





## **Network Guideline for the use of Anti-emetics in Adults Receiving Anti-Cancer Drug Therapy**

**West Midlands Expert Advisory Group for Systemic Anti-Cancer  
Therapy (SACT)**

# West Midlands Clinical Networks and Clinical Senate

## Coversheet for Network Expert Advisory Group Agreed Documentation

This sheet is to accompany all documentation agreed by the West Midlands Clinical Network Expert Advisory Groups. This will assist the Clinical Network to endorse the documentation and request implementation.

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<b>Document Purpose</b>	This Guideline has been produced to support the management of patients who experience, or are likely to experience, anti-cancer treatment related nausea and vomiting.	
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<b>References</b>		
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# Guideline for the use of Anti-emetics in Adults Receiving Anti-Cancer Drug Therapy

## 1. Scope of the Guideline

1.1 This Guideline has been produced to support the following:

- The management of patients who experience, or are likely to experience, anti cancer treatment related nausea and vomiting.

1.2 This guideline is intended for nurses, pharmacists and doctors who are treating oncology and haematology patients with anti cancer therapy. It may also be used by GPs and other doctors within the Trust who would be looking for breakthrough treatment for patients who came to see them or who were admitted with nausea and vomiting when already taking prophylactic anti emetics.

## 2. Guideline Background

2.1 In 2006 the American Society for Clinical Oncology (ASCO) published its anti emetic guidelines (Kris MG et al). These guidelines have been used throughout the United Kingdom to optimise prophylactic use of anti emetics, and form the basis for the recommendations contained in these guidelines.

2.2 The ASCO guidelines were updated in 2011 (Basch et al) and have been reviewed for this guideline. These updated ASCO guidelines widely recommend the use of aprepitant, however, the license for this agent in the UK is narrower so it cannot be used as widely. Consequently the updated Pan Birmingham Guidelines have to reflect this.

2.3 Nausea and vomiting are known side effects of many of the chemotherapy agents. The risk and severity of symptoms largely depends upon the dose and combination of cytotoxic agents used. Patients who receive the same chemotherapy may experience different levels of nausea and vomiting. Prophylaxis (prevention) and treatment guidelines need to take this issue into account. Prophylaxis of nausea and vomiting from the first course of treatment is essential as uncontrolled symptoms can contribute to anorexia, fluid, electrolyte imbalance, and anticipatory nausea and vomiting.

2.4 There are five types of nausea and vomiting associated with chemotherapy:

- a) **ACUTE** – usually within several hours of chemotherapy administration
- b) **DELAYED** – can be delayed for several days after the treatment
- c) **ANTICIPATORY** – If nausea and vomiting is not controlled with chemotherapy then the patient may experience a conditioned response of nausea and vomiting before treatment.
- d) **BREAKTHROUGH**- If one level of anti-emetic fails then the patient should be stepped up to the next level of anti-emetic prophylaxis
- e) **REFRACTORY** – Nausea and vomiting occurs despite all levels of anti-emetic

2.5 These areas of nausea and vomiting are interrelated. If the acute phase is poorly controlled then the patient is more susceptible to delayed symptoms. If acute and delayed symptoms are poorly controlled then the patient is at high risk of anticipatory symptoms.

2.6 Risk factors that make some patients more susceptible to nausea and vomiting include females, younger patients, previous history of vomiting whilst receiving chemotherapy, high

levels of anxiety, other disease, symptoms of disease or side effects of other treatments such as radiotherapy. Use a locally agreed risk assessment tool to assess the patients at high risk of nausea (See references)

### 3. Guideline statements

- 3.1 Risk factors should be assessed for all patients before first cycle of chemotherapy.
- 3.2 Prevention is the key to stopping a downward cycle and the development of dehydration or anticipatory emesis.
- 3.3 Anti emetics should be given prophylactically - before moderate to highly emetogenic chemotherapy. The tables in the appendix one identify the emetogenic potential of a number of cytotoxic agents and doses where appropriate.
- 3.4 Oral anti emetic medication needs to be given at least 30 minutes before treatment commences.
- 3.5 There is no significant benefit to using intravenous anti emetics over oral medication.
- 3.6 The following tables identify the recommended anti emetic regimen and the options for breakthrough nausea and vomiting.

