Clinical Policy for the Management of Systemic Anti-Cancer Therapy Induced Nausea and Vomiting in Adult Patients

Lead Author/Coordinator:	Reviewer:	Approver:
Katherine Cowie, Specialist Oncology Pharmacist, NHS Tayside Louise McKee, Specialist Oncology Pharmacist, NHS Grampian Leanne Miller, Specialist Oncology Pharmacist, NHS Highland	Judith Jordan Regional Lead Pharmacist (on behalf of North SACT Delivery Group - NSDG)	Ian Rudd Director of Pharmacy, NHS Highland (on behalf of North SACT Governance Group - NSGG)

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Contents

1. Scope

This document covers both prevention and treatment of nausea and vomiting induced by systemic anti-cancer therapy (SACT) in adults. Please refer to the appropriate guidelines for paediatric patients or nausea and vomiting related to other causes.

2. Area of Application

This policy applies to all adult SACT services across the North region, except for the administrative areas of Argyll and Bute in NHS Highland which are linked to the WOSCAN CEL (2012) 30 governance framework.

3. Definitions

Acute nausea and vomiting -	Symptoms occurring within 24 hours of administration of SACT
Delayed nausea and vomiting -	Symptoms occurring 24 hours to 7 days after administration of SACT
Anticipatory nausea and vomiting -	Symptoms Occurring days to hours prior to SACT
Refractory nausea and vomiting -	Nausea and vomiting unresponsive to the prescribed anti-emetic regimen
Anti-emetic failure -	2 or more episodes of nausea and vomiting in 24hours and/or prolonged and distressing nausea

4. Emetic Classification of Systemic Anti-Cancer Therapy

The emetic potential of SACT varies, depending on the drugs used, their doses and the route of delivery e.g. oral or intravenous.

The emetogenicity of SACT can be divided into high, moderate, low and minimal risk.

High Risk >90% of patients at risk	Anthracycline/ Cyclophosphamide combination Carmustine Cisplatin Cyclophosphamide >1500mg/m^2 Dacarbazine Dactinomycin	Ifosfamide >2g/m^2/dose Melphalan (IV >100mg/ m^2) Methotrexate >1000mg/ m^2 Mustine Procarbazine Streptozocin Treosulphan (BMT conditioning doses)	
Moderate Risk 30-90% of patients at risk	Asparaginase Alemtuzumab Azacitidine Bendamustine Bosutinib Carboplatin Clofarabine Ceritinib Crizotinib Cyclophosphamide iv <1500mg/m^2 or oral* Cytarabine >200mg/m^2	Daunorubicin* Doxorubicin* Epirubicin* Idarubicin* Ifosfamide Imatinib Interferon α >10mu Irinotecan Lenvatinib Lomustine Methotrexate 250 - 1000mg/ m^2	Mitoxantrone >12mg/m^2* Mitotane Oxaliplatin Raltitrexed Temozolamide Vinorelbine (oral)

Low Risk 10-30% of patients at risk	Aflibercept Afatinib Axitinib Belinostat Blinatumomab Bortezomib Carfilzomib Capecitabine Cabzitaxel Catumaxomab Cetuximab Cytarabine <200mg/m^2 Dabrafenib Dasatinib Docetaxel Doxorubicin liposomal Eribulin Etoposide	Everolimus 5-Fluorouracil Gemcitabine Ibrutinib Idelalisib Interferon α 5-10mu Inotuzumab ozogamicin Ipilimumab Ixazomib Lapatinib Lenalidomide Methotrexate 50-250mg/m^2 Mitomycin Mitoxantrone <12mg/m^2 Nab-paclitaxel Nilotinib Nintedanib Olaparib Olaratumab	Pablociclib Panitumumab Pazopanib Pemetrexed Pomalidamide Ponatinib Regorafinib Sunitinib Tegafur/Uracil Temsirolimus Thalidomide Thiopeta Topotecan Trabectedin Trastuzumab-emtansine Vandetanib Venetoclax Vinflunine Vorinostat
Minimal Risk <10% of patients at risk	Abiraterone Alemtuzumab Anagrelide Arsenic Trioxide Bevacizumab Bleomycin Busulfan Chlorambucil (low dose oral) Cladribine Daunorubicin Liposomal Daratumumab Dasatinib Erlotinib Enzalutamide	Fulvestrant Fludarabine Gefitinib Hydroxycarbamide Ofatumumab Melphalan (oral) Mercaptopurine Methotrexate <50mg/m^2 or oral Nivolumab Obinutuzumab Ofatumumab Pegasparaginase Peginterferon Pertuzumab	Pembrolizumab Pentostatin Pixantrone Rituximab Sorafenib Trastuzumab Thioguanine Trametinib Tretinoin Vemurafenib Vinblastine Vincristine Vindesine Vinorelbine (IV) Vismodegib

