NHS Barnsley Clinical Commissioning Group

Anti-emetics in primary care guidelines

Summary of available anti-emetics and their licensed indications:

Please refer to **Appendix A** for details on the cautions, contra-indications, side effects, MHRA advice and significant interactions of these agents.

Drug	Nausea & Vomiting	Motion Sickness*For the treatment of motion sickness Barnsley self-care guidance applies.	Vertigo	Post op Nausea & Vomiting	Chemotherapy Induced Nausea & Vomiting	Radiotherapy induced Nausea & Vomiting	Nausea & Vomiting in Meniere's disease	Vertigo in Meniere's disease	Nausea and Vomiting in Palliative care
Betahistine							✓	✓	
Cinnarizine		✓	✓				✓	✓	
Cyclizine	✓	✓ (over 6yrs)	✓	✓		✓	✓	✓	✓
Domperidone	✓								✓
Metoclopramide	✓				✓	✓			✓
Ondansetron				✓	✓	✓			
Prochlorperazine	✓		✓					✓	
Promethazine	✓	✓	✓						

Prescribers should refer to the BNF and SPC for more details in relation to specific drugs and should assess each patient on an individual basis prior to making a decision on the most appropriate agent.

Prescribers may also want to use this as an opportunity to assess if there is an on-going need for an anti-emetic.

Barnsley self-care guidance can be accessed at: https://best.barnsleyccg.nhs.uk/clinical-support/medicines/prescribingguidelines/Self_Care_Guidance.pdf?UNLID=265932794202011109193 8

Prescribing in pregnancy summary

further details about the safety of these drugs during pregnancy

	Drug	Dose
First line use	Cyclizine	PO: 50mg every 8 hours
	Promethazine	PO: 10-25mg every 6 to 8 hours
	Prochlorperazine	PO: 5-10mg every 6 to 8 hours.

Prescribing in palliative care

Please refer to **Appendix B** for

For guidance on the treatment of nausea and vomiting in palliative care please refer to the palliative care formulary available at: http://best.barnsleyccg.nhs.uk/clinical-support/medicines/prescribing-guidelines/Palliative%20Care%20Formulary.pdf

Antiemetics used primarily in secondary or specialist services have been excluded from these guidelines e.g. Droperidol (red drug), levomepromazine (used in palliative care)

Appendix A: contra-indications, cautions, MHRA advice, side effects and significant interactions

Please refer to BNF (www.bnf.org.uk) and the SPC (https://www.medicines.org.uk/emc/) for complete information					
Drug	**Contra-Indications**	**Cautions**	**MHRA Advice**	**Side Effects**	**Significant interactions**
Betahistine	Phaeochromocytoma	Asthma History of peptic ulcer Porphyria Severe hypotension Urticaria, rashes or allergic rhinitis		Nausea Dyspepsia Headache	Antihistamines Caution is recommended with MAO inhibitors
Cinnarizine	Hypersensitivity to the active substance or to any of the excipients	Prostatic hypertrophy Urinary retention Glaucoma Gastro- Intestinal obstruction Epilepsy Parkinson's disease Hepatic or renal insufficiency		Nausea Dyspepsia Somnolence/fatigue Weight increased Antimuscarinic side effects	Alcohol CNS depressants e.g. TCAs MAO Inhibitors
Cyclizine	Acute alcohol intoxication Hypersensitivity to the active substance or to any of the excipients	Severe heart failure Acute MI Hypertension Prostatic hypertrophy(males) Urinary retention Glaucoma Gastro- Intestinal obstruction Epilepsy Phaechromocytoma Hepatic disease Severe heart failure Porphyria (should be avoided) Not recommended for children under 6 years		Nausea Dyspepsia Somnolence Weight increased Antimuscarinic side effects Hallucinations Anxiety and agitation (high doses)	Additive effects with alcohol and other central nervous system depressants e.g. hypnotics, tranquillisers, anaesthetics antipsychotics, barbiturates and opioids including methadone. Compound side effects with other anticholinergic drugs (both tricyclics and MAOIs) Note: Reports of abuse of cyclizine for its euphoric or hallucinatory effects have been noted. Prescribers should exercise caution in prescribing to those with a history of addiction or abuse or requests for large quantities

