively. This follows completion of the comprehensive safety reviews by NPCB into the benefit-risk ratio of these drugs, including evaluation of available scientific papers, current local data on adverse events, actions taken by other international regulatory agencies, feedback from Ministry of Health (MOH) and private sector specialists, and discussion with experts in related fields during MADRAC and Drug Control Authority (DCA) meetings.

A summary of the new changes to the prescribing information are tabulated on pages 4-5, however please refer to the DCA directives for full details. Following concerns raised on the lack of cost-effective parenteral antiemetic available for use in MOH facilities, dimenhydrinate was recently included in the MOH Drug Formulary (FUKKM). Dimenhydrinate is not indicated for the treatment of gastroesophageal reflux disease (GERD), however domperidone may still be used for this indication in patients who have symptoms of nausea and vomiting, unless contraindicated.

METOCLOPRAMIDE: RESTRICTION OF USE TO MINIMISE THE RISK OF NEUROLOGICAL ADVERSE EFFECTS

Metoclopramide is a substituted benzamide, which has antiemetic properties and a stimulating action on gastrointestinal motility. Its activity results from antagonism of dopaminergic D2 receptors, antagonism of serotonergic 5-HT3 receptors, and agonism of 5-HT4 receptors. Metoclopramide crosses the blood-brain barrier and is associated with serious neurological adverse events, mainly extrapyramidal disorders which are of particular concern in children.

On 8 January 2015, the DCA issued a directive *[Bil. (24) dlm. BPFK/PPP/07/25]* to tighten the indications and limit the dosage of all metoclopramide-containing products. All product registration holders are required to update their local package inserts with these new safety changes.

CONTENT

To join the NPCB Safety Information Mailing List, please send an email to fv@bpfk.gov.my

This newsletter is also available on our website: portal.bpfk.gov.my

To report an adverse drug reaction:
1. Visit portal.bpfk.gov.my
2. Click on the circle: 'ADR Reporting'.
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Alternatively, please contact:
The Drug Safety Monitoring Centre,
National Pharmaceutical Control Bureau,
Ministry of Health
PO Box 319, Jalan Sultan,
46730 Petaling Jaya,
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Background

The safety review on metoclopramide was initiated in 2011 by the French Agency for Medicinal and Health Products Safety (ANSM), which had conducted a national assessment and concluded that there was insufficient evidence of efficacy in children. This led to contraindication of metoclopramide products in children below 18 years old in France.

ANSM also triggered an EU-wide assessment to review the benefit-risk profile of metoclopramide products in children and the elderly. In December 2013, the European Medicines Agency (EMA) recommended the following:

- Restricted indications in adults and children aged between 1-18 years
- A contraindication in children below 1 year of age
- Restricted doses and treatment duration, as well as modified dose intervals to minimise the known risks of potentially serious neurological side effects

In the United States of America (USA), only **parenteral** metoclopramide is approved for use in children, specifically for gastrointestinal intubation. In Australia, metoclopramide is only indicated as **second-line therapy** for those aged between 1-20 years.

Local scenario

There are currently 31 products containing metoclopramide registered in Malaysia comprising different dosage forms, namely 10mg tablets, syrup [1mg/ml], injections [5mg/ml], and 10mg suppositories.

Between years 2000 to 2014, the National Drug Safety Monitoring Centre, NPCB, received **558 reports** with 972 adverse events suspected to be related to metoclopramide. From this total, **426 reports (76.3%)** involved **neurological adverse events**, namely oculogyric crisis and extrapyramidal symptoms. The remaining 132 reports (23.7%) comprised mainly of allergy-related adverse events such as rash, itching, increased sweating, and shortness of breath.

Further analysis of the reports related to **neurological adverse effects** revealed that more than half (51.6%; 220/426 reports) involved **paediatric patients** aged below 18 years. Neurological adverse effects were clearly linked to use of suppositories in paediatric patients, especially those aged under 1 year. This supports the **contraindication** for use of metoclopramide-containing **suppositories in patients aged 18 years or less.**

Based on the ADR data from the NPCB database, it is evident that neurological adverse events are a **cause for concern in Malaysia.** Due to the lack of accurate drug usage data in Malaysia, we are unable to conclude for certain which age group of patients is more prone to developing neurological adverse effects. However, the existence of reports on neurological adverse effects involving paediatric patients, as mentioned above, supports the decision to contraindicate metoclopramide use in patients aged below 1 year, and restrict usage to a second-line option in patients aged between 1-18 years.