Table developed from ASCO[1], MASCC[2], NCCN[4] guidelines, Summary of Product Characterisitics[5] BC Cancer agency [11]

Where sources vary in classification of risk, the agent has been included in the higher risk group. If a SACT is not listed please refer to the SPC or other sources.

***** A combination of anthracycline and cyclophosphamide is considered high risk

5. Patient risk factors for Systemic Anti-Cancer Therapy-induced nausea and vomiting

Although the greatest impact on the risk of nausea and vomiting is from the emetogenic potential of the SACT agent administered, patient risk factors can also contribute to the overall risk of SACT induced nausea and vomiting (SINV).

Increased Risk of emesis	Reduced Risk of emesis
Previous SACT treatment Previous uncontrolled SINV Younger patients (<50) Female patients (especially if history of sickness in pregnancy) History of travel or anaesthetic sickness Anxiety	History of alcohol excess Smoker

6. Principles of Anti-Emetic Treatment

Poor control of SINV in the acute phase may lead to delayed nausea and vomiting within the first cycle of treatment and poorer control with subsequent cycles.

To prevent nausea and vomiting:

- Use optimal doses of anti-emetics appropriate to the risk category of the SACT
- For combination SACT regimens, the anti-emetic regimen for the agent with the highest degree of risk should be prescribed
- If the patient is at increased risk of emesis due to additional emesis risk factors consider escalating anti-emetic treatment.
- Consider patient or disease factors e.g. electrolyte disturbances, brain metastases, concurrent medication, infection (viral and bacterial), tumour infiltration of the bowel or gastric obstruction. Reverse / treat if possible prior to next cycle of treatment.
- Advise patient to keep well hydrated throughout treatment and on lifestyle measures that may reduce risk of nausea and vomiting e.g. small meals frequently

7. Prevention of Systemic Anti-Cancer Therapy induced nausea and vomiting from intravenous treatment

This table covers prevention of nausea and vomiting related to IV treatment. For prevention of nausea and vomiting related to oral treatments, see individual SACT protocol or Chemocare® prescription.

Oral and IV routes are equally effective for anti-emetic agents as long as the patient is not vomiting and there are no barriers to gastrointestinal absorption.

Oral anti-emetics should be given one hour prior to SACT. Intravenous anti-emetics should be given 30 minutes prior to SACT.

See table on next page

Recommended First Line Anti-emetic regimen according to risk

Recommendations are based on MASCC and ASCO guidelines taking into account Scottish Medicines Consortium restrictions

(Please refer to local formulary for locally approved anti-emetics)

