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PHARMACY BULLETIN: MEDICATION SAFETY EDITION

Patient Safety
WORLD PATIENT SAFETY DAY
17 SEPTEMBER 2022

IN THIS ISSUE:

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STATINS RELATED MUSCLE PAIN

- Tharani A/P Gunasakaran, Pharmacist UF 44-

Statins remain among the most widely prescribed drugs for the correction of dyslipidaemia and prevention of cardiovascular events. The drugs work as a reversible inhibitors of HMG-CoA reductase aid in lowering the production of low-density lipoprotein (LDL) ("bad") cholesterol in liver. [1]

MUSCULAR ADVERSE EFFECT

Statins may affect a protein in muscle cells, which;

⬇ **Muscle growth**

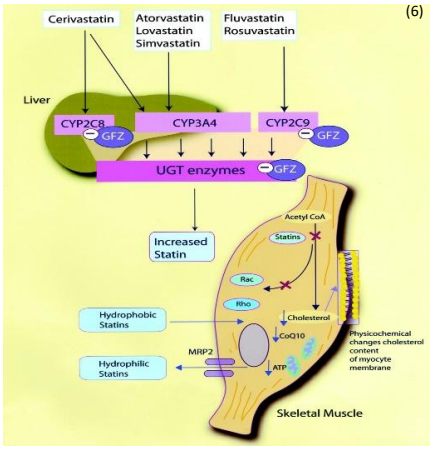
OR

⬇ **Levels of Coenzyme Q10 (Natural substance in body)**

Leading to symptoms like muscle weakness, cramps, myalgia with and without CK elevations and clinically serious events such as myositis and rhabdomyolysis.

Simvastatin, Lovastatin, and Atorvastatin are metabolized by isoenzyme cytochrome P4503A4 (CYP3A4). Drugs of CYP3A4 inhibitors (as listed in **Table 1**) can interact with these statins and increase the plasma concentration, thus increasing the risk of muscular adverse effects.

Whereas, Fluvastatin, Rosuvastatin & Pravastatin are relatively insensitive to CYP3A4 inhibitors and therefore clinically significant interactions are less likely. [2]



Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors
• HIV protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) • Azole antifungals (e.g.Itraconazole, ketoconazole, posaconazole, voriconazole) • Macrolide antibiotics (e.g. erythromycin, clarithromycin) • Danazol • Cyclyosporine • Gemfibrozil	• Amlodipine • Amiodarone • Verapamil • Diltiazem • Warfarin • Niacin (>1g/day)

Table 1: Examples of CYP3A4 inhibitors that interact with statins

STATINS WITH CALCIUM CHANNEL ANTAGONIST

Simvastatin with calcium channel blockers is also commonly co-prescribed. Concurrent use causes significant increase in blood levels of Simvastatin. In patients on Amlodipine 10mg with Simvastatin 20mg, the effect is similar to receiving Simvastatin 40mg alone.

Consideration for patient taking Amlodipine + Simvastatin 40mg

Reduce Simvastatin dose to 20mg

Staying on Simvastatin

- to discuss risk and benefit of this 'off label' option. Be aware that, exposure to adverse effect is similar to that associated with Simvastatin 80mg.

Change to alternative statin

- Pravastatin*, Fluvastatin* or Rosuvastatin* do not interact with Amlodipine. Atorvastatin is less susceptible with CYP3A4 and can be given at dose (20mg/40mg) if more potent statin is needed.

*Not available in Hospital Beaufort Formulary

NOTES FOR HEALTHCARE PROFESSIONALS

1. Since cholesterol biosynthesized peaks at midnight, statins with **shorter half-lives** (Lovastatin, Simvastatin & Fluvastatin) should be administered in the evening. In contrast, statins with **longer half-lives** (Atorvastatin, Rosuvastatin & Pravastatin) can be administered during the day.
2. Hepatic transaminases should be measured at baseline and at **1 to 3 months** after starting treatment and/or following a change in dose of statins.
3. Care should be taken when prescribing high doses of Simvastatin (>20 mg/daily) together with certain other medications that inhibit the cytochrome P450 pathway.
4. When a statin myopathy is suspected, **discontinue for 2-3 weeks**. If symptoms have not resolved, it is unlikely to be statin related and the patient should be continued on the same dose of statin. If symptoms have resolved, lowering the dose or decreasing the frequency to less than daily or alternate dosing such as every other day (EOD) or twice a week (2x/week) with atorvastatin or rosuvastatin.
5. Fibrates (Gemfibrozil or fenofibrate) should preferably be taken in the morning and statins in the evening to minimize peak dose concentrations and decrease the risk of myopathy.
6. Please **report all adverse events** suspected to be associated with statins. [5]