Although it is a known side effect in clinical practice, it is important for all healthcare professionals to adhere to the dosing guidelines based on patient weight (Table 1). Furthermore, a **minimum interval of 6 hours** between two administrations is to be respected, even if vomiting or rejection of the dose occurs.

Table 1: Recommended Dosing Table for Paediatric Patients

Age	Body Weight	Dose	Frequency
1-3 years	10-14kg	1mg	Up to 3 times daily (minimum interval of **6 hours between doses**, even if vomiting or rejection of dose occurs)
3-5 years	15-19kg	2mg	
5-9 years	20-29kg	2.5mg	
9-18 years	30-60kg	5mg	
15-18 years	Over 60kg	10mg	

DOMPERIDONE: RESTRICTION OF USE FOLLOWING RISK OF CARDIOVASCULAR ADVERSE EFFECTS

Domperidone is a prokinetic agent and a dopamine antagonist with anti-emetic properties. It is thought to exert its antiemetic effect through antagonism of dopamine receptors in the gut and the chemoreceptor trigger zone. Studies have shown that oral domperidone increases lower oesophageal pressure, improves antroduodenal motility and accelerates gastric emptying.

Domperidone has been repeatedly associated with causing serious cardiovascular adverse effects, such as QT interval prolongation, ventricular arrhythmias and sudden cardiac death. The **injectable form** of domperidone was **withdrawn in the EU** in 1985 due to cardiotoxicity and fatalities.

On 3 June 2015, the Drug Control Authority (DCA) of Malaysia issued a directive *[Bil. (28) dlm. BPFK/PPP/07/25]* to restrict the use of all domperidone-containing products. All product registration holders are required to update their local package inserts with these new safety changes.

Background

The safety review on domperidone was initiated by NPCB following the European Commission decision announced on 1 September 2014, which confirmed the recommendations by EMA to restrict the use of this drug.

The review by EMA was based on both non-clinical and clinical data which indicated a risk of serious cardiovascular adverse effects including QTc prolongation, *torsade de pointes*, serious ventricular arrhythmias and sudden cardiac death. This risk was found to be higher in the following groups:

(i) those aged above 60 years;
(ii) total daily dose of domperidone above 30mg/day;
(iii) concomitantly using other QT-prolonging drugs or CYP3A4 inhibitors.

As a result of NPCB's local review, a decision was made to tighten the indications, restrict the maximum daily dose and recommended duration of use, while adding new contraindications for domperidone. This decision is in line with the risk minimisation steps implemented by EMA, the Australian Therapeutic Goods Administration (TGA), dan Health Canada. Domperidone is not registered for use in the USA.

Local scenario

There are currently 25 products containing domperidone registered in Malaysia comprising 10mg tablets, or 1mg/ml oral suspensions.

Since year 2000, the National Drug Safety Monitoring Centre, NPCB, received **16 reports** with 35 adverse events suspected to be related to domperidone. The most frequently reported adverse events were urticaria (5 reports), itching (3), rash (3), shortness of breath (2), periorbital oedema (2) and gynaecomastia (2).

There was one report of **QT prolongation** involving a child aged 6 months, who was given domperidone suspension (dose: 0.3-0.45mg/kg 3-4 times daily) for gastroesophageal reflux disease.

The proposed package insert safety updates submitted by the innovator product registration holder have been approved by the NPCB. A Direct Healthcare Professional Communication (DHPC) approved by NPCB has also been distributed by the holder.

Please refer to **Table 2** for a summary of the new safety changes.

