The Christie NHS
NHS Foundation Trust

CLINICAL GUIDANCE

FOR THE PREVENTION AND MANAGEMENT OF CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING IN ADULTS

Procedure reference:	2196	Version:	V2.1
Document owner:	Robert Duncombe, The Director of Pharmacy	Accountable committee:	Systemic Anticancer Delivery Group
Date approved:	December 2015	Review date:	December 2017
Target audience:		All staff involved in treating patients with systemic anticancer therapy and/or Chemotherapy or Radiotherapy Induced Nausea and Vomiting	

Key points

- Use an individualised patient approach
- Prophylactic antiemetics should be prescribed according to the emetogenicity of the regime
- A step wise approach is recommended for management of vomiting patients
- Patients with refractory nausea and vomiting should be referred to the supportive care team

CONTENTS

1. ASSOCIATED DOCUMENTS

Pain and Symptom Control Palliative Care Guidance version 1.2 Ref CP73
Guidelines for the management of patients with diabetes or at risk of developing diabetes version 1.1 Ref CP44
Disease group guidelines
Specific treatment protocols

2. INTRODUCTION

2.1 Purpose

To provide Trust wide guidance on the safe and effective use of antiemetics for the prevention and treatment of chemotherapy and radiotherapy induced nausea and vomiting.

2.2 Scope

This document is applicable to all medical, nursing and pharmacy staff involved in the recommendation, prescribing, administration and monitoring of antiemetic therapy.

3. DEFINITIONS

Term	Meaning
Acute nausea and vomiting	Nausea and/or vomiting occurring up to 24 hours after administration of treatment
Anticipatory nausea and vomiting	Nausea and/or vomiting occurring in the days or hours prior to treatment
bd	Twice a day
CINV	Chemotherapy Induced Nausea and Vomiting
CYP3A4	A member of the cytochrome P450 family of oxidizing enzymes involved in drug metabolism.
Delayed nausea and vomiting	Nausea and/or vomiting occurring later than 24 hours after administration of treatment, can be up to 3 – 5 days post treatment.
IM	Intramuscularly
IV	Intravenously
NG	Nasogastric
NK1 receptor	A subfamily of the neurokinin receptors that bind the neurotransmitter substance P
od	Once a day
PEG	Percutaneous Endoscopic Gastrostomy
PEJ	Percutaneous Endoscopic Jejunostomy
PO	Orally
PRN	When required
SACT	Systemic Anticancer Therapy
SC	Subcutaneously
tds	Three times a day
qds	Four times a day
$5HT_3$	A subfamily of the 5-hydroxytryptamine receptor that bind the neurotransmitter serotonin

4. GUIDANCE FOR THE USE OF ANTIEMETICS

General priniciples

- These guidelines are written for the management of adult patients only.
- Always consider the patient as an individual within the context of these guidelines taking into account age, comorbidities, concomitant medication and other issues such as swallowing difficulties before recommending an antiemetic.
- The emphasis should always be on the prevention of nausea and vomiting, therefore, antiemetics should be administered regularly and prophylactically.
- Optimal emetic control in the acute phase is essential to reduce the risk of nausea and vomiting in the delayed phase.
- Always commence anti-emetics before treatment.
- Oral premedication doses of ondansetron and dexamethasone are as effective as intravenous doses. Oral premedication must be administered at least 30 minutes before treatment.

- For patients who are unable to tolerate oral anti-emetics, consider an alternative route eg: buccal, IM, IV, subcutaneous syringe driver or rectal. However, suppositories should not be used in neutropenic patients because of the risk of perianal sepsis
- Anticipatory nausea and vomiting is believed to be a learned response to treatment. If post-treatment nausea and vomiting does not occur, anticipatory nausea and vomiting is very unlikely.
- Patients must be given the standard anti emetic letter for their GP when they receive their first cycle of treatment (Appendix 1).
- In the case of anti-emetic failure, subsequent cycles of treatment should be supported by the use of anti-emetics recommended for the next higher group. In the case of the highest group (high emetic potential and anthracycline and cyclophosphamide containing regimes) consideration should be given to the use of palonosetron and if not already in use, aprepitant.

