

Guidelines for the Use of Anti-Emetics with Chemotherapy

The purpose of this document is to provide guidance on the rational use of anti-emetics for prevention and treatment of chemotherapy-induced nausea and vomiting in adult patients. They are not intended to address nausea and vomiting in palliative care.

These guidelines provide a framework to support clinical practice, but they cannot cover every clinical situation and good common clinical sense and clinical experience will be required when approaching the management of individual patients.

Definitions

Acute	nausea and vomiting (n&v) experienced during the first 24-hour period immediately after chemotherapy administration
Delayed	nausea and vomiting occurring more than 24 hours after chemotherapy and which may continue for up to 6 or 7 days
Anticipatory	nausea and vomiting which occurs prior to the beginning of a new cycle of chemotherapy. It is either a learned response following chemotherapy-induced n&v on a previous cycle or an anxiety response. It is most common after 3 to 4 cycles of chemotherapy with very badly controlled acute or delayed symptoms.

Grading of Nausea and Vomiting

	Nausea	Vomiting
Grade 1	Able to eat	1 episode in 24 hours
Grade 2	Oral intake significantly decreased	2-5 episodes in 24 hours
Grade 3	No significant intake; IV fluids	≥ 6 episodes in 24 hours, or need for IV fluids
Grade 4	-	Requiring TPN, or physiologic consequences requiring ITU; haemodynamic collapse

Optimal emetic control in the acute phase is essential to prevent nausea and vomiting in the delayed phase.

Anti-emetics should be administered regularly, prophylactically and orally where possible.

At equivalent doses for the prevention of acute emesis, 5HT₃ antagonists have equal efficacy and safety. However, for financial reasons, ondansetron is the 5HT₃ antagonist of choice.

See relevant chemotherapy protocol for agreed classification of emetogenicity of regimen, then follow guidelines below.

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First Line Anti-emetic Selection

First Line Anti-Emetics (Oral and IV are equally efficacious; use the oral route where possible)		
	Acute Phase (the First 24 Hours ^a)	Delayed Phase (24-72 hours post chemo)
Mildly Emetic Chemotherapy	No anti-emetic required routinely <i>or</i> Domperidone ^b 10 mg po before chemotherapy	Domperidone ^b 10mg tds prn
Moderately Emetic Chemotherapy	<i>Before chemotherapy:</i> Dexamethasone ^e 8mg po or IV	Domperidone ^b 10mg tds regularly for 3 days, starting on the day of chemotherapy, then 10mg up to tds prn
Highly Emetic Chemotherapy	<i>Start before chemotherapy:</i> Ondansetron 8mg po or IV ^h <i>plus</i> Dexamethasone ^{c, d} 8mg po or IV <i>plus</i> Ondansetron 8mg ^f po in the evening (approx 8-12 hours after pre-chemo ondansetron)	Dexamethasone ^{c, d} 4mg bd x 2-3 days (depending on cycle length), starting the morning after chemotherapy <i>plus</i> Domperidone ^b 10mg tds regularly for 3 days, starting on the day of chemotherapy, then 10mg up to tds prn
Chemotherapy containing cisplatin ≥ 70mg/m²	<i>Start before chemotherapy:</i> Aprepitant 125mg po ^g 20-60 minutes pre chemo <i>plus</i> Ondansetron 8mg po or IV ^h <i>plus</i> Dexamethasone ^{c, d} 12mg po or IV <i>plus</i> Ondansetron 8mg po in the evening (approx 8-12 hours after pre-chemo ondansetron)	Aprepitant 80mg po Day 2 and Day 3 Plus Dexamethasone ^{c, d} 4mg bd x 3 days, starting the morning after chemotherapy <i>plus</i> Domperidone ^b 10mg tds regularly for 3 days, starting on the day of chemotherapy, then 10mg up to tds prn

Key (for both first line and second line anti-emetic tables)

^a Patients receiving fractionated chemotherapy will require the acute phase anti-emetics to be administered on each day that chemotherapy is given.

^b Substitute domperidone with oral metoclopramide 10mg tds (max daily dose 30mg) if the patient is receiving cytotoxic therapy, or other medicines, known to prolong the QT interval e.g. crizotinib, dabrafenib, dasatinib, eribulin, nilotinib, sorafenib, vemurafenib, erythromycin.
Metoclopramide or cyclizine should also be considered as an alternative, in patients with cardiac conduction conditions or underlying cardiac disease, or receiving potent CYP3A4 inhibitors (e.g. clarithromycin, itraconazole, posaconazole), or with severe hepatic impairment.