### 4. Table of Recommended Anti Emetic Regimens

#### 4.1 Table of Daycase Regimens:

<u>Emetogenic potential</u>	<u>Treatment</u>
None	None required
Mild	<p><b>Pre-medication (to be administered 30-60 minutes prior to cytotoxic drug administration)</b> Domperidone 10 mg po stat or Metoclopramide 10mg po/IV stat</p> <p><b>TTO's</b> Domperidone 10 mg po tds or Metoclopramide 10 mg tds as required (prn) for 2-3 days post chemotherapy</p>
Low	<p><b>Pre-medication (to be administered 30-60 minutes prior to cytotoxic drug administration)</b> 5-HT3 antagonist po/IV stat Dexamethasone 4-8mg po/IV stat (Oncology only)*</p> <p><b><u>NB for regimens containing Paclitaxel and Docetaxel dexamethasone dose is variable.</u></b></p> <p><b>TTO's</b> Domperidone 10 mg po tds or Metoclopramide 10mg tds for 2-3 days post chemotherapy Dexamethasone 2-4mg po bd – tds for 2-3 days post chemotherapy</p>

<p><b>Moderate</b></p>	<p><b>Pre-medication (to be administered 30-60 minutes prior to cytotoxic drug administration)</b>  5HT3 antagonist po/IV stat  Dexamethasone 8mg po/IV stat*</p> <p><b><u>NB for regimens containing paclitaxel, dexamethasone dose is variable</u></b></p> <p><b>TTO's</b>  5HT3 antagonist po for 2-3 days post chemotherapy  Dexamethasone 2 - 4mg po bd/tds for 2-3 days (Oncology only)*  Domperidone 10 mg po tds or Metoclopramide 10mg tds for 2-3 days prn post chemotherapy</p> <p>Palonosetron 250 microgam IV bolus pre chemotherapy should be considered for prophylaxis for anthracyclines and where there is a need to spare the steroid dose (such as for haematology)</p>
<p><b>High</b></p>	<p><b>Pre-medication</b>  Dexamethasone 4 - 20mg IV stat* 30 – 60 min prior to chemotherapy  5HT3 and a NK1 receptor antagonist 60 min pre chemotherapy</p> <p><b>TTO's</b>  Dexamethasone 4mg po bd/tds for 2 -3 days (Oncology only)*  Domperidone 10 mg po tds or Metoclopramide 10 mg tds prn post chemotherapy for a maximum 3 days</p> <p>When the combination product of 5HT3 and NK1 receptor antagonist is not available then a 5HT3 and NK1 receptor antagonist will need to be continued on days 2-3</p> <p>Where a patient is unable to swallow</p> <p><b>Pre-medication (to be administered 30-60 minutes prior to cytotoxic drug administration) IV or oral</b>  5HT3 antagonist IV**  Dexamethasone 4 - 20mg IV stat* 30 - 60 prior to chemotherapy  Fosaprepitant 150mg IV infusion over 20 – 30 min</p> <p><b>TTO's</b>  5HT3 antagonist po for 3 days post chemotherapy  Dexamethasone 4 mg po bd for 2-3 days (Oncology only)*  Domperidone 10 mg po tds or Metoclopramide 10 mg tds prn post chemotherapy for a maximum 3 days</p> <p>**Palonosetron 250 microgam IV bolus pre chemotherapy should be considered for prophylaxis where there is a need to spare the steroid dose (such as for haematology)</p>

Notes:

- With combination chemotherapy use the recommended treatment for the agent with the highest emetogenic potential.

- For **haematology** patients avoid dexamethasone where possible and only use with highly emetic agents/regimens or where previous anti emetic regimens have failed.
- Consider the benefit versus risk of using steroid in patients with **diabetes** and/or **hypertension**.
- Omit dexamethasone in regimens where other steroids are prescribed such as prednisolone with CHOP and PMitCEBO.
- For weekly regimens with agents with moderate or higher emetogenic potential consider reducing the dose or decreasing the number of the days of the dexamethasone treatment.
- Although NK1 receptor antagonists are not licensed for highly emetic regimens (other than with cisplatin) these drugs should be considered for patients with high risk of emesis such young, female patient or those with a history of travel sickness.
- Fosaprepitant is available as the intravenous form of aprepitant and one dose is active for four days so further oral doses are not required. Currently the dose (150mg) has to be prepared in an exact volume of 150ml sodium chloride 0.9% which is difficult to make on the ward level.
- Akynzeo and Aprepitant (an NK1 receptor antagonist) are licensed for the use in moderately emetic regimens