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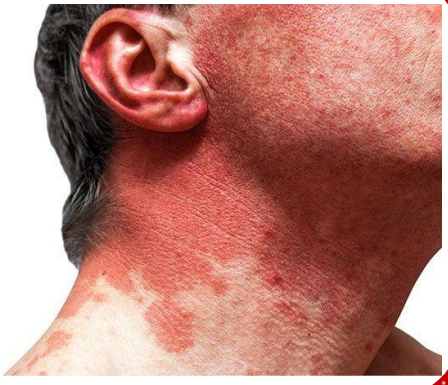
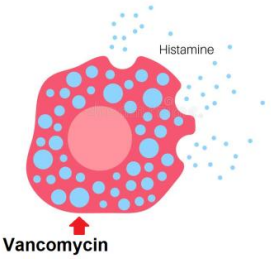
Vancomycin Infusion Reaction (VIR) aka Red Man Syndrome

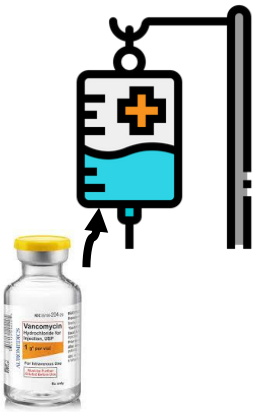


- Su Yi Xiang, Pharmacist UF41-

What is VIR?

VIR is an infusion-related anaphylactoid reaction independent of IgE-mediated mechanism. The direct degranulation of mast cells and basophils by vancomycin results in release of histamine, hence causing the associated symptoms.





Risk of VIR:

- Route of Vancomycin Administration: Intravenous > Oral *> Topical
- Rapid infusion rate (1g in <1 hour)
- Concomitant administration with medication† which predispose to mast cell activation

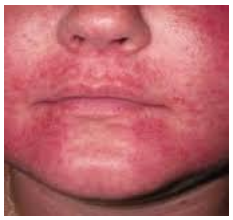
*Oral vancomycin has poor systemic absorption, however detectable serum level may occur in some patients with poor renal function or inflamed gastrointestinal tract, high doses with prolonged duration and etc

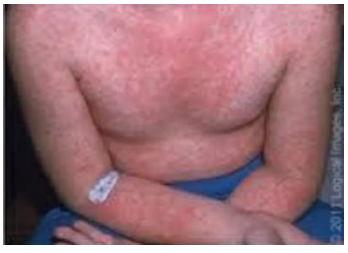
Symptoms of VIR?

- Flushing
- Erythema, and pruritus, usually affecting the upper body, neck, and face more than the lower body.
- Pains and muscle spasms in the back and chest
- Dyspnoea, and hypotension

Symptoms may manifest as soon as 4 minutes after the start of vancomycin administration. Delayed reactions near the end of infusion have been seen in those receiving therapy longer than 7 days.

Although rarely life-threatening, severe cardiovascular toxicity and cardiac arrest can occur





Reaction Severity:

- Mild: tolerable flushing and other symptoms
- Moderate: uncomfortable flushing or pruritus but hemodynamically stable and does not have chest pain or muscle spasms
- Severe: presence of muscle spasms, chest pain, and/or hypotension

Prevention of Initial Reaction

Slower infusion rate

- Vancomycin injection should be infused at a rate **NO HIGHER THAN 10 mg/minute**
- Even slower rates of infusion is suggested for patients who are also receiving opioids or other predisposing medications†

Empiric Premedication

- Oral or IV H1 antihistamines (eg. diphenhydramine 50mg) monotherapy or combination of both an H1 and H2 antihistamine (eg. ranitidine 50mg, or famotidine 20mg) can be given prior to vancomycin infusion
- They are not usually necessary, and may be considered if more rapid infusions of vancomycin (>10mg/min) are required in emergency or presurgical settings