Please refer to BNF (www.bnf.org.uk) and the SPC (https://www.medicines.org.uk/emc/) for complete information					
Drug	**Contra-Indications**	**Cautions**	**MHRA Advice**	**Side Effects**	**Significant interactions**
Domperidone	Prolactinoma Domperidone should not be used when stimulation of gastric motility could be harmful: gastro-intestinal haemorrhage, mechanical obstruction or perforation Cardiac disease, heart failure, pre-existing QT prolongation or conditions where cardiac conduction is/could be impaired Concomitant use of drugs that prolong QT interval Hypersensitivity to domperidone or any of the excipients Concomitant use of CYP3A4 inhibitors Moderate or severe hepatic impairment Renal impairment	Not recommended for children under 12yrs, if used obtain an ECG before and during treatment The elimination half-life of domperidone is prolonged in severe renal impairment Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals (particularly QTc), in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), bradycardia, or in patient with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia Patients over 60 years Maximum duration of issue one week https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects	Domperidone is no longer indicated for the relief of nausea and vomiting in children aged under 12 years or those weighing less than 35 kg There is an increased risk of serious ventricular arrhythmia or sudden cardiac death with domperidone. Domperidone should be avoided in at risk patients See summary of MHRA guidance below Appendix C.	Dry mouth Numerous unknown frequency side effects including but not limited to: Gastro-intestinal disturbances, Galactorrhoea, Gynaecomastia, Hyperprolactinaemia Arrhythmias QT interval prolongation Seizure Sudden cardiac death Movement disorders	Concomitant use of the following substances is contraindicated QTc-prolonging medicinal products • anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine) • anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol) • certain antipsychotics (e.g., haloperidol, pimozide, sertindole) • certain antidepressants (e.g., citalopram, escitalopram) • certain antibiotics (e.g. , erythromycin, levofloxacin, moxifloxacin, spiramycin) • certain antifungal agents (e.g., pentamidine) • certain antimalarial agents (in particular halofantrine, lumefantrine) • certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride) • certain antihistaminics (e.g., mequitazine, mizolastine) • certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine) • certain other medicines (e.g., bepridil, diphemanil, methadone) (see section 4.3). • apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled. Please refer to the apomorphine SPC. Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e : • protease inhibitors • systemic azole antifungals • some macrolides (erythromycin, clarithromycin and telithromycin)

Please refer to BNF (www.bnf.org.uk) and the SPC (https://www.medicines.org.uk/emc/) for complete information					
Drug	**Contra-Indications**	**Cautions**	**MHRA Advice**	**Side Effects**	**Significant interactions**
Metoclopramide	Hypersensitivity to metoclopramide or the excipients Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation 3–4 days after gastrointestinal surgery phaeochromocytoma 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 Avoid use in children younger than 1 year due to the increased risk of extrapyramidal disorders	Elderly Young adults and children (those under 20 years of age) Neurological disorders Cardiac disorders Renal impairment Hepatic impairment Asthma Atopic allergy May mask underlying disorders such as cerebral irritation	Long term or high dose treatment the risks of extrapyramidal side effects outweighed the benefits. It was noted that the risk of these adverse effects is higher in children than in adults. To help minimise the risk of potentially serious neurological adverse effects, note the restrictions to indications, dose and duration of use in the Summary of MHRA alert below (Appendix C) Please note dose and length of course may differ in palliative care Please seek specialist advice	Extrapyramidal effects (particularly in those under 20 years of age) QTc prolongation Asthenia Depression Diarrhoea Drowsiness Hypotension AV block Cardiac arrest Syncope Tremor Blood disorders Acute dystonic reactions (including facial and skeletal muscle spasm) can occur in the very young (mainly girls and young women) and the very old Menstrual cycle irregularities (During prolonged treatment)	Levodopa Dopaminergic agonists Alcohol Antipsychotics