#### 4.2 **Table of Multiple Day Regimens:**

<b>Emetogenic Potential</b>	<b>Continuous Prophylaxis anti emetics for in-patient chemotherapy regimens</b>
<b>Minimal</b>	Domperidone 10 mg po tds prn or Metoclopramide 10mg tds prn for a maximum 5 days
<b>Low</b>	5HT3 antagonist po/IV daily Domperidone 10mg po tds or Metoclopramide 10mg tds x 2-3 days prn Dexamethasone 2-4mg po bd –tds 5 days
<b>Moderate</b>	5HT3 antagonist 24 hour post chemotherapy (Granisetron patch is useful where a patient has chemotherapy lasting more than 2-3 days) Dexamethasone 4-8mg po bd – tds * Domperidone 10mg po tds or Metoclopramide 10mg tds for maximum 5 days
<b>High</b>	5HT3 and a NK1 receptor antagonist 60 min pre chemotherapy (If the individual drugs are used rather than the combination product; then the doses of 5HT3 will need to be repeated for the duration of the chemotherapy) Dexamethasone mg po/IV stat* then 2-4mg po bd for 3 days Domperidone 10mg po tds or Metoclopramide 10mg tds for 3 days prn post chemotherapy

4.2.1 Patients receiving chemotherapy as an in-patient should have regular prophylactic anti emetics prescribed for the duration of treatment (see table 4.2).

- 4.2.2 Select the appropriate pre chemotherapy prophylaxis for the first day of the multi-day regimen and on discharge choose the take home anti emetics for the agent with the highest emetogenic potential.
- 4.2.3 Pre chemotherapy anti emetic should be prescribed with the chemotherapy as discussed in table 4.1.

Notes:

- For **haematology** patients avoid dexamethasone where possible and only use with highly emetic regimen or where previous anti emetic regimens have failed. Consider the benefit versus risk of using steroid in patients with **diabetes** and **hypertension**.
- Although Akynzeo and Aprepitant (or IV fosaprepitant) are not licensed for highly emetic regimens it should be considered for patients with high risk of emesis such young, female patient or those with a history of travel sickness

## 5. ANTI EMETIC FAILURE:

Failure of first line anti emetics is defined as prolonged and distressing nausea and/or  $\geq 2$  episodes of vomiting in 24 hours

- 5.1 Failure of first line anti emetics should be dealt with swiftly. The next course of treatment should be commenced with anti emetics for the next level of emetogenicity (e.g. move from moderate to high or from high to very high).
- 5.2 Where patient is having breakthrough on the highest level of anti-emetics:  
Extend use of steroids or consider:
- Lorazepam 1-2mg po 1 hour prior to treatment and PRN (especially for anticipatory emesis).
  - Change Domperidone/ Metoclopramide to Cyclizine 50mg tds.
  - Methotrimeprazine 6.25mg po tds or 6.25 – 12.5mg IV or via subcutaneous pump over 24 hours.
  - It is proposed that 5HT3 and NK1 receptor antagonist is used for secondary prophylaxis of nausea and vomiting
  - Consider Fosaprepitant 150mg IV infusion on day 1 and Granisetron patches or palonosetron IV for patients not tolerating oral medication
  - Olanzapine, used off license but has benefit in refractory nausea and vomiting

**NB Consider IV drugs if orals not tolerated. Suppositories may be an option for discharged patients who cannot take oral anti emetics.**

- 5.3 The reason for anti emetic failure should be considered carefully to ensure appropriate treatment intervention.
- 5.3.1 **Acute emesis**- if adequate time was given between the administration of the pre medication and commencing chemotherapy consider changing the pre medication to include 5HT3 antagonist, Lorazepam or Cyclizine.
- 5.3.2 **Delayed emesis** (i.e. that which occurs  $>24$  hours post chemotherapy) Most common with cisplatin and ifosfamide but may occur with any regimen if acute emesis is not controlled effectively.



- If anti emetics fail in the first 24 hours and the patient is already receiving 5HT3 antagonist, consider adding or increasing the Dexamethasone, or Cyclizine 50mg tds.
- If anti emetics fail on stopping the 5HT3 antagonist, prolong use of 5HT3 antagonist for further two days.

