Anti-emetic 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	Vertigo	Chemotherapy induced N&V	N&V in Meniere's disease
Betahistine					√
Cinnarizine		√	√		√
Cyclizine	√	√	√		√
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.

Prescribing in pregnancy (Unlicensed)

Please refer to **Appendix B** for 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. PR: 25mg daily
Second line use	Ondansetron	PO: 4-8mg every 6 to 8 hours
Third line use	Metoclopramide	PO: 10mg every 8 hours

Palliative Care

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

*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 guidance has recently been updated to include the management of nausea and vomiting in early pregnancy. These guidelines were approved at the APC on 11th April 2018*

Appendix A

Please refer to BNF (www.bnf.org.uk) and the SPC (www.emc.medicines.org.uk) for complete information					
Drug	**Contra- Indications**	**Cautions**	**MHRA advice**	**Side Effects**	**Significant interactions**
Betahistine	Phaeochromocytoma	Asthma History of peptic ulcer Not recommended for children		Nausea Dyspepsia Headache	Antihistamines Caution is recommended with MAO inhibitors
Cinnarizine	Porphyria Severe hepatic disease Children under 5 years of age	Prostatic hypertrophy Urinary retention Glaucoma Gastro- Intestinal obstruction Epilepsy Parkinson's disease		Nausea Dyspepsia Somnolence Weight increased Antimuscarinic side effects	Alcohol CNS depressants TCAs
Cyclizine	Porphyria Severe hepatic disease	Severe heart failure Prostatic hypertrophy Urinary retention Glaucoma Gastro- Intestinal obstruction Epilepsy Parkinson's disease Not recommended for children under 6 years		Nausea Dyspepsia Somnolence Weight increased Antimuscarinic side effects	Additive effects with alcohol and other central nervous system depressants e.g. hypnotics, tranquillisers, anaesthetics. 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.
Domperidone	Prolactinoma; Conditions where increased gastric motility is harmful Conditions where cardiac conduction is/could be impaired Concomitant use of drugs that prolong QT interval Concomitant use of CYP3A4 inhibitors Hepatic impairment-avoid	Not recommended for children Patients over 60 years	There is an increased risk of serious ventricular arrhythmia or sudden cardiac death with domperidone. See summary of MHRA alert below.	Gastro-intestinal disturbances, Galactorrhoea, Gynaecomastia, Hyperprolactinaemia	Erythromycin, Citalopram and other drugs known to prolong the QT interval. Ketoconazole should be avoided due to risk of ventricular arrhythmias.

Drug	Contra- Indications	Cautions	MHRA advice	Side Effects	Significant interactions
Metoclopramide	Gastro-intestinal obstruction, perforation or haemorrhage Phaeochromocytoma Children younger than 1 year	Elderly Young adults and children (those under 20 years of age) Atopic allergy (including asthma) Cardiac conduction disturbances Electrolyte imbalance Bradycardia Parkinson's disease Epilepsy	A review demonstrated that in long term or high dose treatment the risks of extrapyramidal and cardiovascular effects outweighed the benefits. It was noted that the risk of these adverse effects is higher in children than in adults. See summary of MHRA alert below.	Extrapyramidal effects (particularly in those under 20 years of age) Hyperprolactinaemia	Ciclosporin
Ondansetron	Congenital long QT syndrome	Risk of QT prolongation 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. Erythromycin, Domperidone, Citalopram and other drugs known to prolong the QT interval.

Drug	Contra- Indications	Cautions	MHRA advice	Side Effects	Significant interactions
Prochlorperazine	Avoid in children under 10kg	Elderly Epileptics- due to lower seizure threshold Cardiovascular disease or family history of QT prolongation		Extrapyramidal symptoms	Acute withdrawal symptoms including nausea, vomiting, sweating and insomnia have been described after abrupt cessation.
Promethazine	Contraindicated for use in children less than 2 years of age because of the potential for fatal respiratory depression	Asthma Bronchitis Bronchiectasis Bladder neck or pyloroduodenal obstruction Severe coronary artery disease Narrow angle glaucoma Epilepsy Hepatic and renal insufficiency Children and adolescents with signs and symptoms suggestive of Reye's Syndrome		Drowsiness, Dizziness, Restlessness, Headaches, Nightmares, Tiredness, Disorientation	Action of anticholinergic agents, tricyclic antidepressants, sedatives or hypnotics is enhanced. Alcohol should be avoided. Urine pregnancy tests can produce false-positive or false-negative results whilst taking promethazine.