Treatment of VIR

Mild reaction

- Symptoms typically resolve in minutes, vancomycin infusion discontinuation and antihistamines may not be necessary.
- Infusion rate can be halved

Moderate Reaction

- Interrupt the infusion
- Treat with antihistamine
- Symptoms usually subside promptly.
- The infusion can then be restarted at one-half the original rate or 10 mg/minute, whichever is slower

Severe reaction

- Stop the infusion
- Treat with antihistamine
- Give IV fluids if hypotension is present
- Once symptoms have resolved, restart vancomycin infusion over four or more hours/ continuous infusion
- Premedication with antihistamines can be repeated prior to next doses, together with prolonged infusion and close hemodynamic monitoring.
- Check and stop unnecessary predisposing medicine, if any.

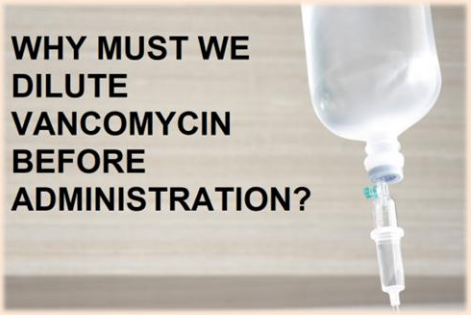
Some patients with mast cell disorder may experience recurrent and persistent symptoms, despite premedication and slower infusion rates. In these individuals, alternative antibiotics have to be considered, or desensitisation can be attempted if there is no alternative available

Examples of Predisposing Medication†:

1. Antibiotics (eg. Vancomycin, fluoroquinolones)
2. Barbiturates (eg. thiopental)
3. Narcotic analgesics (eg. morphine, meperidine)*
4. Neuromuscular antagonist (eg. quaternary amine-succcinylcholine, benzylisoquinoinium compounds- atracurium)
5. Plasma expander (eg. Dextran, Polygeline)
6. Radiocontrast agents

*Fentanyl rarely induces histamine release

When possible, avoid administering these medications simultaneously or in close approximation with Vancomycin



Vancomycin has acidic pH, administration of concentrated solution may lead to higher risk of **phlebitis**.

It should be **diluted to a concentration of 5mg/mL**, and **administer slowly with rate not exceeding 10mg/min**.

Concentration up to **10 mg/mL may be used in those with fluid restriction**; however risk of infusion-related reactions is increased.

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Cough and Cold Medications (CCMs) in Pediatrics

- Gan Siaw Thing, Pharmacist UF44-

Cough and cold are often distressing to children, prompting parents to seek for symptom-relieving-medication for solution. CCMs, however, are not recommended for use in young children. In fact, health agencies worldwide including United Sates Food and Drug Agency (USFDA), Health Canada and New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) have released their statements to restrict CCMs usage in young pediatrics[1] (age restriction might differ among agencies), here's why:

1. **Efficacy**
   There is no sufficient strong evidence from studies or systemic review on efficacy of these medications as compared to placebo in children [2,3,4,5]

2. **Safety**
   - CCMs usage have been associated with emergency department visits, either due to overdose or adverse events[5]; fatal overdose in children younger than two years of age may occur[6]
   - Dosing guidelines for these medications are mostly extrapolated from adult data; toxicity may be enhanced in this population due to varying pharmacokinetics profiles[7]

3. **High potential for medication error (overdose/ drug interaction)[6]**
   - Failure to use proper measuring devices for dose measurement
   - Erroneous use of products intended for adults
   - Polypharmacy, especially with combination products

In Malaysia, CCMs such as antihistamine, anti-tussives and decongestants are categorized as Group C Poison, which can be supplied by registered medical practitioner without prescription. Some of the preparations such as topical aromatics can be sold over-the-counter (OTC), where they can be bought without prescription in departmental stores, convenience stores or sundry shops.[8]

In February 2008, National Pharmaceutical Control Bureau under Ministry of Health Malaysia has issued an advisory letter on the prescribing of CCMs to children less than 2 years old[9]. Besides, Malaysian Drug Control Authority (DCA) in 2009 has made it compulsory to include safety warning in the labels and package inserts of all CCMs containing anti-histamine, anti-tussive, expectorant and decongestant. These medications are not to be used in children less than 2 years old; whereas those aged between 2-6 years may be prescribed with these products with caution and qualified medical practitioners advice[10].