5.3.3 **Anticipatory nausea and vomiting** (that is vomiting that commences up to 24 hours prior to commencing chemotherapy). Consider the use Lorazepam 1mg the evening before and morning of treatment

5.2.4 **Nabilone:** A synthetic cannabinoid with anti emetic properties. It may benefit patients whose nausea and vomiting is unresponsive to conventional anti emetics (such as patients receiving cisplatin or ifosfamide). Initially 1 mg twice daily increased if necessary to 2mg twice daily throughout cytotoxic therapy and for up to 48 hours after the last dose of chemotherapy. The first dose should be given the night before and the second dose 1 - 3 hours before the initiation of chemotherapy.

## 6. SIDE-EFFECTS OF COMMONLY USED ANTI EMETICS:

Anti-emetics have a number of side effects these are covered in the Summary of Product Characteristics (SPC) on [www.medicines.org.uk](http://www.medicines.org.uk)

### 6.1 Contraindications for use of dexamethasone as an anti emetic:

- a) Diabetes, unless arrangements are made to monitor the patient closely.
- b) Steroid induced side effects such as myopathy, gross weight gain, gastrointestinal effects, or psychosis with previous course.
- c) Patients already receiving high dose steroids e.g. prednisolone with CHOP chemotherapy.
- d) Patient is already receiving dexamethasone as part of their treatment protocol.

### 6.2 Concerns when using Domperidone

There are also concerns around cardiac side effects and the MHRA have issued guidance on dosing.

<https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects>

### 6.2 Concerns when using Ondansetron

The MHRA has also issued guidance on the use of ondansetron (including a maximum recommended dose):

<https://www.gov.uk/drug-safety-update/ondansetron-for-intravenous-use-dose-dependent-qt-interval-prolongation>

## 7. ABBREVIATIONS:

po:	orally
IV:	intravenous
Sc	Subcutaneous
bd:	twice daily
tds:	three times daily
qds:	four times daily
prn:	as required
mg:	milligrams
mcg	micrograms
MHRA:	Medicines and Healthcare Regulations Agency

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## Appendix 1: Emetogenic Potential of Individual Anti Cancer Drugs

These tables give a guide as to the emetogenic potential of agents but some patients experience higher levels of emesis due to their disease, other treatments such as radiotherapy and such factors should also be considered when prescribing antiemetics.

**Table 1 Table of Minimal Emetogenic Agents**

Individual drugs	Comments
Alemtuzumab	
Asparaginase	
Bleomycin	
Bortezomib	
Busulfan	Doses <10mg
Capecitabine	
Cetuximab	
Chlorambucil	
Cladribine	
Cytarabine	< 100 mg/m <sup>2</sup>
Decitabine	
Dexrazoxane	
Erlotinib	
Etoposide	Standard dose (Oral and IV)
Everolimus	
Fludarabine	
Fluorouracil	
Gefitinib	
Gemtuzumab	
Hydroxyurea	
Imatinib	
Interferon alpha	≤5 million international units/m <sup>2</sup>
Ipilimumab	
Liposomal Daunorubicin	
Liposomal Doxorubicin	
Melphalan	Oral
Mercaptopurine	
Methotrexate	Doses ≤50mg/m <sup>2</sup>
Nelarabine	
Ofatumumab	
Panitumumab	
Pegasparginase	
Pentostatin	
Pertuzumab	
Rituximab	
Sunitinib	
Temsirolimus	
Thioguanine	
Trastuzumab	
Vatubicin	
Vinblastine	
Vincristine	
Vindesine	
Vinorelbine	IV

**Table 2 Table of Low Emetogenic Agents**

Individual drugs	Comments
Arsenic	
Amifostine	≤ 300 mg
Aldesleukin	< 12 million international units/m <sup>2</sup>
Cabazitaxel	
Carmustine	<100mg/m <sup>2</sup>
Cyclophosphamide	≤750mg/m <sup>2</sup>
Cytarabine	<900mg/m <sup>2</sup>
Daunorubicin	<50mg/m <sup>2</sup>
Docetaxel	
Doxorubicin	>20mg or <60mg/m <sup>2</sup>
Doxorubicin Liposomal	
Eribulin	
Etoposide	➤ 100 mg/m <sup>2</sup>
Gemcitabine	
5-Fluorouracil	
Floxuridine	
Fludarabine	
Interferon	alfa ≥10 million international units/m <sup>2</sup>
Ixabepilone	
Methotrexate	>50mg to ≤ 250mg/m <sup>2</sup>
Mitomycin C	
Mitoxantrone	
Paclitaxel	
Paclitaxel Albumin	
Pemetrexed	
Pentostatin	
Procarbazine	
Temozolomide	
Thiotepa	
Topotecan	
Vinorelbine	oral