5. SYSTEMIC ANTICANCER THERAPY (SACT)

Emetic Risk of SACT

- The recommended agents for the prophylaxis of SACT induced nausea and vomiting are dependent on the emetogenicity of the regimen, see Table 1.
- The emetic risk of treatment is shown in Appendices 2 and 3.
- For combination therapy choose the appropriate regimen for the most emetogenic drug to be administered. However, combination therapy may have a greater emetogenicity than the sum of the single agents used alone, for example anthracycline plus cyclophosphamide containing regimens are deemed to be of high emetogenic potential.
- For multiple day regimens choose the appropriate pre-treatment regimen for each day and on discharge give the anti-emetics suggested for the SACT agent with the highest emetogenic potential.
- In multiple day treatment regimens it may be appropriate to administer IV antiemetics prior to treatment on a daily basis depending on the emetogenicity of the agents. In this instance oral anti-emetics would not commence until completion of IV treatment.
- **See individual Disease Group guidelines for recommendations of anti-emetic use with specific protocols**.
- Patients with 3 or more known risk factors for emesis should be considered for additional anti-emetics at the outset of treatment. These risk factors include:
  Female
  <30 years old
  Pre-existing nausea and vomiting
  Poor control with prior treatment
  History of sickness: in pregnancy/travel sickness/with surgery
  Anxiety
  A history of high alcohol intake, substance misuse or smoking can have a protective effect and reduce the risk of emesis

Table 1: Initial choice of anti-emetics for SACT induced emesis

Low emetogenic potential - risk in 10 – 30% of patients

Pre treatment	On completion of tretament	Anti-emetic failure (see Table 2)
No routine antiemetics necessary	No routine anti-emetics necessary, however, consider: metoclopramide 10mg PO tds PRN 5/7	Breakthrough nausea and vomiting: Commence with 1st line anti-emetics Subsequent cycles as for moderately emetogenic therapy

Moderate emetogenic potential – risk in 30 – 90% of patients

Pre treatment	On completion of treatment	Anti-emetic failure (see Table 2)
Option 1: Ondansetron 8mg IV*/PO Dexamethasone 7.6mg IV / 8mg PO	Dexamethasone 4mg PO bd 2/7 Ondansetron 8mg PO bd 2/7 Metoclopramide 10mg PO tds PRN 5/7	Breakthrough nausea and vomiting: Commence with 2nd line anti-emetics. Subsequent cycles as for highly emetogenic therapy
Option 2: Palonosetron 250micrograms IV Dexamethasone 7.6mg IV / 8mg PO	Dexamethasone 4mg PO bd 2/7 Metoclopramide 10mg PO tds PRN 5/7	

High emetogenic potential – risk in nearly all patients >90% and Anthracycline & Cyclophosphamide combination regimens

Pre treatment	On completion of treatment	Anti-emetic failure (see Table 2)
Option 1: Ondansetron 8mg IV*/PO Dexamethasone 7.6mg IV / 8mg PO Aprepitant 125mg PO	Ondansetron 8mg PO bd 2/7 Dexamethasone 4mg PO bd 2/7 Metoclopramide 10mg PO tds PRN 5/7 Aprepitant 80mg PO od on days 2 & 3	Breakthrough nausea and vomiting: Commence with 3rd line anti-emetics Treat on subsequent cycles with Akynzeo® (netupitant/palonosetron) 300/0.5mg PO pre treatment in lieu of aprepitant. Consider a continuous SC infusion of metoclopramide or cyclizine for 3-5 days post each subsequent treatment

*Following a drug safety update IV ondansetron **must** be administered as an infusion in 50-100ml of sodium chloride 0.9% over at least 15 minutes to **all patients over 65 years** of age due to the risk of prolongation of the QT interval.

7. BREAKTHROUGH NAUSEA AND VOMITING

- Anti-emetic failure is defined as prolonged, distressing nausea or 2 or more episodes of vomiting in 24 hours.
- Patients must be told to contact the GP or Hotline if they start vomiting at home.
- It is easy to assume that nausea and vomiting in a patient who has recently received SACT is the result of treatment. However, other causes of nausea and vomiting must always be considered, such as:
  - Anxiety
  - Bowel obstruction
  - Constipation

- Infection
- Fluid and electrolyte imbalances (hypercalcaemia, renal failure)
- Inner ear dysfunction
- Metabolic abnormalities
- Metastases eg: liver, brain
- Raised intracranial pressure
- Other medications eg: antibiotics, strong opioids
- Indigestion, peptic ulcer disease
- Radiotherapy

- The $5HT_3$ receptor antagonists are no more effective than other agents in treating established delayed nausea and vomiting. A detailed analysis of clinical trial data has failed to demonstrate that the combination of $5HT_3$-receptor antagonist plus dexamethasone is superior to dexamethasone alone in delayed emesis. Prolonged use of $5HT_3$ antagonists may result in drug induced constipation which may worsen nausea and therefore should be discouraged.
- The recommendations for the treatment of breakthrough nausea and vomiting are detailed in table 2 below.

Table 2: Choice of anti-emetics for breakthrough nausea and vomiting

If patients suffer breakthrough nausea and vomiting whilst receiving the recommended anti-emetics the following should be considered as additional therapy.