	Cisplatin containing regimen	High Risk (Including combination anthracycline and cylophosphamide regimens)	Moderate Risk	Low Risk	Minimal Risk
Prevention of acute symptoms	Aprepitant[a)] 125mg oral **Or** Fosaprepitant 150mg IV **with** Ondansetron 8mg IV or 16mg oral (as 8mg twice daily)[e)] **AND** Dexamethasone 12mg (Oral/IV) **Or** Netupitant / Palonosetron (Akynzeo)[b)] 300mg /0.5mg oral **AND** Dexamethasone 12mg (Oral/IV) **Or** Rolapitant 180mg[f)] **with** Ondansetron 8mg IV once or 16mg oral (as 8mg twice daily) **AND** Dexamethasone 20mg (Oral/IV)	Ondansetron 8mg IV or 16mg oral (as 8mg twice daily)[e)] **AND** Dexamethasone 20mg (Oral/IV) **OR** Aprepitant[a)] 125mg oral **with** Ondansetron 8mg IV or 16mg oral (as 8mg twice daily) **AND** Dexamethasone 12mg (Oral/IV) **OR** Rolapitant 180mg[f)] **with** Ondansetron 8mg IV once or 16mg oral (as 8mg twice daily) **AND** Dexamethasone 20mg (Oral/IV)	Ondansetron 8mg IV or 16mg oral (as 8mg twice daily)[e)] **AND** Dexamethasone 8mg (Oral/IV)	Dexamethasone 4-8mg (Oral/IV) **Or** Ondansetron 8mg (Oral/IV)[e)] **Or** Dopamine Receptor Antagonist	No anti-emetic required
Prevention of delayed symptoms	**Aprepitant Regimen-** Aprepitant 80mg oral on days 2 and 3 (not required if fosaprepitant given) **AND** Dexamethasone 8mg oral once daily on days 2 to 4 **Netupitant / Palonosetron (Akynzeo)[b] Regimen** – Dexamethasone 8mg oral once daily on days 2-4 **Rolapitant regimen** – Dexamethasone 8mg oral twice daily on days 2 to 4	**No NKI** Dexamethasone 8mg oral twice daily on days 2 to 4 **Aprepitant Regimen-** Aprepitant 80mg oral on days 2 and 3 (not required if fosaprepitant given) **AND** Dexamethasone 8mg oral once daily on days 2 to 4 **Rolapitant regimen** – Dexamethasone 8mg oral twice daily on days 2 to 4	Dexamethasone 8mg oral once daily for days 2 and 3	No anti-emetic required	No anti-emetic required
Treatment of breakthrough symptoms	[d)] Domperidone/ Metoclopramide	[d)] Domperidone/ Metoclopramide	[d)] Domperidone/ Metoclopramide	[d)] Domperidone/ Metoclopramide	[d)] Domperidone/ Metoclopramide

[a] **Aprepitant** capsules can be opened and contents taken orally, but should not be administered via NG or PEG tube due to risk of blockage
[b] **Netupitant / Palonosetron (Akynzeo®)** cannot be opened, crushed or administered via nasogastric or enteral tube.

[c]Akynzeo and Aprepitant are moderate inhibitors of CYP 3A4 and therefore the doses of dexamethasone prescribed are lower.

[d] See anti-emetic dosage table for dosage advice.

[e] Other -5HT$_3$-receptor antagonists may be used in place of ondansetron see Appendix 1 – Anti-emetic dosage table for dosage advice.

[f]Rolapitant **cannot** be administered at less than a 2 weeks interval.

EXCEPTIONS

- Patients receiving **paclitaxel, docetaxel or pemetrexed** should receive dexamethasone **PRIOR** to SACT administration to reduce risk of hypersensitivity reactions. See individual SACT protocol/prescription
- Anti-emetics for **multi-day SACT / high-dose SACT / transplant regimens / research trials / haematology regimen already containing steroids** may vary. See individual SACT protocol/prescription.

8. Treatment of Systemic Anti-Cancer Therapy induced nausea and vomiting

Treatment should be based on individual patient requirements taking into account; severity and timing of symptoms, co-morbidities, concomitant medication and availability of the oral route.

Assess the timing of symptoms and consider other causes of nausea and vomiting particularly if symptoms occur more than 7 days after SACT (constipation, infection, radiotherapy, obstruction, brain metastases, opioids or other new or changed medication, electrolyte imbalance including hypercalcaemia, indigestion/acid reflux, and other cancer related causes)

Assessment of patient

Patients should be assessed using the common toxicity criteria and the UKONs triage tool

	Nausea	Vomiting
Grade 1	Loss of appetite without alteration in eating habits	1 episode in 24 hours
Grade 2	Oral intake decrease without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 hours	2–5 episodes in 24 hours IV fluids indicated <24 hours
Grade 3	Inadequate oral calorific or fluid intake; IV fluids, tube feeding or total parenteral nutrition (TPN) indicated >24 hours	≥6 episodes in 24 hours IV fluids or TPN indicated >24 hours
Grade 4	Life-threatening consequences	Life-threatening consequences