**Table 3 Table of Moderately Emetogenic Agents**

Individual drugs	Comments
Aldesleukin	> 12-15 million international units/m <sup>2</sup>
Altretamine	Treat only using 5-HT <sub>3</sub> antagonist not steroid
Amifostine	> 300 mg/m <sup>2</sup>
Amsacrine	
Arsenic Trioxide	
Azacitidine	
Bendamustine	
Busulfan	Oral
Carboplatin	
Carmustine	>100mg/m <sup>2</sup>
Cisplatin	<50mg/m <sup>2</sup>
Clofarabine	
Cyclophosphamide	Doses >750mg/m <sup>2</sup> to ≤1500mg/m <sup>2</sup>
Cytarabine	Doses >200mg/m <sup>2</sup>
Dactinomycin	
Daunorubicin	>/=50mg/m <sup>2</sup>
Doxorubicin	</=60mg/ m <sup>2</sup>
Epirubicin	</= 75mg/m <sup>2</sup>
Estramustine	
Idarubicin	
Ifosfamide	<3g/m <sup>2</sup>
Interferon alfa	≥10 million international units/m <sup>2</sup>
Irinotecan	
Lomustine	
Melphalan	Doses IV >100mg/m <sup>2</sup>
Methotrexate	Doses > 250mg/m <sup>2</sup>
Oxaliplatin	
Streptozocin	
Temozolomide	

**Table 4 Table of Highly Emetogenic Agents**

Combination chemotherapy including an anthracycline

Individual drugs	Comments
Busulfan	Conditioning doses
Carmustine	≥250mg/m <sup>2</sup>
Cisplatin	≥50mg/m <sup>2</sup>
Cyclophosphamide	>1500mg/m <sup>2</sup>
Dacarbazine	
Doxorubicin	>60 mg/m <sup>2</sup>
Epirubicin	>90 mg/m <sup>2</sup>
Ifosfamide	≥3g/m <sup>2</sup> /day
Mechlorethamine	
Streptozocin	

**Table 5 Emetic Potential of Chemotherapy Regimens**

<b>Minimal Incidence &lt; 30%</b>	<b>Low Incidence 30 – 60%</b>	<b>Moderate Incidence 60 – 90 %</b>	<b>High Incidence &gt; 90%</b>
5Fluorouracil/Folinic Acid	CDT	AC	ABVD
Modified DeGramont	ChIVPP	ADE (High D1-5, otherwise moderate)	BEAM (treat as moderate on D2-5)
VAD	ChIVPP/PABLOE	CAF	BEP 3/7
VAMP	CVP	CAP	BEP 5/7
Vinc/bleo	Cyclo-dex	CAV-PE	Carboplatin/etoposide
	FAD	CHOP	Dox/Cis(PAM)
	FMD	CMF	Dox/Ifos
	Mitomycin/FU (low on FU days)	CODOX-M (High D1, otherwise moderate)	EC90
	MM	C-VAMP (Moderate D2-4)	ESHAP (High D2-5)
	MMM	C-Z-dex	FEC
	PABLOE	DA (High D1,3,5 otherwise moderate)	FLAG-Ida
		EC	FU/Cisplatin
		ECF	Gem/Cisplatin
		FAC	High dose MTX
		Flu/Cyclo	
		ICE	IVAC
		IVE	MAP
		MACE	PE
		MidAC (Moderate D4-5)	VAC
		Mini-BEAM (treat as moderate D2-5)	VAI
		MVP	VIDE
		PCV	
		PMitCeBo	
		POMB- ACE	
		Z-dex	

The tables are not an exclusive list. Antiemetics for regimens not listed in this table should be based on the agent in the regimen with the highest emetogenic potential. In the Paclitaxel Gemcitabine regimen Paclitaxel has the higher emetogenic potential and the patients should be given anti emetics for a moderate emetogenic regimen.

In this table ‘incidence’ refers to the proportion of patients that experience emesis. It does not refer to the severity of the symptoms. Some agents can cause delayed nausea and vomiting for several days such as cyclophosphamide.