^c Omit anti-emetic dexamethasone when steroids are included as part of the chemotherapy regimen or pre-medication, or when the patient is already on maintenance steroids equivalent to at least the required anti-emetic dose.

^d For haematology patients where a steroid is not desirable, consider substituting with a prolonged course of ondansetron, usually until 2-3 days after highly emetic chemotherapy is completed.

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^e For haematology patients where a steroid is not desirable, consider substituting with ondansetron 8mg bd (po or IV) on the day of moderately emetic chemotherapy.

^f A 4mg dose of ondansetron may be considered or preferred for patients receiving regimens that contain vincristine, to reduce problems with severe constipation or paralytic ileus.

^g For patients who cannot swallow capsules, the aprepitant capsule may be opened and the contents sprinkled on the tongue and swallowed.

For patients who have a feeding tube, it is not recommended to use the feeding tube for administration of the contents of the capsule. Instead, a single dose of fosaprepitant 150mg IV over 20-30 minutes is recommended immediately before chemotherapy.

^h Ondansetron 8mg IV doses should be given in 50-100ml sodium chloride 0.9% (or glucose 5%) over at least 15 minutes.

Other points regarding dexamethasone:

- Dexamethasone is the most useful agent in preventing delayed emesis.
- For patients on maintenance steroids at a dose equivalent to less than the daily anti-emetic dexamethasone dose, the maintenance steroid should be omitted on each day that anti-emetic dexamethasone is prescribed, and re-started on the morning after anti-emetic dexamethasone is completed.
- For diabetics, be aware that dexamethasone will cause blood glucose to be raised, and should be used with extra monitoring if possible:
insulin-dependent diabetics may be able to adjust their insulin dose according to blood glucose results;
it is preferable for non-insulin-dependent diabetics to check their blood glucose morning and evening whilst on dexamethasone and to contact their GP if any concerns;
for patients who do not self-monitor their glucose, they should be advised to contact their GP if they become symptomatic (increased thirst, increased need to urinate).
Contact the diabetic team if concerned about an individual patient.
- If dexamethasone is contra-indicated for any reason, ondansetron may be prescribed as an alternative as required.
- For patients who develop indigestion on dexamethasone, omeprazole or ranitidine may be prescribed to cover the duration of steroid.
- Consider reducing the length of the oral dexamethasone course for patients on a weekly regimen (e.g. weekly carboplatin regimens may usually be managed with dexamethasone 2mg bd x 2 days)

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Anti-Emetics for Failure of Emetic Control

If any episode of vomiting, or persistent nausea of any grade occurs with the above first-line anti-emetics, the following options should be considered for subsequent cycles of chemotherapy before referring to the table on page 6:

- Evaluate how poor the emetic control was, including the timing and duration of nausea and vomiting.
- Ensure that the correct anti-emetic schedule was prescribed in the first cycle.
- Check patient compliance with the anti-emetics.
- Consider concurrent disease and medication factors.
- Anticipatory nausea and vomiting (i.e. nausea or vomiting in the days to hours before chemotherapy) is best prevented by adequate control of emesis in the first cycle of chemotherapy. If it does develop, give lorazepam 0.5 - 1mg orally or sublingually the evening before and the morning of chemotherapy. N.B. Lorazepam causes drowsiness; counsel patients not to drive when taking this medication.
- Lorazepam may also be used prophylactically with the first cycle of chemotherapy in patients who are considered at high risk of nausea and/or who have significant anxiety before treatment.
- Ensure future anti-emetics cover the full period of delayed nausea. Dexamethasone duration may be increased to 5-7 days as indicated.
- What to do if 30mg per 24 hours of dopamine antagonist is not sufficient:
 - The MHRA maximum recommended adult dose for both domperidone and metoclopramide is 10mg three times a day.
However, for control of chemotherapy-associated n&v, the dose may be increased up to a maximum of 20mg tds - qds **only** in circumstances where the clinician feels that it is clinically appropriate for the patient to receive a higher dose following a risk-benefit review.
The active decision to increase the total daily dose above 30mg must be clearly documented.
The lowest effective dose should be used for the shortest possible time.
 - Consider the substitution of domperidone (or metoclopramide) with levomepromazine 6.25 – 12.5mg po od – bd.
 - Consider the addition of cyclizine 50mg po tds to the regimen. (Although cyclizine may oppose the peripheral prokinetic action of domperidone or metoclopramide on the bowel, it may still provide additional benefit when used in combination due to differing modes of action)
- To ensure absorption, consider the use of subcutaneous or IV administration of cyclizine (150mg/day) or levomepromazine, or suppositories (if rectal route not CI).
 - Subcutaneous infusion of levomepromazine 6.25 – 25mg/day via a syringe driver may be considered in patients with intractable nausea and vomiting. Note that s/c or IV levomepromazine is twice as potent as the oral route and therefore likely to be more sedating.
 - Only ondansetron is currently available in suppository form (16mg PR od)