Please refer to BNF (www.bnf.org.uk) and the SPC (https://www.medicines.org.uk/emc/) for complete information					
Drug	**Contra-Indications**	**Cautions**	**MHRA Advice**	**Side Effects**	**Significant interactions**
Ondansetron	Congenital long QT Syndrome Hypersensitivity to ondansetron or any of the excipients	Prolonged QT interval (dose dependent manner) SSRI's (monitor patient) Gastro-intestinal obstruction Adenotonsillar surgery	Caution must be used if administering ondansetron to patients at risk of QT prolongation or arrhythmias Hypokalaemia and hypomagnesaemia should be corrected before ondansetron administration	Constipation Headache Flushing	Phenytoin, Carbamazepine and Rifampicin reduce the effectiveness of ondansetron QT prolonging drugs e.g. erythromycin, ketoconazole, chlorpromazine, citalopram, domperidone, etc Anti-arrythmics (amiodarone and beta blockers) Tramadol (may cause reduced analgesic effect)
Prochlorperazine	Avoid in children under 10kg Hypersensitivity to the active substance or any of the excipients CNS depression Comatose states Phaeochromocytoma	Elderly Epileptics- due to lower seizure threshold Cardiovascular disease or family history of QT prolongation Stroke Depression Photosensitivity Skin reactions Venous thromboembolism Diabetics Dystonic reactions in the paediatric population even with low dose 0.5mg/kg Acute withdrawal symptoms including nausea, vomiting, sweating and insomnia have been described after abrupt cessation		Extrapyramidal Symptoms Insomnia Agitation Convulsions	Alcohol Barbiturates Sedatives Lithium Antihypertensives Anti-parkinsons drugs Alcohol Antipsychotics QT prolonging drugs MAO Inhibitors

Please refer to BNF (www.bnf.org.uk) and the SPC (https://www.medicines.org.uk/emc/) for complete information					
Drug	**Contra-Indications**	**Cautions**	**MHRA Advice**	**Side Effects**	**Significant interactions**
Promethazine	Contraindicated for use in children less than 2 years of age because of the potential for fatal respiratory depression Avoid in patients with coma or CNS depression Hypersensitivity to promethazine or any of the excipients Avoid in MAOI patients (up to 14 days previously)	Asthma, Bronchitis, Bronchiectasis, Bladder neck or pyloroduodenal obstruction Severe coronary artery disease Narrow angle glaucoma Epilepsy Hepatic and renal insufficiency Promethazine may mask the warning signs of ototoxicity caused by ototoxic drugs e.g. salicylates Children and adolescents with signs and symptoms suggestive of Reye's Syndrome		Drowsiness Dizziness Restlessness Headaches Nightmares Tiredness Disorientation Photosensitive skin reactions (avoid strong sunlight)	Anticholinergic agents Tricyclic antidepressants Sedatives Hypnotics Alcohol should be avoided. Urine pregnancy tests can produce false-positive or false-negative results whilst taking promethazine

Information from BNF online (01/03/2021), www.medicines.org.uk/emc and www.mhra.gov.uk
Please note that Appendix A is not an exhaustive list of cautions, contra-indications, side effects and interactions. Please consult individual product monographs for a complete list.

This guidance was originally produced following the MHRA alerts around the safety of metoclopramide and domperidone in 2014 (please refer to Appendix C for more information in relation to these alerts). The MHRA has recently published updated guidance regarding domperidone and ondansetron.

Appendix B: Nausea and Vomiting in Pregnancy[1]

Nausea and vomiting are extremely common symptoms of pregnancy, generally reported between weeks 6-16. In a minority of women symptoms persist for longer**.** The majority of cases can be managed by lifestyle measures**.** Other pathological causes should be excluded by clinical history, focused examination and investigations.