1st line (for patients not taking regular antiemetics)	Metoclopramide 10mg PO/IV/IM/SC tds Or Domperidone 10mg PO tds

2nd line	Cyclizine 50mg PO/IV/IM/SC tds
	Ondansetron 8mg PO/IV stat if less than 24 hours after treatment (NB. max daily dose is 32mg although this should be reduced in moderate to severe liver impariment)

3rd line	Levomepromazine 6mg PO qds prn or 6.25 - 25mg over 24 hours SC/IV bolus injection or by continuous SC infusion
	Cyclizine 150mg/24hr by continuous SC infusion
	Haloperidol 1.5-3mg SC/IV or continuous SC infusion 5-10mg/24hr

Additional Points:

- Sub-cutaneous administration of anti-emetics should be considered for in-patients who are unable to tolerate oral medication. Drugs that may be administered via SC injection or continuous SC infusion include cyclizine, metoclopramide, levomepromazine, haloperidol, dexamethasone (initially 1-2mg/24hrs, this dose may be increased if no irritation).
- If anxiety is thought to be a significant contributor to a patient's nausea and vomiting, then subcutaneous midazolam (usually 10 – 30mg/24hrs) can be added to a syringe driver.
- Compatibility for drugs mixed in SC syringe drivers should be checked with the ward pharmacist or supportive care team.
- Use of other anti-emetics (such as haloperidol 1.5 – 5mg PO daily in divided doses) may be considered if patients do not respond to the standard breakthrough schedules.
- Prochlorperazine may be used in place of metoclopramide. This is available as a buccal preparation which may be of benefit to ensure absorption. However, it should be used with caution in the elderly.
- The hospital supportive care team should be contacted for advice about refractory nausea and vomiting that has not resolved with standard anti-emetics.
- Patients are at risk of dehydration, consider starting intravenous fluids until nausea is controlled.
- Where appropriate the dedicated syringe driver prescription chart should be used and cross referenced on the inpatient prescription and administration record.

8. RADIOTHERAPY

- Most patients receiving fractionated radiotherapy do not require antiemetics.
- Patients can be categorised as low, moderate of high risk of emetogenicity dependent upon the type of radiotherapy – see table 3.
- High risk patients should have prophylactic oral antiemetics prior to radiotherapy, usually with an oral $5HT_3$ receptor antagonist. Treatment should be continued for 24 hours after completion of radiotherapy.

- Moderate risk patients should have prophylactic oral antiemetic therapy either with ondansetron, metoclopramide or domperidone.
- Prolonged courses of ondansetron should be avoided because of the risk of severe constipation.
- Low risk e.g. breast, head & neck, limb or brain radiotherapy does not require routine antiemetic therapy. If these patients experience emesis, other causes of nausea and vomiting should be excluded before assuming that it is due to radiotherapy.
- Radiotherapy fields including the inner ear can cause nausea which responds well to prochlorperazine.
- Nausea/vomiting can occur due to mild cerebral oedema in patients who are having treatments that include all or part of the brain, in which case a short course of dexamethasone works well.

Table 3 – initial choice of prophylactic antiemetics in patients undergoing radiotherapy

Emetogenic risk	Radiotherapy	Recommended treatment
High	TBI Hemi body radiation Radiotherapy to upper abdomen Single fraction to lower thoracic or upper lumbar spine	Prophylaxis with ondansetron 8mg PO 30-60 minutes prior to treatment.
Medium	Fractionated abdominal or pelvic radiotherapy	Ondansetron 8mg PO 30-60minutes prior to treatment *OR* Metoclopramide 10mg PO tds PRN *OR* Domperidone 10mg PO tds PRN
Low	Radiotherapy to breast, head and neck, limb or brain Brachytherapy	No standard prophylaxis required

9. DRUG INFORMATION

Please also consult the BNF and individual drug monographs at www.medicines.org.uk

9.1 Akynzeo® (NEPA netupitant/palonosetron)

Mode of action: this is a combination preparation containing the NK1 antagonist netupitant and the long acting $5HT_3$ antagonist palonosetron.

Preparations available: Hard capsules containing 300mg netupitant and 0.5mg palonosetron. The hard capsule is filled with 3 tablets and 1 soft capsule.

Dose: One 300/0.5mg capsule should be administered orally at least one hour prior to treatment.

Side effects: Constipation, headache, fatigue.

Notes:

- This preparation is only approved for use for the prevention of CINV in patients who require a long acting $5HT_3$ antagonist in combination with a NK1 antagonist.
- Not to be used in combination with other NK1 or $5HT_3$ receptor antagonists either IV or oral.
- Give in combination with a corticosteroid.
- According to the product literature the recommended oral dexamethasone dose should be reduced by approximately 50 % when co-administered with Akynzeo unless it forms part of a recognised treatment protocol e.g: DHAP, R-CHOP. The concomitant antiemetic dose of dexamethasone administered in clinical trials was 12mg PO on day 1 and 4mg BD on days 2-4.
- Multiple drug interactions, consult product literature.