Table 2: Metoclopramide vs. Domperidone: Comparison of Updated Prescribing Information
**(please refer to the DCA directives/ updated package inserts for full details)

INDICATIONS				
	METOCLOPRAMIDE		DOMPERIDONE	
Dosage Form	**Adult**	**Paediatric (aged 1- 18) (Contraindicated in less than 1 year old)**	**Adult**	**Paediatric**
Injection	- 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.	- Prevention of delayed chemotherapy-induced nausea and vomiting (CINV) as a **second-line** option. - Prevention of post-operative nausea and vomiting (PONV) as a **second-line** option.	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.	
Oral	- 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.	- Prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a **second-line** option.		
Rectal	- Prevention of delayed chemotherapy induced nausea and vomiting (CINV). - Prevention of radiotherapy induced nausea and vomiting (RINV).	**Not indicated**		

RECOMMENDED DOSAGE				
	Adult Dosing	**Paediatrics (1- 18 years of age)**	**Body Weight ≥35kg**	**Body Weight <35kg**
Injection	10mg per dose, repeated up to 3 times daily. Maximum recommended daily dose: is 30mg or 0.5mg/kg body weight. A minimum interval of 6 hours between two administrations is to be respected, even if vomiting or rejection of the dose occurs	The recommended dosage is 0.1 to 0.15mg/kg body weight, repeated up to 3 times daily. The maximum dose in 24 hours is 0.5mg/kg body weight. Tablets are not suitable for use in children weighing less than 30kg. *(please refer to the dosing table for pediatrics)*	10mg three to four times daily. The lowest effective dose for the individual situation should be used, typically 30mg/day and can be increased if necessary to a maximum daily dose of 40mg.	0.25mg/kg three to four times per day. The lowest effective dose for the individual situation should be used, maximum daily dose of 1mg/kg but no more than 35mg.
Oral				
Rectal		Contraindicated in children aged <18 years.		

DURATION OF USE			
	METOCLOPRAMIDE		DOMPERIDONE
Dosage Form	Adult	Paediatric (aged 1- 18) (Contraindicated in less than 1 year old)	
Injection	Treatment duration should be as short as possible and a switch to administration via oral or rectal route should be instituted as quickly as possible.	For the prevention of delayed CINV, the maximum treatment duration is 5 days. For the prevention of PONV, the maximum treatment duration is 48 hours.	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.
Oral	The maximum recommended treatment duration is 5 days.	For the prevention of delayed CINV, the maximum treatment duration is 5 days.	
Rectal	The maximum recommended treatment duration is 5 days.	**Not indicated**	
DOSAGE ADJUSTMENTS			
All	**Renal impairment:** Creatinine clearance (ClCr) **≤15ml/min:** reduce daily dose by 75% ClCr **>15ml/min:** reduce daily dose by 50% **Severe hepatic impairment:** reduce dose by 50% Rectal dosage forms may not be suitable for these patient populations.		**Severe renal impairment:** Serum creatinine >0.6 mmol/L: - reduce dosing frequency to once or twice daily - dose may need to be reduced (review regularly) **Moderate or severe hepatic impairment:** Contraindicated
CONTRAINDICATIONS			
All	• 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 • **Injection/ oral:** Use in children less than 1 year of age **Rectal:** Use in children less than 18 years of age		• 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 (see Interactions) • 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.

ROTAVIRUS VACCINE: RISK OF INTUSSUSCEPTION
By Deborah Quah

Rotavirus is the leading cause of severe dehydrating diarrhoea in children aged under 5 years[1]. The World Health Organisation (WHO) estimated that it caused 453,000 rotavirus gastroenteritis-associated child deaths worldwide. In Malaysia, rotavirus accounts for 30.3% of childhood acute gastroenteritis hospitalisation[2].

Background of Safety Issue

Intussusception, an invagination of the intestines, is a serious and potentially fatal condition that commonly occurs in children aged between 4 months to 2 years. The first marketed rotavirus vaccine, Rotashield®, was withdrawn by the United States Food and Drug Administration (US FDA) in June 1999, just nine months after it became available, when researchers observed an increased risk by one or two cases of intussusception per 10,000 infants vaccinated with Rotashield®[3].

Currently, there are two oral rotavirus vaccines available internationally, namely Rotarix® and Rotateq®. Large clinical trials for these two vaccines involving 60,000 to 70,000 infants have been carried out to study the risk of intussusception, as previously observed with Rotashield®. Although the results showed no increased risk when compared to placebo[4], market surveillance has detected cases of intussusception with risk varying in different populations, as described below.