Management:

1) Offer lifestyle advice:
   - Reassurance.
   - Advise rest.
   - Avoiding any foods or smells that trigger symptoms (for example spicy or fatty foods).
   - Eating plain biscuits or crackers in the morning before getting up.
   - Eating bland, small, frequent meals low in carbohydrate and fat but high in protein.
   - Cold meals may be more easily tolerated if nausea is smell-related.
   - Drinking little and often rather than large amounts, as this may help to prevent vomiting.
   - Ginger.
   - Acupressure.
2) If applicable, change iron supplement to a different formulation, or stop if clinically appropriate.
3) Antacids, Histamine H2 receptor antagonists (H2RA) or proton pump inhibitors (PPI) may be used for women developing gastro-oesophageal reflux disease, oesophagitis or gastritis.
4) Consider drug treatment with an anti-emetic for women who do not respond to lifestyle advice options and have persistent symptoms Response to drug treatment should be assessed after 24 hours, if response is good, continue and reassess each week. If response is inadequate, and woman is not dehydrated and there is no ketonuria, change to drug from a different class. Stop treatment using clinical judgement in line with the prescribing information detailed in the following table.
5) Decide when to stop medication using a pragmatic approach (for example, it may be possible to stop anti-emetic medication at around 12-16 weeks, by which time symptoms have usually improved) in conjunction with clinical judgement (for example severity of symptoms, response to treatment in previous pregnancies, preference of the woman).
6) Pregnant women with nauseas and vomiting should be advised to seek urgent medical advice at any point if they experience:
   - Very dark urine, or no urination for more than 8 hours.
   - Abdominal pain or fever.
   - Severe weakness or feeling faint.
   - Vomiting blood.
   - Repeated, unstoppable vomiting.
   - Inability to keep down food or fluids for 24 hours.
   - Severe headaches, visual problems, severe pain below the ribs, sudden swelling of the face, hands or feet (symptoms of pre-eclampsia).
7) Consider admitting to hospital if the woman has one of:
   - Continued nausea and vomiting and is unable to keep down liquids or oral antiemetics.
   - Continued nausea and vomiting with ketonuria and/or weight loss (>5% of body weight), despite treatment with oral antiemetics.
   - A confirmed or suspected comorbidity (for example she is unable to tolerate oral antibiotics for urinary tract infection.
   - Any co-existing health condition which may be adversely affected by nausea and vomiting e.g. diabetes.

Drug treatment for nausea & vomiting in pregnancy[2,3]

Drug treatment with an anti-emetic may be considered when conservative management options have failed to achieve an adequate response. It is generally accepted that all drugs should be avoided if possible during the first trimester and should be taken only when the benefits of medication outweigh potential risks. The decision to prescribe any medication in pregnancy should only be following a full assessment and discussion with the patient of potential risks vs. benefits of treatment. The discussion should be clearly documented in the patient's notes.

NICE's guidelines antenatal care for uncomplicated pregnancies CG62 (2008) and the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum (2016 Green-top Guideline No.69) recommends antihistamines as first line treatment options. RCOG also recommend prochlorperazine as a possible first line treatment option.
Metoclopramide, or ondansetron maybe be considered second line treatment options after discussions with the patient of benefits vs. potential risks.

Although many medicines used in the treatment of nausea and vomiting are not officially licensed for use in pregnancy, most have been used in pregnancy without any known adverse effects on the developing baby.[4]

Overview of pregnancy safety data for anti-emetic medication[3]

Choice	Drug	Dose	Use in Pregnancy	Comment
1st Line	Cyclizine: 50mg tablets	PO: 50mg every 8 hours	Both cyclizine and promethazine use in pregnancy is unlicensed. Extensively used during pregnancy. Large amount of safety data available for antihistamines in general, with no evidence of increased rate of major congenital malformations or other adverse pregnancy outcomes. Published data specifically for cyclizine and promethazine are limited, but do not overall suggest an increased risk of congenital malformation.	Reassess after 24 hours; Continue if effective. Review patient ONCE a week thereafter.
	Promethazine hydrochloride: 10mg & 25mg tablets 5mg/5ml oral solution SF	PO: 10 – 25mg every 6 to 8 hours PRN		
	Prochloperazine: 5mg tablets 5mg/5ml solution	PO: 5-10mg every 6 – 8 hours	Prochloperazine use in pregnancy is unlicensed. A large meta-analysis examining pregnancy outcome after exposure to various and multiple phenothiazines did not provide evidence of increased risk of congenital malformations. Nor did a case control study examining malformation rates after exposure specifically to Prochloperazine. Data on other pregnancy outcome are lacking.	Buccastem M Buccal tablets are contra-indicated in pregnancy. Reassess after 24 hours; Continue if effective. Review patient ONCE a week thereafter