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- The three-drug combination of aprepitant, ondansetron and dexamethasone is approved for use in patients who have failed to achieve adequate anti-emetic control on ondansetron and dexamethasone, and are receiving the following chemotherapy:
 - breast cancer patients receiving “AC” (anthracycline and cyclophosphamide-containing) chemotherapy (mainly FEC) who have experienced Grade 2 + nausea & vomiting on ondansetron and dexamethasone
 - patients receiving a highly emetic chemotherapy regimen and whose nausea and vomiting has resulted in a hospital admission (i.e. Grade 3 / 4 nausea and vomiting)

- Check for aprepitant interactions **but** ignore any recommendations to reduce dexamethasone dose.
 - Aprepitant is contra-indicated with pimozide, terfenadine or astemizole.
 - It should not be prescribed for patients also prescribed fentanyl patches.
 - As it may reduce the anticoagulant effect of warfarin, monitor INR closely for 2 weeks after each 3 day course of aprepitant.
 - Contraceptive failure of hormonal contraceptives during and for 28 days following administration of aprepitant is possible. Alternative or back-up methods of contraception should be used during treatment with aprepitant and for 2 months after last dose.

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Second Line Anti-Emetics		
	Acute Phase (the first 24 Hours ^a)	Delayed Phase (24-72 hours post chemo)
Mildly Emetic Chemotherapy	As Moderately Emetic First Line: <i>i.e. before chemotherapy:</i> Dexamethasone ^e 8mg po or IV	Domperidone ^b 10mg** po tds regularly for 3 days, starting on the day of chemotherapy, then 10mg** up to tds prn
Moderately Emetic Chemotherapy	As Highly Emetic First Line: <i>i.e. start before chemotherapy:</i> Ondansetron 8mg po or IV ^h <i>plus</i> Dexamethasone ^{c, d} 8mg po or IV <i>plus</i> Ondansetron 8mg po in the evening (approx 8-12 hours after pre-chemo ondansetron)	Dexamethasone ^{c, d} 4mg bd x 2-3 days, starting the morning after chemotherapy <i>plus</i> Domperidone ^b 10mg** tds regularly for 3 days, starting on the day of chemotherapy, then 10mg** up to tds prn Also consider all the options discussed above and adjust anti-emetic cover accordingly.
Highly Emetic Chemotherapy (unless it fits the criteria below)	For lack of control in the first 24 hours, manage as for First Line, but increase the post-chemotherapy ondansetron to: Ondansetron 8mg po + 8 hours and + 16 hours after pre-chemo ondansetron. Consider need for lorazepam pre-chemotherapy if any anticipatory nausea, or for anxious patients.	For lack of control in the delayed phase, increase the post-chemotherapy ondansetron to: Ondansetron 8mg po every 12 hours x 3 doses, starting the evening of chemotherapy. Increase the duration of dexamethasone (up to 5 - 7 days) if prolonged nausea beyond 72 hours. Consider all other options listed above. Levomepromazine or cyclizine may be used as a substitute, or in addition, to domperidone*.
Highly Emetic Chemotherapy resulting in hospital admission for n&v OR Grade 2+ n&v with "AC" combinations for breast cancer	Aprepitant may be added to the schedule above as follows: Aprepitant 125mg po 20 – 60 minutes before chemotherapy starts, followed by aprepitant 80mg po once daily on the morning of Day 2 and Day 3. <i>plus</i> Consider increasing the Day 1 dexamethasone dose to 12mg po or IV	

** Domperidone standard maximum dose for adults and adolescents >35kg is 10mg three times a day, as recommended by MHRA, April 2014. However, for control of chemotherapy-associated n&v, the dose may be increased up to a maximum of 20mg qds **only** in circumstances where the clinician feels that it is clinically appropriate for the patient to receive a higher dose following a risk-benefit review.