- Netupitant is a moderate inhibitor of CYP3A4 and can increase the exposure of chemotherapeutic agents that are substrates for CYP3A4 e.g. docetaxel, irinotecan Therefore, patients should be monitored for increased toxicity of these agents Furthermore, netupitant may also affect the efficacy of chemotherapeutic agents that need activation by CYP3A4 metabolism.

9.2 Aprepitant

Mode of Action: Neurokinin (NK) 1 receptor antagonist
Preparations available: 125mg and 80mg capsules
Dose: 125mg 1 hour before treatment, then 80mg daily for two days.
Side effects: hiccups, dyspepsia, diarrhoea, constipation, anorexia, asthenia, headache, dizziness.
Notes:

- Give in combination with a corticosteroid and a $5HT_3$ receptor antagonist.
- Multiple drug interactions, consult product literature.
- Aprepitant is a moderate inhibitor of the hepatic drug metabolising isoenzyme CYP3A4. Therefore, in theory, aprepitant has the potential to increase plasma levels of cytotoxic drugs metabolised by this enzyme eg: irinotecan, but in many cases this is unlikely to cause a clinically significant increase. However, patients on concomitant therapy should be closely monitored for signs of toxicity.
- Concomitant daily dose of dexamethasone should not exceed 8mg unless it forms part of a recognised treatment protocol e.g: DHAP
- Aprepitant should not be given in combination with ifosfamide as it predisposes the patient to encephalopathy.
- NK1antagonists are only recommended in certain circumstances e.g.:
  In combinations with a $5HT_3$ receptor antagonist and dexamethasone for highly emetogenic cancer treatment and regimes containing both an anthracycline and cyclophosphamide.
- However, aprepitant may be considered for use following treatment failure with standard antiemetic regimen in regimens of moderate emetogenicity.
- Extended courses of aprepitant (80mg od on days 4 and 5) have been used in clinical trials. However, based on this Phase IIb clinical dose-range study, it is not known if dosing aprepitant after Day 3 improved control of nausea or vomiting in this clinical setting. This is an unlicensed dosing schedule and is only permitted under the direction of a consultant.
- The manufacturer states that from a stability point of view aprepitant capsules can be opened and the blended beads mixed with drinks or soft foods eg: yoghurt for ease of administration in patients with swallowing difficulties with the caveat that there have been no assurances of the drug's efficacy using this approach. However, the blended beads may not be administered via NG, PEG or PEJ tubes as tube blockage is likely to occur.
- Aprepitant is available as an IV formulation, fosaprepitant, which is administered as a single 150mg dose prior to treatment. Due to a complex dilution required pre-administration this is not currently available within the Trust.
- Any patient requiring an NK1 antagonist in combination with palonosetron should be prescribed Akynzeo®

9.3 Cyclizine

Mode of action: Cyclizine is an antihistaminic antimuscarinic anti-emetic which exerts its action on the vomiting centre.
Preparations available: 50mg tablets, 50mg/ml injection
Dose: 50mg tds PO/IV/IM/SC or 150mg continuous subcutaneous infusion over 24 hours
Side effects: drowsiness, urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances
Notes: Metoclopramide or Domperidone should not be given concomitantly with cyclizine as they have antagonistic actions.

9.4 Dexamethasone

Mode of action: Dexamethasone is a corticosteroid which also has anti-emetic action
Preparations available: 2mg & 500 microgram dexamethasone tablets, 2mg/5ml dexamethasone sodium phosphate oral solution.
In 2014 the Organon preparation of 4mg/ml injection was discontinued. The Trust now stock the Aspen brand of dexamethasone base - 3.8mg/ml injection (as 5mg/ml dexamethasone sodium phosphate).
Dose: varies - see individual treatment regimens
Side effects: adverse effects of single dexamethasone doses are rare, although elevations of serum glucose levels, epigastric discomfort and sleep disturbances occur - see product literature for more details.
Notes:

- In general low doses and short courses are to be preferred to avoid the long term effects of corticosteroid use.
- Dexamethasone should be given no later than 6pm to minimize wakefulness unless being used as a pre med to prevent allergic reactions.
- Prescribed concomitantly it enhances the efficacy of ondansetron and metoclopramide.
- An extended course of up to 7 days can be prescribed if delayed nausea and vomiting is a problem.
- Some patients may experience withdrawal effects after a short course of dexamethasone. For these patients a short reducing course over 3 to 5 days may be more appropriate.
- Supraphysiological doses of corticosteroids (eg: dexamethasone > 0.75mg per day) can induce diabetes or worsen blood glucose control in patients with pre-existing diabetes.
- All patients should have a random laboratory blood glucose taken prior to receiving the first cycle of a treatment regime containing dexamethasone as an antiemetic agent.
- Additional monitoring should be taken in those patients with diabetes as corticosteroids can elevate blood sugar levels. See Management of patients with diabetes or at risk of developing diabetes for further advice on monitoring capillary blood glucose.
- Rapid injection of dexamethasone can cause perineal irritation with patients experiencing a sensation of urgency. Patients should be warned of this effect (this is largely avoided by administering as a short infusion).
- Where corticosteroids are part of a treatment regimen they should be given before treatment as they will enhance the effects of any co-prescribed anti emetics.
- Omit dexamethasone from the antiemetic regime if the patient is on a regimen containing high dose steroids e.g. CHOP.
- For patients receiving a taxane, the anti-emetic dose of dexamethasone should be the same as that given for prophylaxis of hypersensitivity.
- Consider omitting steroid or reducing length of course if the patient is on a weekly regimen or an oral cytotoxic course longer than 3 days.

9.5 Domperidone

Mode of action: Domperidone is a D_2-receptor antagonist with some prokinetic action.
Preparations available: 10mg tablet, 5mg/5ml suspension
The suppositories have been discontinued.
Dose: 10 tds times a day PO for up to 7 days.
Side effects: rarely gastro-intestinal disturbances (including cramps), raised prolactin concentration
Notes:

- Domperidone is associated with a small increased risk of serious cardiac side effects. Its use is now restricted to the relief of symptoms of nausea and vomiting and the dosage and duration of use have been reduced. Domperidone is now contraindicated in those with underlying cardiac conditions, patients taking concomitant medication known to prolong QTc or potent CYP3A4 inhibitors and those with severe hepatic impairment.
- It does not cross the blood brain barrier so is useful in patients who cannot tolerate metoclopramide eg: patients with Parkinson's Disease

- Domperidone should not be given concomitantly with cyclizine as they have antagonistic actions

9.6 Granisetron
Mode of action: Granisetron is a $5HT_3$ receptor antagonist
Preparations available: 1mg tablet, 1mg in 1ml or 3mg in 3ml injection, 3.1mg patches
Dose: 1-3mg IV prior to treatment then 1-2mg PO daily usually for 48 hours.
3.1mg/24 hours transdermally.
Side effects: Constipation, headache, rash
Notes:

- Granisetron patches (Sancuso®) are only approved for use in the following patient populations:
  - As an alternative to continuous syringe drivers of $5HT_3$ antagonists for patients who are unable to tolerate oral $5HT_3$ antagonists under the direction of the supportive care team.
- As an alternative to IV palonosetron for second line treatment in patients who have experienced uncontrolled delayed severe nausea or emesis due to ondansetron failure and who are unable to swallow.
- The patch should be applied 24-48 hours prior to and removed at least 24 hours post treatment. Patches may be worn for up to 7 days.
- The patches must not be used in combination with other $5HT_3$ receptor antagonists either IV or oral

9.7 Haloperidol
Mode of action: Haloperidol is a specific D_2-receptor antagonist which acts on the area postrema.
Preparations available: 500 microgram capsules, 1.5mg tablets, 1mg/ml liquid, 5mg/ml injection
Dose:1.5-3mg SC/ IV or continuous SC infusion 5-10mg over 24hr.
1.5-5mg PO daily
Side effects: extra pyramidal effects and drowsiness although these are not usually problematic at doses less than 2.5mg daily

9.8 Levomepromazine
Mode of action: Levomepromazine is a potent D_2, $\alpha_1$receptor and $5HT_3$ antagonist anti-emetic which is widely used as a 2nd or 3rd line agent
Preparations available: 25mg tablets (not stocked by the Trust), 25mg/ml injection. Unlicensed preparation: 6mg tablets
Dose: 6 - 25mg over 24 hours PO/SC/IV or continuous SC infusion
Side effects: Doses greater than 6mgs daily are often associated with sedation.

9.9 Lorazepam
Mode of action: Lorazepam has limited activity as an anti-emetic but with its sedative and anxiolytic properties it is helpful in treatment of anticipatory symptoms
Preparations available: 1mg tablets, 4mg/ml injection
Dose: 0.5-1mg orally, sublingually (standard non film coated tablets will dissolve under the tongue) or IV 15-30 minutes prior to treatment
Side effects: drowsiness and lightheadedness. If affected do not drive. Avoid alcoholic drink
Notes: Some patients may benefit from oral lorazepam the night before or on the morning of admission for treatment.