Information from BNF 74, www.medicines.org.uk/emc and www.mhra.gov.uk

Appendix B: Nausea and Vomiting in Pregnancy

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]

1) Offer lifestyle advice:
   - Reassurance
   - Advise rest.
   - The following may also be tried:
     - ✓ 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 if dietary advice has failed and the woman has persistent symptoms. If response to first line treatment 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.

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.

Antiemetics, for which human pregnancy data are very limited or not available, should NOT be used in preference to preparations for which epidemiological data showing no evidence of adverse foetal effects are available, unless there is a clinically justifiable argument to do so, and the potential for foetal risk has been considered

References used for anti-emetic use in pregnancy:

1. Clinical Knowledge Summaries. Nausea and Vomiting in pregnancy. June 2017. Available at: https://cks.nice.org.uk/nauseavomiting-in-pregnancy Accessed <30th January 2018>
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 <30th January 2018>
3. TOXBASE. Nausea and vomiting in pregnancy. May 2015. Available at: https://www.toxbase.org/poisons-index-a-z/n-products/nausea-and-vomiting-in-pregnancy/ Accessed <30th January 2018>

Choice[2]	Drug	Dose	Use in Pregnancy[3]	Comment[1]
1st Line	Cyclizine: 50mg tablets	PO :50mg every 8 hours	Extensively used during pregnancy. Large amount of safety data available regarding antihistamines in general. No increase in rate of major congenital malformations observed. Published data specifically for cyclizine are limited, but no increase in congenital malformation has been reported with either cyclizine or promethazine use during pregnancy. Other pregnancy outcomes have not been studied for either drug.	Reassess after 24 hours; Continue if effective Review woman 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 PR: 25mg daily	A large meta-analysis examining pregnancy outcomes after exposure to various and multiple phenothiazines did not provide evidence of increased risk of congenital malformations. Neither did a case-control study examining outcomes after exposure specifically to prochlorperazine.	
2nd Line	Ondansetron: 4mg and 8mg tablets	PO: 4-8mg every 6 to 8 hours	One population-based cohort study and one unpublished conference abstract reported an association between ondansetron exposure and cardiac defects. One case-control study found a possible link with isolated cleft palate but two cohort studies found no evidence of increased risk cleft palate.	Reassess after 24 hours; **MAXIMUM 5 days treatment** Review woman ONCE a week thereafter
3rd line	Metoclopramide 10mg tablets 5mg/5ml oral solution SF	PO : 10mg every 8 hour	Foetal exposure data limited to one large case control and a small cohort study. No increase in congenital malformations in exposed pregnancies. Cohort study showed 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**.**	

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

Appendix C: Summary of MHRA guidance on domperidone and metoclopramide

Domperidone MHRA alert May 2014 https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects

Advice for healthcare professionals

Indication

• Domperidone is now restricted to use in the relief of the symptoms of nausea and vomiting
• It should be used at the lowest effective dose for the shortest possible time

Contraindications

• Domperidone is now contraindicated in people:
  - with conditions where cardiac conduction is, or could be, impaired
  - with underlying cardiac diseases such as congestive heart failure
  - receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors
  - with severe hepatic impairment

• Patients with these conditions should have their treatment reviewed at their next routine appointment and be switched to an alternative treatment if required

Posology

Oral formulations

• For adults and adolescents over 12 years of age and weighing 35 kg or more, the recommended maximum dose in 24 hours is 30mg (dose interval: 10mg up to three times a day)
• In children under 12 years of age and weighing less than 35 kg, the recommended maximum dose in 24 hours is 750mcg/kg body weight (dose interval: 250mcg/kg body weight up to three times a day)

Suppository formulation (unlicensed special)

• Suppositories should only be used in adults and adolescents weighing 35 kg or more; the recommended maximum daily dose in 24 hours is 60mg (dose interval: 30mg twice a day)

Duration of treatment

• The maximum treatment duration should not usually exceed one week

• Patients currently receiving long-term treatment with domperidone should be reassessed at a routine appointment to advise on treatment continuation, dose change, or cessation

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 Domperidone to promote lactation has been produced by UKMI and can be found at the following link: http://www.midlandsmedicines.nhs.uk/filestore/S00003.pdf

Advice relating to the use of domperidone in babies and children has been issued by the Neonatal and Paediatric Pharmacists Group. The guidance can be accessed via the home page at: http://www.nppg.scot.nhs.uk/

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.