West Midlands Cancer Alliance Guideline for the use of Antiemetics in Adults Receiving Anticancer Drug Therapy

NHS England and NHS Improvement

West Midlands Cancer Alliance

Coversheet for Cancer Alliance Expert Advisory Group Agreed Documentation

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

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Document Title	Guideline for the use of Antiemetics in Adults Receiving Anti-Cancer Drug Therapy	
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0.1	24/04/17	Comments from the West Midlands Chemotherapy EAG added to the former Pan Birmingham Cancer Guidelines
0.2	6/6/17	Comments from the West Midlands Chemotherapy EAG added
1	19/07/17	Final version agreed
2	12/12/19	Final revision of version 1 agreed.

Guideline for the use of Antiemetics in Adults Receiving Anticancer 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 antiemetics.

2. Guideline Background

2.1 In 2006 the American Society for Clinical Oncology (ASCO) published its antiemetic guidelines (Kris MG et al). These guidelines have been used throughout the United Kingdom to optimise prophylactic use of antiemetics 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 West Midlands Cancer Alliance 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 antiemetic.

2.5 These five 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 Antiemetics should be given prophylactically - before moderate to highly emetic chemotherapy. The tables in Appendix 1 identify the emetogenic potential of a number of cytotoxic agents and doses where appropriate.

3.4 Oral antiemetic medication needs to be given at least 30 minutes before treatment commences.

3.5 There is no significant benefit to using intravenous antiemetics over oral medication.

3.6 The following tables identify the recommended antiemetic regimen and the options for breakthrough nausea and vomiting.

4. Table of Recommended Antiemetic Regimens

4.1 Table of day-case regimens*:*

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

	TTOs 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
Moderate	**Pre-medication (to be administered 30-60 minutes prior to cytotoxic drug administration)** 5HT3 antagonist po/IV stat Dexamethasone 8mg po/IV stat* **<u>NB for regimens containing paclitaxel, dexamethasone dose is variable</u>** **TTOs** 5HT3 antagonist po for 3 days post chemotherapy Dexamethasone 2 - 4mg po bd for 2-3 days (Oncology only)* Domperidone 10 mg po tds or Metoclopramide 10mg tds for 3 days prn post chemotherapy Palonosetron 250 microgram IV bolus or Granisetron patch pre-chemotherapy should be considered for prophylaxis for anthracyclines and where there is a need to spare the steroid dose (such as for haematology)
High	**Pre-medication** Dexamethasone 4 - 20mg po / IV stat* 30 – 60 min prior to chemotherapy 5HT3 and a NK1 receptor antagonist 60 min pre-chemotherapy **TTOs** Dexamethasone 4mg 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 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 Where a patient is unable to swallow **Pre-medication (to be administered 30-60 minutes prior to cytotoxic drug administration)** 5HT3 antagonist IV** Dexamethasone 4 - 20mg IV stat* 30 - 60 prior to chemotherapy Fosaprepitant 150mg IV infusion over 20 – 30 min **TTOs** 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 Use syrups and PR route where possible- seek pharmacy advice if needed

	*For **haematology** patients avoid dexamethasone where possible and only use with highly emetic agents/regimens or where previous antiemetic regimens have failed. **Palonosetron 250 microgram IV bolus or Granisetron patch pre-chemotherapy should be considered for prophylaxis where there is a need to spare the steroid dose (such as for haematology)

Notes:

- With combination chemotherapy use the recommended treatment for the agent with the highest emetogenic potential.
- 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 antagonists) are licensed for the use in moderately emetic regimens

4.2 Table of Multiple Day Regimens:

Emetogenic Potential	**Continuous Prophylaxis antiemetics for in-patient chemotherapy regimens**
Minimal	Domperidone 10 mg po tds prn or Metoclopramide 10mg tds prn for a maximum 5 days
Low	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*
Moderate	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.
High	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 8mg 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 *For **haematology** patients avoid dexamethasone where possible and only use with highly emetic regimen or where previous antiemetic regimens have failed.

4.2.1 Patients receiving chemotherapy as an in-patient should have regular prophylactic antiemetics 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 antiemetics for the agent with the highest emetogenic potential.