A study conducted by CC Yong *et al* in Kuala Lumpur (2015) has shown that knowledge significantly affects parents' perceptions on safety and effectiveness of CCMs, as well as the attitude towards the use of such medications[11].

48.4% admitted to give CCMs to their ill children for sleepiness effect

11.3% administer CCMs to their children aged <2 years old

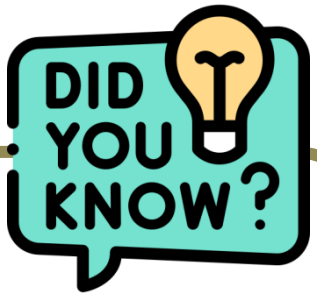
57.6% rated CCMs as safe/ very safe

59.6% thought CCMs are effective/ very effective for their children

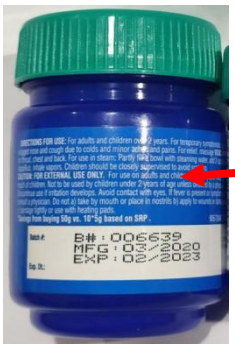
CC Yong *et al* (2015)

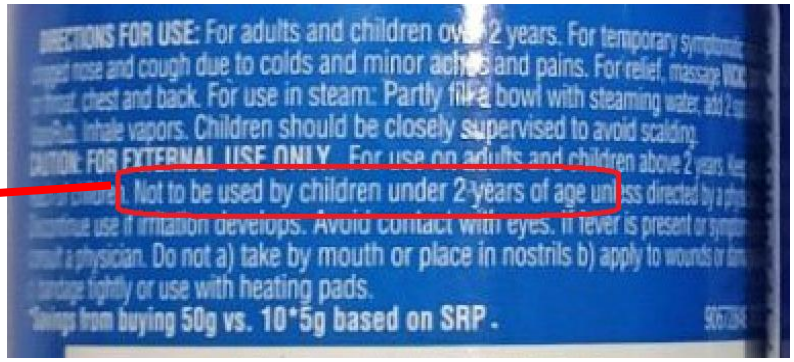
Active ingredients	Potential Adverse Events
Antihistamine Chlorpheniramine, Diphenhydramine, Promethazine	• Sedation • Paradoxic excitability (irritability, insomnia, tremor, convulsion) • Dizziness • Respiratory depression • Hallucination • Tachycardia, heart block, arrhythmia • Anticholinergic effect: Dry mouth, Urinary retention, Blurred vision • Dystonic Reactions
Narcotic Antitussives Codeine	• Respiratory depression • Nausea and vomiting, Constipation • Dizziness • Palpitation
Non-narcotic Antitussives Dextromethorphan	• Neurobehavioral changes (including euphoria, hallucinations, psychosis, agitation and coma) • CNS depression • Serotonin syndrome (tachycardia, mydriasis, ataxia) • Respiratory depression
Oral decongestants Pseudoephedrine, Phenylephrine	• Hypertension (may be severe and associated with seizures, altered mental status and organs damage) • Tachycardia or dysrhythmias • Anorexia, nausea, vomiting • Headache • Irritability, agitation, sleeplessness
Topical decongestants Oxymetazoline, phenylephrine	• Coma, bradycardia, respiratory depression, sedation (if accidentally ingested) • Rebound nasal congestion (rhinitis medicamentosa) • Nose bleeds • Drying of nasal membrane
Topical Aromatics Menthol, Camphor, Eucalyptus Oil	• GI and CNS effects if accidentally ingested • Mild irritation of skin, nose or eyes • Neurotoxicity (agitation and seizures) if overdose *toxicity from topical absorption of camphor is less common than from ingestion but has been described before. Camphor is lipophilic and well-absorbed through skin and mucous membranes, especially in young infants
Expectorants Guaifenesin	• Gastrointestinal irritation
Mucolytics N-Acetylcysteine, bromhexine	• Brochospasm, • GI disturbance • Fever

Table 2: Possible adverse event of cough and cold medications [12]



Vicks Vaporub, an OTC product easily available at sundry shops, **SHOULD NOT** be used in paediatrics below 2 years old due to its aromatics content!