Research Findings

In a study conducted by Patel *et al*. (published in June 2011), the potential risk of intussusception with Rotarix® was investigated after routine immunisation of infants in Brazil and Mexico[5]. The study revealed an increased risk of intussusception in Mexican infants at 1 – 7 days after **first dose** of Rotarix®, but no significant risk observed in Brazilian infants after the first dose. However, there was a small increased rate of intussusception 1 – 7 days following **second dose** of vaccine in Brazilian infants. The study attributed an annual excess of approximately 96 cases of intussusception to the vaccine, in Mexico and Brazil combined.

Another study on intussusception following rotavirus vaccination in Australia, where both Rotarix® and Rotateq® are commercially available, allowed estimation of product-specific risk[6]. Findings were similar for both vaccines, showing an increased risk of intussusception 1 – 21 days after first dose and 1 – 7 days after the second dose. It was estimated that the risk of intussusception with rotavirus vaccination was 14 excess cases per year.

In February 2014, the WHO Global Advisory Committee on Vaccine Safety acknowledged the risk of intussusception following administration of Rotarix® and Rotateq®, particularly during the first seven (7) days following first dose[7].

Local Scenario

In Malaysia, rotavirus vaccination is not included in the national immunisation programme, but it is available in private healthcare facilities. There are three (3) registered rotavirus vaccines in Malaysia, all in the form of oral suspensions, as shown in **Table 3**. The risk of intussusception is stated in the product information for all the vaccines in Malaysia, and it is contraindicated in infants with a history of intussusception[8,9].

Table 3: Rotavirus Vaccines Registered in Malaysia

	RotaTeq® (rotavirus vaccine, live, oral, pentavalent)	Rotarix® rotavirus vaccine	Rotarix® oral vaccine
Registration number	MAL20071649A	MAL20061522A	MAL20091875A
Applicator	Squeezable tube	Squeezable tube	Oral applicator
Rotavirus serotype	Pentavalent (G1, G2, G3, G4, P1[8])	Monovalent (RIX4414)	
Year of registration	2007	2006	2009
Dosing schedule	Three-dose course	Two-dose course	

The National Pharmaceutical Control Bureau (NPCB) has received 89 adverse event reports associated with rotavirus vaccine since year 2007[10]. The number of cases reported for Rotarix® and Rotateq® were 48 and 41 cases respectively. Of the 159 adverse events reported, more than half (93; 58%) involved the gastro-intestinal system, such as diarrhoea (34), vomiting (15) and intussusception (13). Other top adverse events reported were fever (15), rotavirus infection (8) and loss of appetite (4).

From the 13 cases of intussusception reported, eight (8) cases involved Rotateq® and five (5) cases involved Rotarix®. No clustering of intussusception cases was observed. The time to onset of intussusception was between 1-7 days post-vaccination (5 cases), 8-21 days (3 cases), and more than 22 days (4 cases).

Conclusion

Overall, the risk of intussusception remains small compared to the benefits of preventing severe rotavirus gastroenteritis[7]. In order to facilitate better risk assessment, healthcare professionals are encouraged to report suspected cases of intussusception related to rotavirus vaccination to the NPCB Drug Safety Monitoring Centre. Healthcare professionals should also counsel parents on the risk of intussusception, and advise them to seek immediate medical attention if the child shows signs and symptoms of the said condition.

References:

1. World Health Organisation (2013). Rotavirus Vaccine WHO Position Paper – January 2013. *Weekly Epidemiological Records* 88:49-64.
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3. United States Centre for Disease Control and Prevention: Rotavirus Vaccine (Rotashield®) and Intussusception. [Accessed 26 June 2015]
4. Rao TS, *et al*. (2014). Insights from Global Data for Use of Rotavirus Vaccines in India. Vaccine 32S: A171-A178.
5. Patel MM, *et al*. (2011). Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil. *The New England Journal of Medicine* 364: 2283-2292.
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7. World Heath Organisation (2014). Update on Intussusception following Rotavirus Vaccine Administration. [Accessed 26 June 2015]
8. Rotarix® Package Insert, Malaysia [Version: June 2011]
9. Rotateq® Package Insert, Malaysia [Version: June 2012]
10. The Malaysian Adverse Drug Reaction Database, NPCB. [Accessed: 18 June 2015]

EARLY DETECTION OF SERIOUS SKIN REACTIONS: AUXILIARY WARNING LABEL

In 2014 alone, the NPCB received reports on 322 patients who suffered serious adverse cutaneous drug reactions, of which eight (8) resulted in deaths suspected to be due to the reactions. On top of the suffering and distress caused to patients, the reactions also prolong hospitalisation and carry high cost implications. Treating just one case of SJS has been estimated to cost more than RM12,000.00. Early recognition and cessation of the suspected drug is vital to reduce morbidity and mortality.