The active decision to increase the total daily dose above 30mg should be clearly documented.

The lowest effective dose should be used for the shortest possible time.

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Emetic Potential of Individual Cytotoxic Agents

Recent publications, including the 2011 ASCO guidelines for anti-emetics, have categorised the emetic potential of individual cytotoxics into four emetic risk groups according to the incidence of emesis without anti-emetics, as specified in the table below.

These 4 groups do not correlate totally with our grouping of Mildly Emetic, Moderately Emetic and Highly Emetic - our guidelines fit in with this categorisation as follows:

Emetic Risk < 10%: follow guidelines for Mildly Emetic Chemotherapy

Emetic Risk 10% - 30%: follow guidelines for Mildly Emetic Chemotherapy **or** Moderately Emetic Chemotherapy as indicated

Emetic Risk 30 – 90%: follow guidelines for Highly Emetic Chemotherapy

Emetic Risk > 90%: follow guidelines for Highly Emetic Chemotherapy*

Please note that all individual chemotherapy regimens specify the emetogenicity of the regimen within the protocol document, and this should be the primary point of reference for prescribing anti-emetics.

Emetic Risk < 10% (equivalent to "Mildly")	Emetic Risk 10 - 30% (equivalent to "Mildly" or "Moderately" as indicated)		Emetic Risk 30 - 90% (equivalent to "Highly")	Emetic Risk > 90% (equivalent to "Highly")
Asparaginase	Mildly	Moderately	Amsacrine	Carmustine
Bevacizumab	Capecitabine	Bortezomib	Azacitidine	Cisplatin*
Bleomycin	Cetuximab	Cabazitaxel	Bendamustine	Cyclophosphamide \geq 1500mg/m ²
Busulfan PO	Cyclophos PO	Caelyx	Carboplatin	Dacarbazine
Chlorambucil PO	Fluorouracil	Cytarabine \leq 1000 mg/m ²	Cyclophosphamide < 1500mg/m ²	Dactinomycin
Cladribine	Gemcitabine	Docetaxel	Cytarabine > 1000mg/m ²	Streptozocin
Fludarabine	Mitomycin	Eribulin	Daunorubicin	
Hydroxycarbamide	Methotrexate 50- 250mg/m ²	Etoposide IV	Doxorubicin	
Melphalan PO	Paclitaxel	Mitoxantrone	Epirubicin	
Mercaptopurine	Pemetrexed	Raltitrexed	Idarubicin IV	
Methotrexate PO	Pentostatin		Ifosfamide	
Rituximab	Topotecan IV		Irinotecan	
Vinblastine	Trastuzumab		Lomustine	
Vincristine			Melphalan IV	
Vindesine			Oxaliplatin	
Vinorelbine			Methotrexate > 250mg/m ²	
			Temozolomide	

* aprepitant approved for first-line use in patients receiving cisplatin \geq 70mg/m²

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Assessing the Emetogenicity of a Regimen

For new combination regimens which do not have a protocol, the following is recommended:

- Aprepitant should be included for any regimen containing cisplatin $\geq 70\text{mg/m}^2$.
- A regimen containing any other agent that has emetic risk 30–90% or > 90%, treat as Highly Emetic Chemotherapy
- A regimen containing two or more Moderately Emetic agents, treat as Highly Emetic Chemotherapy
- A regimen containing one Moderately Emetic agent from the 10-30% risk group plus any number of Mildly Emetic agents (whether from < 10% **or** 10-30% risk group), treat as Moderately Emetic Chemotherapy.
- A regimen containing one or more Mildly Emetic agents (whether from < 10% **or** 10-30% risk group) should be treated as Mildly Emetic Chemotherapy.

References: Basch, E et al; JCO 2011; 29 (31): 4189 – 4198 (ASCO guidelines)
 MASCC guidelines; Supportive Care in Cancer 2011; 19, suppl 1
 Roila, F et al; Annals of Oncology 2010; 21 (suppl 5): 232 – 243
 LCNDG 2010 Antiemetic Guidelines for Adult patients receiving Chemotherapy and Radiotherapy

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