Considering the higher risk than benefit, the use of these products in children < 2 years old should not be encouraged; for children of other age group, overdose should be avoided. Parent education about the self-limiting nature of coughs and colds, as well as the rational use of these drugs has to be emphasized. They can also be advised on other supportive therapies such as humidified air, bulb suctioning, saline nasal drops and increased fluid intake.

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LOOK ALIKE, SOUND ALIKE (LASA) MEDICATIONS

-Mohd. Aizat bin Jamil, Pharmacist UF 52 -

Look Alike Sound Alike (LASA) medications involve medications that are visually similar in physical appearance or packaging and names of medications that have spelling similarities and/or similar phonetics. Confusing medication names and similar product packaging may lead to potentially harmful medication errors.

STRATEGIES TO AVOID ERRORS

1

STORAGE LABELLING USING TALLMAN LETTERING

Tall Man lettering is the practice of writing part of a medicines name in upper case letters to help distinguish sound- alike, look-alike medications from one another to avoid medication errors.

Example: **BISO**prolol – **METO**prolol - **ATE**nolol

Drug Name With Tall Man Letters	Confused With
BISOprolol	**ATE**nolol **METO**prolol **LABE**tolol **CARVE**dilol **PROPRA**nolol
AMLOdipine	**FELO**dipine **NIFE**dipine **TRIMETA**zidine
PERINdopril	**CAPTO**pril
pro**CHLOR**perazine	pro**METHA**zine

Drug Name With Tall Man Letters	Confused With
cef**OTAX**ime	cef**TAZID**ime cef**TRIAXONE** ce**FAZOLIN** ce**FUROX**ime ce**FEP**ime
DOBUTamine	**DOP**amine
strepto**KINASE**	strepto**MYCIN**
iron **SUCROSE**	Iron **DEXTRAN**
flu**PENTIXOL**	flu**PHENAZINE**
BENZYLpenicillin	**BENZATHINE** penicillin

2

STORAGE LABELLING BOXING STRENGTH FOR MEDS WITH MULTIPLE STRENGTH

For medication with multiples strength, it is recommended to box the strength of the meds to highlight multiple strength availability.

Example of Boxing Strength:
Tab Bisoprolol **5mg**, Tab Bisoprolol **2.5mg**

Tab Prazosin **1mg**, Tab Prazosin **2mg**, Tab Prazosin **5mg**

3

READ & CHECK LABELS

Emphasize the need to read labels rather than relying on visual recognition and location.

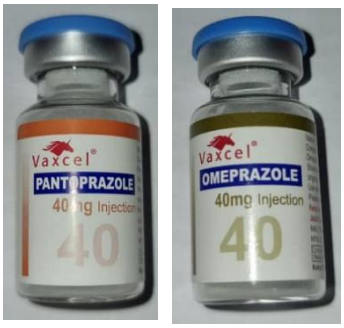
Check actual medicines against medication labels and against the prescriptions.

Pharmacist and person in charge of meds in ward must familiarize with the appearance of meds.

Do not skip procedure of counter checking and dispensing.

LOOK ALIKE MEDICATIONS: EXAMPLES

Inj Ranitidine | Inj Haloperidol | Inj Vitamin K | Inj Adrenaline



Inj Pantoprazole | Inj Omeprazole

Inj Nalbuphine | Inj Naloxone | Inj Hyoscine

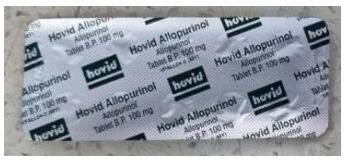
Inj Metoclopramide | Inj Frusemide | Inj Dexamethasone

Inj Cloxacillin 500mg | Inj Ampicillin 500mg | Inj Benzylpenicillin 1MIU

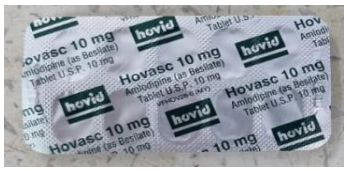
Inj Ceftazidime 1gm | Inj Ceftriaxone 1gm | Inj Cefuroxime 750mg | Inj Cefotaxime 1gm | Inj Cefuroxime 1.5gm | Inj Ceftazidime 2gm

Inj Hepatitis B Vaccine (Adult)

Inj Hepatitis B Vaccine (Peadiatric)



Tab Allopurinol 100mg



Tab Amlodipine 10mg

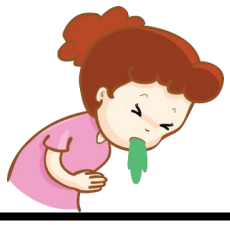
Tab Perindopril 4mg

Tab Clopidogrel 75mg

Tab Pantoprazole 40mg

References:

Guides on Handling Look Alike, Sound Alike Medications, First Edition (2021). Ministry of Health Malaysia.