Choice	Drug	Dose	Use in Pregnancy	Comment
2nd Line	Metoclopramide; 10mg tablets 5mg/5ml oral solution SF	PO: 5-10mg every 8 hour	Metoclopramide use in pregnancy is unlicensed. Data from one large case-control (n=28,486 exposures) and one small (n=175 exposures) cohort study provide no evidence of increased risk of congenital malformations. A large cohort study found no associations with miscarriage or stillbirth. However, a small cohort study showed a higher incidence of premature delivery after metoclopramide exposure. Manufacturer advises can be used if clinically indicated, but avoid at end of pregnancy due to risk of extrapyramidal symptoms in newborn. Use in younger adults has been associated with dystonias and should therefore **NOT** routinely used as first-line treatment**.**	Reassess after 24hours. **MAXIMUM 5 days treatment** Metoclopramide should only be prescribed following a full assessment and discussion with the patient of potential risks vs. benefits of treatment Review patient ONCE a week thereafter
	Ondansetron: 4mg and 8mg tablets	PO: 4-8mg every 6 to 8 hours	Ondansetron use in pregnancy is unlicensed. Statistically robust study shows increased risk of orofacial clefts (absolute risk still small). While some studies show increased risks of cardiac defects (mostly uncomplicated septal defects), others including large statistically robust study do not replicate this finding. Data on other pregnancy outcomes generally reassuring but limited. Please see Appendix C MHRA Alert January 2020 Ondansetron: small increased risk of oral clefts following use in the first 12 weeks of pregnancy for further information. Possible associations between gestational ondansetron exposure and renal malformations have also been observed. These observations require further investigation before conclusions can be drawn.	Ideally be avoided in the first trimester Reassess after 24hours. **MAXIMUM 5 days treatment** Ondansetron should only be prescribed following a full assessment and discussion with the patient of potential risks vs. benefits of treatment. Use of Ondansetron can be extended longer than 5 days with full risk/benefit analysis and specialist input

Please refer to the BNF (www.bnf.org.uk) and the SPC (www.emc.medicines.org.uk) for complete information.

<u>References used for anti-emetic use in pregnancy:</u>

1. Clinical Knowledge Summaries. Nausea and Vomiting in pregnancy. October 2018. Available at: https://cks.nice.org.uk/nauseavomiting-in-pregnancy Accessed <6th February 2021>
2. RCOG. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum. June 2016 Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg69-hyperemesis.pdf Accessed <6th February 2021>

3. UKTIS. Nausea and vomiting in pregnancy. September 2019. Version 2 Available at: www.toxbase.org <Accessed 6th February 2021>

Appendix C: Summary of MHRA guidance on domperidone, metoclopramide and ondansetron.

Domperidone MHRA Alert December 2019 Domperidone for nausea and vomiting: lack of efficacy in children; reminder of contraindications in adults and adolescents

https://www.gov.uk/drug-safety-update/domperidone-for-nausea-and-vomiting-lack-of-efficacy-in-children-reminder-of-contraindications-in-adults-and-adolescents

Domperidone is no longer licensed for use in children younger than 12 years or those weighing less than 35kg.

Results from a placebo-controlled study in children younger than 12 years with acute gastroenteritis did not show any difference in efficacy at relieving nausea and vomiting compared with placebo.