4.2.3 Pre-chemotherapy antiemetic should be described with the chemotherapy as discussed in table 4.1.

Notes:

- 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. Antiemetic failure:

Failure of first line antiemetics is defined as prolonged and distressing nausea and/or ≥2 episodes of vomiting in 24 hours

5.1 Failure of first line antiemetics should be dealt with swiftly. The next course of treatment should be commenced with antiemetics for the next level of emetogenicity (e.g. move from low to moderate or from moderate to high).

5.2 Where patient is having breakthrough on the highest level of antiemetics: 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.
- Levomepromazine (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 antiemetics.

5.3 The reason for antiemetic 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 antiemetics 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 antiemetics 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.

5.3.4 **Nabilone:** A synthetic cannabinoid with antiemetic properties. It may benefit patients whose nausea and vomiting is unresponsive to conventional antiemetics (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 antiemetics:

Antiemetics have a number of side effects. These are covered in the SPCs on www.medicines.org.uk.

6.1 Contraindications for use of dexamethasone as an antiemetic:

a) Diabetes, unless arrangements are made to monitor the patient closely.
b) Steroid induced side effects such as myopathy, gross weight gain, gastro-intestinal 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.

6.3 **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
bd:	twice daily
tds:	three times daily
qds:	four times daily
prn:	as required
mg:	milligrams

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Appendix 1: Emetogenic Potential of Individual Anticancer 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^2
Decitabine	
Dexrazoxane	
Erlotinib	
Etoposide	Standard dose (Oral and IV)
Everolimus	
Fludarabine	
Fluorouracil	
Gefitinib	
Gemtuzumab	
Hydroxyurea	
Imatinib	
Interferon alpha	≤5 million international units/m^2
Ipilimumab	
Liposomal Daunorubicin	
Liposomal Doxorubicin	
Melphalan	Oral
Mercaptopurine	
Methotrexate	Doses ≤50mg/m^2
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^2
Cabazitaxel	
Carmustine	<100mg/m^2
Cyclophosphamide	≤750mg/m^2
Cytarabine	<200mg/m^2
Daunorubicin	<50mg/m^2
Docetaxel	
Doxorubicin	>20mg or <60mg/m^2
Doxorubicin Liposomal	
Eribulin	
Etoposide	➢ 100 mg/m2
Gemcitabine	
Floxuridine	
Interferon	alfa ≥10 million international units/m^2
Ixabepilone	
Methotrexate	>50mg to ≤ 250mg/m^2
Mitomycin C	
Mitoxantrone	
Paclitaxel	
Paclitaxel Albumin	
Pemetrexed	
Procarbazine	
Temozolomide	
Thiotepa	
Topotecan	
Vinorelbine	oral

Table 3: Table of Moderately Emetogenic Agents

Individual drugs	Comments
Aldesleukin	> 12-15 million international units/m^2
Altretamine	Treat only using 5-HT_3 antagonist not steroid
Amifostine	> 300 mg/m^2
Amsacrine	
Arsenic Trioxide	
Azacitidine	
Bendamustine	
Busulfan	Oral
Carboplatin	
Carmustine	>100mg/m^2
Cisplatin	<50mg/m^2
Clofarabine	
Cyclophosphamide	Doses >750mg/m^2 to ≤1500mg/m^2
Cytarabine	Doses >200mg/m^2
Dactinomycin	
Daunorubicin	>/=50mg/m^2
Doxorubicin	</=60mg/ m^2
Epirubicin	</= 75mg/m^2
Estramustine	
Idarubicin	
Ifosfamide	<3g/m^2
Irinotecan	
Lomustine	
Melphalan	Doses IV >100mg/m^2
Methotrexate	Doses > 250mg/m^2
Oxaliplatin	
Temozolomide	

Table 4: Table of Highly Emetogenic Agents
Combination chemotherapy including an anthracycline

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

Table 5: Emetic Potential of Chemotherapy Regimens

Minimal Incidence < 30%	Low Incidence 30 – 60%	Moderate Incidence 60 – 90 %	High Incidence > 90%
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 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.