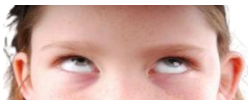
SAFETY OF ANTIEMETICS: METOCLOPRAMIDE AND DOMPERIDONE

- Muhammad Aidil Izmi bin Umar Baki, Pharmacist UF 48-

METOCLOPRAMIDE

Metoclopramide is a substituted benzamide, which has antiemetic and prokinetic properties.

Its activity results from antagonism of dopaminergic D2 receptors, antagonism of serotonergic 5-HT3 receptors, and agonism of 5-HT4 receptors.



ADVERSE EVENTS

Metoclopramide crosses the blood-brain barrier and is associated with serious neurological adverse events, mainly **extrapyramidal disorders** (including **oculogyric crisis**) which are of particular concern in children. Elderly using metoclopramide at high doses or long-term treatment are also at risk of **tardive dyskinesia.**

After reviewing the benefit and risk of this medicine in all age groups, the European Medicines Agency (EMA), in December 2013, has recommended restrictions to the use of metoclopramide to reduce the risk of neurological side effect:

- **Restricted indications** in adults and children aged between 1-18 years
- **Contraindication** in children below 1 year of age
- **Restricted doses** (body weight-based) and **treatment duration**, as well as **modified dose intervals** (Table 2)

In Malaysia, after safety review of metoclopramide conducted by NPRA in 2015, the Malaysian Drug Control Authority (DCA) had issued a directive for product registration holders to update metoclopramide package inserts with the aforementioned information.

Route	Adult	Pediatric (1-18 years)*
	INDICATION	
Parenteral	• Prevention of PONV • Symptomatic treatment of nausea and vomiting (including that induced by migraine attacks) • Prevention of RINV	2nd line** option in: • Prevention of delayed CINV • Prevention of PONV
Oral	• Prevention of delayed CINV • Prevention of RINV • Symptomatic treatment of nausea and vomiting (including that induced by migraine attacks)	2nd line** option in prevention of delayed CINV
Rectal	• Prevention of delayed CINV • Prevention of RINV	CONTRAINDICATED
	DOSE & ADMINISTRATION	
Parenteral	10mg/ dose, repeated up to 3 times per day Max daily dose: 30mg or 0.5mg/kg Parenteral metoclopramide can be given IV/ IM. IV doses must be administered as slow bolus over at least 3 min.	0.1-0.15mg/kg, repeated up to 3 times per day (refer Table 4) Max daily dose: 0.5mg/kg
Oral		Tablets may not be suitable for use in children weighing less than 30kg (risk of inaccurate dose)
Rectal		CONTRAINDICATED

Route	Adult	Pediatric (1-18 years)*
DURATION OF TREATMENT		
Parenteral	As short as possible, switch to **oral** or **rectal** route as quickly as possible	• Prevention of CINV: max duration up to 5 days • Prevention of PONV: max duration up to 48 hours
Oral	Max recommended duration: 5 days	Prevention of CINV: max duration up to 5 days
Rectal		CONTRAINDICATED
FREQUENCY OF ADMINISTRATION		
All dosage form	A minimum interval of 6 hours between 2 administration is to be respected, even if vomiting or rejection of the dose occurs	
DOSE ADJUSTMENT		
All dosage form	Renal impairment: • CrCl <15ml/min: reduce daily dose by 75% • CrCl 15-60ml/min: reduce daily dose by 50% Liver impairment (severe): reduce daily dose by 50%	
CONTRAINDICATION		
All dosage form	• Hypersensitivity to the active substance/ excipients • Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk • Confirmed or suspected pheochromocytoma (risk of severe hypertension episodes) • History of neuroleptic or metoclopramide-induced tardive dyskinesia • Epilepsy (increased crises frequency and intensity) • Parkinson disease • Combination with levodopa or dopaminergic agonists • Known history of methaemoglobinaemia with metoclopramide or NADH cytochrome-b5 deficiency	

Table 3: Metoclopramide Prescribing Information

PONV: Post operative nausea and vomiting
RINV: radiotherapy-induced nausea and vomiting
CINV: chemothearapy-induced nausea and vomting
**contraindicated in children < 1 year old*
*** 1st line treatment: serotonin antagonists (eg. ondansetron, granisetron)*

Age	Body Weight	Dose	Frequency
1-3 years	10-14kg	1mg	Up to 3 times daily (min interval 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	>60kg	10mg	

Table 4: Metoclopramide paediatric dose

DOMPERIDONE

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.