Advice for healthcare professionals

•Domperidone is licensed for the relief of symptoms of nausea and vomiting only in adults and adolescents 12 years of age or older and weighing 35 kg or more

•Consider alternative treatments to domperidone in children younger than 12 years of age who need relief of symptoms of nausea and vomiting

Contraindications

Domperidone is contraindicated:

- In patients with moderate to severe hepatic impairment
- In patients with known existing prolongation of cardiac conduction intervals (particularly QTc)
- In patients with underlying cardiac diseases such as congestive heart failure,
- In patients with significant electrolyte disturbances,
- During co-administration with QT-prolonging drugs (for more information about considerations with apomorphine (see Drug Safety Update, April 2016)
- During co-administration with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects)
- In patients with hypersensitivity to Domperidone
- In patients with a prolactin-releasing pituitary tumour
- In patients in which stimulation of the gastric motility could be harmful (for example, in patients with gastro-intestinal haemorrhage, mechanical obstruction, or perforation)

Patients with these conditions or currently receiving long-term treatment with domperidone should have their treatment reviewed at their next routine appointment and be switched to an alternative treatment if required.

Dose

- For adults and adolescents 12 years of age or older and weighing 35 kg or more, the recommended maximum dose in 24 hours is 30 mg (dose interval: 10 mg up to 3 times a day)
- Domperidone should be used at the lowest effective dose for the shortest possible duration and maximum treatment duration should not usually exceed 1 week
- Report suspected adverse drug reactions associated with domperidone to the Yellow Card Scheme

Domperidone is also used outside of its licensed indications in children in the UK for gastrokinetic effects in

conditions other than nausea and vomiting. If a specialist physician considers, based on their professional judgement and available evidence of the medical condition, that domperidone use in any condition is justified in a child younger than 12 years, the patient or parent/carer should be fully informed of the potential benefits and risks of the different options. Please see previous guidance on off-label use in Drug Safety Update, April 2009 https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities

Reminder on the safe use of domperidone in accordance with the product information.
The 2019 MHRA Alert expands on the previous 2014 MHRA Alert https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects . Healthcare providers are reminder of the risk of serious cardiac adverse drug reactions related to domperidone, including QTc prolongation, torsade de pointes, serious ventricular arrhythmia, and sudden cardiac death.

Administration of liquid formulations

Oral liquid formulations of domperidone should only be given via appropriately designed, graduated measuring devices (eg, oral syringes for children and cups for adults and adolescents) to ensure dose accuracy

Advice relating to the use of anti-emetics can be accessed from SPS website: https://www.sps.nhs.uk/articles/safety-in-lactation-drugs-used-in-nausea-and-vertigo-2/
Advice relating to the use of domperidone in babies and children can be accessed via the cBNF.
The Neonatal and Paediatric Pharmacists Group (NPPG) is currently reviewing its positional statement on the use of Domperidone, which expected mid-2020.
As an interim measure the NPPG has produced the following document
http://nppg.org.uk/wp-content/uploads/2020/01/Domperidone_ECG_Interim_January_2020.pdf

MHRA Alert 2016 Apomorphine with domperiodne: minimisng risk of cardiac side effects. https://www.gov.uk/drug-safety-update/apomorphine-with-domperidone-minimising-risk-of-cardiac-side-effects

Metoclopramide

MHRA alert August 2013 https://www.gov.uk/drug-safety-update/metoclopramide-risk-of-neurological-adverse-effects

Advice for healthcare professionals

Indications and use in adults and children

- In adults, metoclopramide remains indicated for prevention of postoperative nausea and vomiting; radiotherapy-induced nausea and vomiting; delayed (but not acute) chemotherapy-induced nausea and vomiting; and symptomatic treatment of nausea and vomiting, including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics).
- In children, age 1–18 years, metoclopramide should only be used as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and for treatment of established postoperative nausea and vomiting.
- Use of metoclopramide is contraindicated in children younger than 1 year.
- Metoclopramide should only be prescribed for short-term use (up to 5 days).
- This advice does not apply to unlicensed doses of metoclopramide in palliative care.

Dosing

- For adults, the maximum dose in 24 hours is 30mg (or 500mcg per kg bodyweight). The usual dose is 10mg up to three times a day.
- In children age 1 year or older, the recommended dose is 100-150mcg per kg bodyweight, repeated up to three times a day. The maximum dose in 24 hours is 500mcg per kg bodyweight.

Administration

- Intravenous doses should be administered as a slow bolus over at least 3 minutes to reduce the risk of adverse effects.

- Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy in children.

The management of patients taking domperidone/metoclopramide long term for GORD, dyspepsia or gastroparesis

- All patients receiving long-term domperidone or metoclopramide should have their therapy reviewed and risks explained to them.
- A trial of withdrawal of domperidone/metoclopramide therapy should be tried in all patients, with full patient engagement.
- For GORD or dyspepsia, ensure all other therapeutic and lifestyle options are optimised.
    - First line: One month of full dose PPI.
    - If first line not effective check for compliance and reinforce general measures to reduce symptoms.
    - For people whose symptoms persist after 1 month of treatment with a full-dose PPI, offer a further month of full-dose PPI.
    - For people with persistent, severe symptoms, consider doubling the dose of the PPI or switching to an alternative PPI for a further month.
    - For people with a particular problem with nocturnal symptoms that do not respond to PPI therapy, consider adding a H2RA at bedtime in the short term (for example intermittent 2-week courses).
    - Advise the person that symptoms may recur after stopping treatment, and that they should come back for further treatment if they experience persistent or recurrent symptoms.
    - For people who do not respond to a second month of full-dose PPI, or one month of double-dose or alternative PPI, consider referral for further investigation and management of refractory gastro-oesophageal reflux disease.
    - For people who develop alarm features (such as chronic gastrointestinal bleeding or persistent weight loss), refer urgently for endoscopic investigation.
    - If an endoscopy is indicated, stop PPI or H2RA treatment at least 2 weeks before the endoscopy as the treatment may mask serious underlying pathology such as gastric cancer.
    - Patients of any age with gastro-oesophageal symptoms that are persistent, non-responsive to treatment or unexplained should be considered for referral to a specialist.

- For gastroparesis, ensure any iatrogenic cause is identified. Assess and correct nutritional state and in patients with diabetes, check glycaemic control.
    - If symptoms return, a trial of ‘on-demand’ domperidone (up to 10mg TDS for up to one week) could be tried if appropriate. However it should be remembered that domperidone is now contra-indicated in patients with conditions where the cardiac conduction is, or could be, impaired; significant electrolyte disturbances; underlying cardiac diseases such as congestive heart failure; severe hepatic impairment or in patients taking concurrent drugs which are known to cause QT prolongation (for example erythromycin; citalopram, haloperidol or amiodarone) or potent CYP3A4 inhibitors (eg itraconazole, fluconazole). Use with less potent CYP3A4 inhibitors (eg diltiazem or verapamil) is also not recommended. Patients older than 60 years are at increased risk of arrhythmias and it is preferable to avoid domperidone in this patient group.
    - An anti-emetic agent (see list above) may be used to control any symptomatic nausea and vomiting.

<u>Ondansetron</u>

MHRA Alert January 2020 Ondansetron: small increased risk of oral clefts following use in the first 12 weeks of pregnancy

https://www.gov.uk/drug-safety-update/ondansetron-small-increased-risk-of-oral-clefts-following-use-in-the-first-12-weeks-of-pregnancy

Summary of MHRA alert

Recent epidemiological studies report a small increased risk of orofacial malformations in babies born to women who used ondansetron in early pregnancy.
Key evidence was an observational study of 1.8 million pregnancies in the USA of which 88,467 (4.9%) were exposed to oral ondansetron during the first trimester of pregnancy. The study reported that ondansetron use was associated with an additional 3 oral clefts per 10,000 births (14 cases per 10,000

births versus 11 cases per 10,000 births in the unexposed population). This data were recently reviewed within Europe and considered to be robust. As for all licensed medicines, the safety of ondansetron will be continuously monitored by the MHRA and relevant emerging information will be considered as it becomes available.

The recent observational studies have some limitations inherent to the data sources, but the findings are considered sufficiently robust to indicate that use of ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is a growing body of evidence on the use of ondansetron in pregnancy that does not suggest an increase in the risk of overall congenital malformations combined.

If the clinical decision is to offer ondansetron in pregnancy, women must be counselled on the potential benefits and risks of use, both to her and to her unborn baby and the final decision should be made jointly.