- Consider timing of symptoms, co-morbidities, concomitant medication (particularly if symptoms occur >7 days post chemotherapy) see appendix 1
- Availability of oral route
- Consider non-compliance with anti-emetics
- Consider if the patient is absorbing oral medication

Assess

- Frequency / nature of nausea and / or vomiting
- Assess for signs of dehydration: decreased urine output, fever, thirst, dry mucous membranes
- Assess bowels for diarrhoea, constipation or abdominal pain
- Assess oral intake

Where appropriate

- Investigation: FBC, U&Es, LFTs, bone profile, CRP and if appropriate cultures
- Observations: Temperature, pulse, blood pressure, respiration rate, O2 saturations: calculate early warning score

NOTE, IF A PATIENT HAS A RAISED TEMPERATURE PLEASE REFER TO LOCAL NEUTROPENIC SEPSIS GUIDELINES.

Principles of management of emesis after failure of prophylactic anti-emetics

- Advise regular anti-emetics if not already taking
- Add agent of different class

Antiemetic	Dopamine antagonist	Histamine antagonist	Muscarinic antagonist	Serotonin type 2 antagonist	Serotonin type 3 antagonist	Serotonin type 4 antagonist	NK 1 receptor antagonist
Akynzeo					+++		+++
Aprepitant							+++
Cyclizine		++	++				
Dexamethasone	Activity against prostaglandin and peritumoural inflammation						
Domperidone	++					++	
Fosaprepitant							+++
Granisetron					+++		
Haloperidol	+++						
Levomepromazine	++	+++	++	+++			
Metoclopramide	++					++	
Ondansetron					+++		
Palonosetron					+++		
Prochloperazine	++	+					
Rolapitant							+++

- Consider route. If oral route is not likely to be possible, consider IV, subcutaneous, transdermal and rectal routes
- Use round the clock dosing
- Multiple concurrent agents with alternating schedules, or alternating routes may be necessary, but ensure side effect profiles and conflicting mechanism of actions (i.e. cyclizine and metoclopramide/domperidone) are considered
- Consider concurrent problems that may contribute to nausea and vomiting e.g. constipation, gastritis and treat accordingly e.g. laxative or PPIs
- Ensure adequate hydration and fluid replacement, ensuring that electrolytes are checked and corrected
- Step anti-emetic treatment up to next level (i.e. low to moderate) prior to next cycle

- If unable to control nausea and/or vomiting consult specialists for advice

Anticipatory Emesis

- Use the most active anti-emetic regimens appropriate for the SACT being given to prevent acute or delayed emesis
- Prescribe **lorazepam 0.5-1mg orally** the night before and morning of SACT

9. Radiotherapy

Patients receiving concomitant SACT and radiotherapy should receive the anti-emetic regimen appropriate for the risk category of SACT, unless the risk of nausea and vomiting is higher with radiotherapy in which case the anti-emetics recommended for the radiotherapy risk category should be used, discuss with clinical oncologist or their deputy.

Note: The NOSCAN anti-emetic guidelines consider risk of emesis and not the management of any other cancer/treatment related problems e.g. raised ICP.

Risk factors

Radiotherapy related factors	Patient risk factors
Irradiation site Irradiation Volume Single and total dose Fractionation Radiotherapy technique	Gender Age General health Concurrent or recent chemotherapy Psychological state Tumour Stage

Radiotherapy induced nausea and vomiting risk levels (MASCC)

High Risk >90% of patients at risk	Total Body Irradiation, Total nodal irradiation
Moderate Risk 60-90% of patients at risk	Upper Abdomen, Upper body irradiation, half body irradiation
Low Risk 30-60% of patients at risk	Cranial, craniospinal, Head and Neck, lower thorax region, pelvis
Minimal Risk <30% of patients at risk	Extremities, breast

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Appendix 1 – Anti-emetic Dosage Table