However, domperidone has been repeatedly associated with causing serious cardiovascular adverse effects, such as QT interval prolongation, ventricular arrhythmias and sudden cardiac death.

This risk was found to be higher in the following groups:

- those aged above 60 years
- total daily dose of domperidone above 30mg/day
- concomitantly using other QT-prolonging drugs or CYP3A4 inhibitors

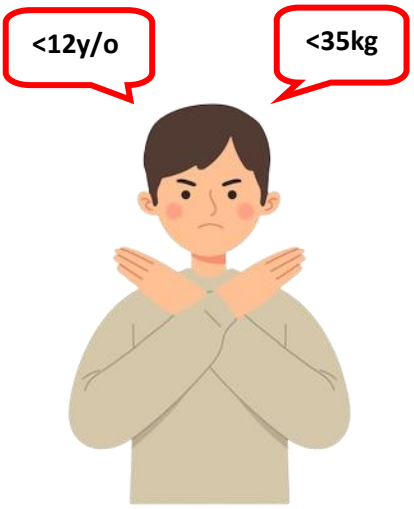
Previously, domperidone can be given to children and adolescents weighing less than 35kg at a dose of 0.25mg/kg up to 3 times daily, capping at 10mg up to 3 times daily in adults and adolescents weighing more than 35kg.

Research

Later in 2019, a randomised control study by Leitz G *et al* showed that the use of domperidone in children below 12 years of age with acute gastroenteritis showed no difference in efficacy when compared to placebo.

Since then, domperidone is no longer suggested for use in children below

12 years old weighing less than **35kg**



National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia in year 2020 has issued a directive for registration holders of domperidone products to update the local package inserts and consumer medication leaflet on this safety information:

Population	Dosage (for acute nausea/ vomiting)
Adults and adolescents ≥12 years of age and weighing ≥ 35kg	Typically 30mg/day (10mg TDS) Max: 40mg/day (10mg QID) Use the lowest effective dose For acute nausea and vomiting, treatment duration should **not exceed 1 week.** Patients should consult their physician if symptoms persist.
Children <12 years of age and weighing ≥ 35kg	
Adults and adolescents (≥12 years of age) weighing <35kg	Weight- dependent dose: 0.25mg/kg TDS- QID Max: 1mg/kg/day Use the lowest effective dose For acute nausea and vomiting, treatment duration should **not exceed 1 week**. Patients should consult their physician if symptoms persist. Due to the need for accurate dosing, tablets may not be suitable for use in this population

Population	Dosage (for acute nausea/ vomiting)
Infants and children < 12 years of age and weighing <35kg	The efficacy has not been established (not recommended)
Renal impairment (serum creatinine > 0.6mmol/L)	Reduce dosing frequency to OD or BD, dose may need to be reduced. To review patient regularly
Hepatic Impairment	Mild (Child-Pugh 5-6): no dosage adjustment necessary Moderate-Severe (Child Pugh ≥7): Contraindicated

Table 5: Dose of Domperidone based on Population

CONTRAINDICATION

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-release pituitary tumour (prolactinoma)
- Known existing prolongation of cardiac conduction intervals, particularly etc
- Significant electrolyte disturbance or underlying cardiac diseases
- Concomitantly taking qt-prolonging drugs or potent CYP3A4 inhibitors
- Whenever stimulation of gastric motility might be dangerous (eg. Gastro-intestinal haemorrhage, mechanical obstruction or perforation)

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3. Leitz G *et al* (2019). Safety and Efficacy of Low-dose Domperidone for Treating Nausea and Vomiting Due to Acute Gastroenteritis in Children. Pediatr Gastroenteral Nutr; 69(4): 425-430.
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