9.10 Metoclopramide
Mode of action: Metoclopramide is a prokinetic anti-emetic and is a combined D_2-receptor antagonist and $5HT_4$ receptor agonist. At high doses it also acts as a $5HT_3$ antagonist. It crosses the blood brain barrier.
Preparations available: 10mg tablets, 5mg/5ml solution, 5mg/ml injection
Dose: 10mg tds PO/IV/IM for up to 5 days.

Side effects: extrapyramidal effects (more frequent with high doses and in children and young adults), hyperprolinactinaemia, akathisia

Notes:

- Metoclopramide is associated with a small increased risk of serious cardiac side effects and the dosage and duration of use have been reduced. Metoclopramide is now contraindicated in those with underlying cardiac conditions and other risk factors
- Doses >30 mg daily are unlicensed. Higher than recommended doses may be used on the advice of the supportive care team (up to 120mg daily via SC syringe driver).
- As it blocks the central dopamine receptors there is a risk of developing acute dystonic reactions with facial and skeletal muscle spasms and oculogyric crises. These generally occur within a few days of starting treatment and subside within 24hr of stopping the drug.
- Severe symptoms should be treated with procyclidine IV 5-10mg
- Younger patients are at greater risk of extra pyramidal side effects from metoclopramide and should be considered for domperidone in preference. Domperidone should also be used if patients give a history of previous dystonic reactions with metoclopramide (e.g. jaw stiffness or difficulty swallowing)
- Patients intolerant of metoclopramide should be considered for treatment with domperidone
- Metoclopramide should not be given concomitantly with cyclizine as they have antagonistic actions.
- Prokinetic actions are useful in nausea and vomiting associated with gastric stasis.

9.11 Ondansetron

Mode of action: Ondansetron is a $5HT_3$ receptor antagonist which prevents release of 5HT (serotonin) from entrochromaffin cells in the duodenum.

Preparations available: 4mg and 8mg tablets/oral lyophilisates, 4mg/5ml syrup, 2mg/ml injection, 16mg suppository

Dose: 8mg IV prior to treatment **then** 8mg bd PO usually for 48 hours or 16mg od PR

Side effects: include mild headache, constipation and transient elevations of serum aminotransferases. These can be treated symptomatically with simple analgesics and laxatives e.g. senna. Suppositories may cause rectal irritation.

Patients experiencing side effects due to ondansetron may be offered an alternative $5HT_3$ receptor antagonist such as granisetron (IV 1-3mg oral 1- 2mg daily)

Notes:

- Can be very constipating; consider co-prescribing laxatives especially if being used for more than 48 hours.
- Ondansetron should be avoided in patients with congenital long QT syndrome
- Caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include: electrolyte abnormalities; use of other medicines that prolong QT interval (including cytotoxic drugs) or that may lead to electrolyte abnormalities; congestive heart failure; bradyarrhythmias; or use of medicines that lower heart rate
- Useful resource for checking drug interactions with respect to QT prolongation: www.crediblemeds.org
- Hypokalaemia and hypomagnesaemia should be corrected before ondansetron administration
- All intravenous doses for prevention of CINV in patients aged ≥ 65 years **must** be diluted in 50–100 mL saline or other compatible fluid and infused over at least 15 minutes.
- Patients < 65 years of age may have their IV ondansetron administered either by bolus injection or intravenous infusion.
- Repeat intravenous doses of ondansetron should be given no less than 4 hours apart
- Consider using a single 8mg oral dose pre-treatment. This is as effective as an intravenous dose provided administration is at least 30 minutes prior to treatment.

9.12 Palonosetron

Mode of Action: $5HT_3$ receptor antagonist acting on the area postrema and the gut wall

Preparations available: 250 microgram injection
Dose: 250 micrograms IV prior to treatment
Side effects: diarrhoea, constipation, headache, dizziness
Notes:

- Longer duration of action compared to other $5HT_3$ receptor antagonists is due to its increased half life and different mode of binding to the $5HT_3$ receptor.
- Second line in patients who have experienced uncontrolled delayed severe nausea or emesis due to ondansetron failure.
- Not to be used in combination with other $5HT_3$ receptor antagonists either IV or oral
- Dose should only be administered before treatment administration.
- There is some limited data in the literature describing multi day administration of IV palonosetron on days 1-5 and days 1, 3 and 5 in regimes where highly emetogenic treatment is administered on sequential days for an extended period. The difference between this approach and multi day administration of ondansetron did not achieve a statistically significant improvement in response rate. This is an unlicensed dosing schedule and is only permitted under the direction of a consultant.
- Any patient requiring palonosetron in combination with an NK1 receptor antagonist should be prescribed Akynzeo®

9.13 Prochlorperazine
Mode of Action: Dopamine antagonist, some antimuscarinic and antihistaminic effects.
Preparations available: 5mg tablets, 3mg buccal tablets, 1mg/ml syrup, 12.5mg/ml injection
Dose: 5-10mg BD / TDS orally, 3-6mg bd – tds buccally, 12.5mg IM
Side effects: drowsiness, extrapyramidal effects.
Notes:

- May be used in place of metoclopramide.
- Use with caution in the elderly.