Anti-emetic	Oral Dose	Parenteral Dose	SMC advice available	Indication for treatment of nausea and vomiting out with SACT
Aprepitant	125mg stat, then 80mg on day 2 and 3	See fosaprepitant	Yes	None
Netupitant / Palonosetron (Akynzeo®)	300mg/0.5mg stat	n/a	Yes	None
Fosaprepitant	See aprepitant	150mg stat	Yes	None
Rolapitant	180mg stat	n/a	Yes	None
Ondansetron	8mg twice daily	8-16mg (maximum 16mg)	Yes	Radiotherapy
Granisetron	*Transdermal 3.1mg/24 hour patch*	-	Yes	None
Palonosetron	500 micrograms stat	250 microgram stat	Yes	None
Dexamethasone	Up to 20mg daily (in single or divided dose)	Up to 20mg daily (in single or divided dose)	No	Raised ICP, bowel obstruction, regurgitation unknown cause in combination with levomepromazine
Metoclopramide	10mg 6-8 hourly (max three times daily)	10mg 6-8 hourly (max three times daily). Can be given via CSCI.	No	Constipation, delayed gastric emptying, gastric irritation
Domperidone	10 mg (20mg on specialist advice) 6- 8 hourly (max three times daily)	n/a	No	Delayed gastric emptying
Cyclizine	50mg 6-8 hourly (max three times daily)	50mg 6- 8 hourly (max three times daily). Can be given via CSCI	No	Raised ICP, Complete bowel obstruction, vestibular disorders
Haloperidol	0.5-1.5mg night/twice daily	0.5-1mg twice daily via subcutaneous injection. Can be given via CSCI.	No	Hypercalcaemia Metabolic
Levomepromazine	3-6mg 12 hourly	2.5 - 6.25mg 12 hourly via subcutaneous injection. Can be given via CSCI	No	Hypercalcaemia, Metabolic, unknown cause
Lorazepam	0.5mg evening before and morning of treatment. (0.5mg up to 4 x daily) oral or sublingual	*Available but often restricted due to supply problems, dosing as in oral.*	No	Anxiety
Prochlorperazine	5mg three times daily	12.5mg by deep IM injection repeat after 6 hours if necessary	No	Vestibular disorders
Prochlorperazine (Buccastem)	3-6mg twice daily	n/a	No	Vestibular disorders

Note: parenteral administration is via the intravenous route unless otherwise stated. Please refer to SMC website for SMC advice: www.scottishmedicines.org.uk

Replaces: (detail previous unique identifier if applicable)

Lead Author/Coordinator: Katherine Cowie and Louise McKee

Responsibilities of the Lead Author/Coordinator

- Ensuring registration of this document on Document and Information Silo
- Disseminating document as per distribution list
- Retaining the master copy of this document
- Reviewing document in advance of review date

Key word(s): SACT, nausea, vomiting, anti-emetics, SINV

Document application: To all adult SACT services across the North region, except for the administrative areas of Argyll and Bute in NHS Highland which are linked to WOSCAN.

Purpose/description: To ensure consistent and effective management of SACT Induced Nausea and Vomiting

Policy statement:
It is the responsibility of all staff to ensure that they are working to the most up to date and relevant clinical process documents.

Responsibilities for implementation:

Organisational:	Operational Management Team and Chief Executive
Sector	General Managers, Medical Leads and Nursing Leads
Departmental:	Clinical Leads
Area:	Line Manager

Review frequency and date of next review: (Include a statement that indicates that in the absence of any obvious changes review should occur every 2 years)

Revision History:

Revision Date	Previous Revision Date	Summary of Changes (Descriptive summary of the changes made)	Changes Marked (Identify page numbers and section heading)
30/05/2017	n/a	Drug list updated Akynzeo added to first line anti-emetics Acute management MHRA advice removed Antiemetic table updated	Section 4 pg 3 Section 7 pg 5 Section 8 pg 6-7 Section 10 (removed) Appendix 1.0
01/11/2017	30/05/2017	Rolapitant and Aprepitant added as per SMC advice Section 7 update relating to applicability of oral SACT regimens	Section 7 pg 5-6 Appendix 1.0 pg 10