Malaysian ADR data (2000-2014) indicates that the drugs or classes most commonly associated with causing serious skin reactions are allopurinol, antiepileptics, antibiotics, and non-steroidal anti-inflammatory agents (NSAIDs). The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) proposed that an auxiliary warning label related to serious skin reactions be added during the dispensing process of these drugs. This is to ensure patients are able to **recognise the first signs** of skin reactions and **seek immediate medical advice** to help prevent serious reactions.

Based on the top drugs reported to cause serious skin reactions in Malaysia, six (6) drugs were chosen for the first phase of this auxiliary warning label implementation, namely allopurinol, co-trimoxazole, diclofenac, mefenamic acid, carbamazepine and phenytoin. Since August 2014, all government and private healthcare facilities have been advised to implement the use of these warning labels (in Malay Language or English), as follow:

(a) For drugs which can be stopped immediately:

Allopurinol, Co-trimoxazole, Diclofenac, Mefenamic acid

Sekiranya anda mengalami kesan sampingan seperti ruam, demam, sakit tekak, atau iritasi mata, ***hentikan pengambilan ubat ini SERTA-MERTA*** *dan rujuk dengan doktor/ ahli farmasi.*	If you have side effects such as a rash, fever, sore throat, or eye irritation, **stop using this medication IMMEDIATELY** and consult your doctor/ pharmacist.

(b) For anti-epileptics which should NOT be stopped suddenly without medical advice:

Phenytoin, Carbamazepine

Sekiranya anda mengalami kesan sampingan seperti ruam, demam, sakit tekak, atau iritasi mata, ***dapatkan nasihat*** *doktor/ ahli farmasi dengan* ***SERTA-MERTA.***	If you have side effects such as a rash, fever, sore throat, or eye irritation, **seek medical advice** from your doctor/ pharmacist **IMMEDIATELY.**

REGULATORY MATTERS

PARACETAMOL: RISK OF SERIOUS SKIN REACTIONS

The commonly used analgesic/ antipyretic medication, paracetamol (also known as acetaminophen), has been associated with a risk of rare but serious skin reactions, namely Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP).

The NPCB performed a review on this matter following a drug safety communication issued by the US FDA regarding this risk. The US FDA review of their adverse event reporting system database revealed 107 reports of serious skin reactions, the majority involving single-active ingredient paracetamol products. In the medical literature, there were three (3) case reports involving positive rechallenge, where the patients had a recurrence of serious skin reactions when given paracetamol again.

Local Scenario

In Malaysia, there are currently 268 products containing paracetamol registered with the DCA, including 65 combination products. In general, products containing paracetamol are approved for the treatment of mild pain or fever. Some combination products are also indicated for the relief of cold and flu symptoms.

From year 2000 to Feb 2015, the NPCB has received **1,018 ADR reports** related to paracetamol, with 1,972 adverse events. A total of 790 reports (78%) involved at least one skin reaction, with the most commonly reported ADRs being pruritus, rash, urticaria, and angioedema. There were a total of **30 reports** involving **serious skin reactions**, namely SJS (18 reports), erythema multiforme (5), TEN (4), SJS-TEN overlap (2), and AGEP (1). The time to onset of reaction for these cases ranged from 24 hours (recurrence on second exposure) to several days.

On 3 June 2015, the DCA issued a directive *[Bil. (29) dlm. BPFK/PPP/07/25]* requiring all product registration holders of paracetamol-containing products to update their local product information (including labels, package inserts, and consumer medication information leaflets – RiMUPs) with a warning on the risk of serious skin reactions.

Advice to Healthcare Professionals

- Advise patients to **stop taking** paracetamol and seek medical advice at the **first signs of serious skin reactions**, including fever, sore throat, skin reddening, eye irritation, blisters or rash.
- Patients who have experienced a serious skin reaction with paracetamol should be counselled not to take the drug again and must be provided with an **allergy card or medical alert tag.**
- Please **report** any suspected ADR related to paracetamol use to the NPCB, including situations where several drugs are given concomitantly.