10. CONSULTATION PROCESS

This guidance has been developed by a multidisciplinary clinical working group in collaboration with the supportive care team, SACT delivery group and safe medicines practice committee. Any specific areas requiring specialist advice have been approved by the local experts/managers.

11. DISSEMINATION, IMPLEMENTATION & TRAINING

11.1 Dissemination

Once ratified the procedural document will be sent to the IT helpdesk for publication on the Trust intranet.

11.2 Implementation

The policy will be effective from the date of publication.

11.3 Training/Awareness

All training/awareness will be undertaken within medical, nursing and pharmacy teams as necessary.

12. PROCESS FOR MONITORING EFFECTIVE IMPLEMENTATION

All prescriptions for antiemetics will be clinically screened by pharmacists to ensure clinical appropriateness and compliance with the Trust guidelines.

Outpatient prescriptions will be clinically screened prior to dispensing or supply to the patient. Inpatient prescriptions will be clinically screened within 24 hours or the next working day of prescribed at a weekend or on a bank holiday.

Any inappropriate or erroneous prescribing will be challenged by the pharmacy team by contacting the prescriber or consultant responsible for the care of the patient.

Prescribing errors will be reported using the trust incident reporting system. These errors will be reviewed on a 6 weekly basis by the Safe Medicines Practice Committee and action taken, as appropriate.

13. REFERENCES

1. Hesketh 2008. N Engl J Med 358; 23: 2482-94
2. Hesketh PJ, Kris MG, Grunberg SM et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997: **15**(1);103-109
3. Kris MG, Hesketh PJ, Somerfield MR et al. American Society of Clinical Oncology Guideline for antiemetics in Oncology: Update 2006. *J Clin Oncol* 2006: **24**(18);2932-2947
4. MASCC/ESMO Antiemetic Guideline 2013 accessed at: http://www.mascc.org/assets/documents/mascc_guidelines_english_2013.pdf 09.06.15
5. North London Cancer Network. Anti-emetic Guidelines for Adults receiving chemotherapy. May 2006.
6. Metoclopramide: risk of neurological adverse effects. Drug Safety Update 2013 https://www.gov.uk/drug-safety-update/metoclopramide-risk-of-neurological-adverse-effects accessed 9.6.15
7. Domperidone: risk of cardiac side effects. Drug Safety Update 2014 https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects accessed 9.6.15
8. Ondansetron for intravenous use: dose dependant QT interval prolongation. Drug Safety Update 2014 https://www.gov.uk/drug-safety-update/ondansetron-for-intravenous-use-dose-dependent-qt-interval-prolongation accessed 9.6.15
9. BNF 68th edition 2014, Pharmaceutical press
10. Mattiuzzi GN et al Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. Cancer. 2010 Dec 15;116(24):5659-66
11. Personal correspondence from Merck Sharp and Dome regarding extended administration of aprepitant, letter dated May 2010

    Extended Aprepitant Letter MSD May 2010

12. Personal correspondence from Merck Sharp and Dome regarding opening aprepitant capsules for oral administration, letter dated December 2011

    Aprepitant in patients with swallow

14. VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
2.0	June 2015	Suzanne Frank		Transferred onto new template, updated with regard to Drug Safety Alerts on metoclopramide, domperidone and ondansetron and 2013 MASCC guidance
2.1	December 2016	Suzanne Frank		Updated to include new products approved by DTC: Akynzeo, Sancuso

APPENDIX 1: Letter to GP

The Christie NHS
NHS Foundation Trust

Patient label

Date: ……..

Dear Doctor,

This letter is to inform you that ……..… has commenced treatment today.

Different anticancer drugs cause different side-effects. An information leaflet explaining these side-effects has been given to your patient, along with contact numbers for the Christie hospital. The majority of anticancer drugs have common side-effects, which include myelosuppression and increased risk of infection, anaemia, risk of bleeding, altered taste, sore mouth, nausea and vomiting, and lethargy.

Many of these side-effects can be managed at home, however it is very important that if it is suspected that your patient has an infection, the Christie Hotline should be contacted for further advice on 0161 446 3658. This number is available to patients and health professionals 24 hours a day.

Nausea and vomiting can be a distressing side-effect of treatment. It is important to try to achieve optimal emetic control to improve your patient's quality of life, and to try to prevent them from developing anticipatory nausea and vomiting prior to subsequent treatments.

We have given your patient the following anti-emetics and we hope these will be effective:

……
If however your patient experiences any problems at home with continued nausea and vomiting, some suggestions for alternative oral anti-emetics are given below:

Metoclopramide 10mg 8 hourly
Prochlorperazine 10mg 8 hourly
Domperidone 10mg 8 hourly
Levomepromazine 6mg 8 hourly
Cyclizine 50mg 8 hourly

The $5HT_3$ receptor antagonists, such as ondansetron, are no more effective than other agents in treating established delayed nausea and vomiting. Prolonged use of $5HT_3$ antagonists may result in drug induced constipation which may worsen nausea and therefore should be discouraged.

If required a single IM injection of metoclopramide 10mg or cyclizine 50mg may be useful for patients unable to tolerate oral therapy.

We hope this letter is informative. Should you require any further help or advice, in normal working hours Monday-Friday, please contact the following: Oak Road treatment Centre – 0161 918 7171 or for patients on clinical trials 0161 918 7663 or the Hotline 0161 446 3658 through the night and at weekends.

Yours sincerely,

Signature: Name: Designation:

APPENDIX 2 : Relative emetogenic potential of oral anti-cancer drugs:

For combination treatment choose the appropriate regimen for the most emetogenic drug to be administered. However, drug combinations have an additive emetic effect, combination treatment may have a greater emetogenicity than the sum of the single agents used alone.

This table is not exhaustive – consult specific drug monographs for an indication of the emetogenicity of agents www.medicines.org.uk

See individual Disease Group guidelines for recommendations of anti-emetic use with specific protocols.

High (>90%)	Altretamine	Procarbazine
Moderate (30-90%)	Cyclophosphamide	Idarubicin
	Imatinib	Lomustine
	Temozolamide	Vinorelbine
Low (10-30%)	Capecitabine	Etoposide
	Everolimus	Fludarabine
	Lapatinib	Lenlidomide
	Sunitinib	Thalidomide
Minimal (<10%)	Busulfan	Chlorambucil
	Erlotinib	Gefitinib
	Hydroxycarbamide	Melphalan
	Mercaptopurine	Methotrexate
	Sorafenib	Tioguanine

APPENDIX 3: Relative emetogenic potential of parenteral anti cancer drugs:

For combination therapy choose the appropriate regimen for the most emetogenic drug to be administered. However, drug combinations have an additive emetic effect, combination treatment may have a greater emetogenicity than the sum of the single agents used alone.

This table is not exhaustive – consult specific drug monographs for an indication of the emetogenicity of agents www.medicines.org.uk

See individual Disease Group guidelines for recommendations of anti-emetic use with specific protocols.

High (>90%)	Busulfan >4mg/kg/day Carmustine >250mg/m^2 Dacarbazine Streptozotocin	Cisplatin >50mg/m^2 Cyclophosphamide >1500 mg/m^2 Ifosfamide >3g/m^2

Moderate (30-90%)	Actinomycin-D Amsacrine Bendamustine Carmustine >100 mg/m^2 <250mg/m^2 Clofarabine Cyclophosphamide 750-1500mg/m^2 Doxorubicin >60mg/ m^2 Etoposide >60mg/m^2 Ifosfamide <3g/ m^2 Oxaliplatin Methotrexate >1000mg/m^2	Alemtuzumab Arsenic Carboplatin Cisplatin < 50mg/ m^2 Cytarabine > 1000mg/m^2 Daunorubicin >50mg/m^2 Epirubicin >90mg/m^2 Idarubicin Irinotecan Melphalan >100mg/m^2

Low (10-30%)	Bortezomib Cetuximab Cytarabine <1000 mg/m^2 Docetaxel Doxorubicin liposomal Etoposide < 60mg/m^2 Gemcitabine Melphalan <100mg/m^2 Mitomycin C Paclitaxel Pemetrexed Topotecan	Carmustine <100mg/m^2 Cyclophosphamide <750mg/m^2 Daunorubicin <50mg/m^2 Doxorubicin >20<60 mg/m^2 Eribulin 5 Fluorouracil Ixabepilone Methotrexate 250-1000mg/m^2 Mitoxantrone Panitumumab Temsirolimus Trastuzumab

Minimal (<10%)	Asparaginase Bleomycin Cladribine Fludarabine Methotrexate <50mg/m^2 Rituximab Vincristine Vinorelbine	Bevacizumab Busulfan Daunorubicin liposomal Gemtuzumab Ogazamicin Pentostastin Vinblastine Vindesine