National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting

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1	28 November 2018	Version 1	NCCP
2	16 December 2019	• Addition of new section on drug interactions • Addition of CAR-T to areas excluded from this classification document • Emetogenic classification and treatment recommendations updated in line with references (NCCN updates) • Clarification of IV dexamethasone salt	NCCP

All comments and feedback are welcome at oncologydrugs@cancercontrol.ie

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1 Background

Systemic Anti-Cancer Therapy (SACT) induced nausea and vomiting is one of the most frequent side effects experienced by patients undergoing SACT. Patients often find SACT induced nausea and vomiting distressing, and anxiety about the recurrence of such symptoms on future cycles of SACT may itself become a cause of anticipatory nausea and vomiting. The incidence of nausea associated with SACT is often underestimated by clinicians and it is not as well managed as emesis (1). Modern drug treatments can successfully control SACT induced nausea and vomiting for the majority of patients.

Currently, most hospital delivering HSE funded SACT services maintain their own policy on the management of SACT induced nausea and vomiting and there are some variations between hospitals. The introduction of the National Cancer Information System (NCIS) presents a potential opportunity to include a series of standardised medicines as per the SACT risk categories. The NCCP has developed this document detailing the classification of:

- Emetogenic risk of SACT drugs
- Antiemetics to prevent and treat SACT induced nausea and vomiting

The classification included in this document does not apply to the treatment of:

- Paediatric patients
- Radiation-induced nausea and vomiting
- Patients receiving high-dose SACT for stem cell transplant
- Patients receiving Chimeric Antigen Receptor T-cell (CAR-T) therapy

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2 Introduction

SACT agents are classified into four levels of emetogenicity (high, moderate, low and minimal) based on the percentage of patients who experience emesis having not receiving antiemetic prophylaxis (3, 4). This classification has been used as a framework for treatment guidelines internationally (2-4).

The emetogenic potential of:

- Parenteral SACT is detailed in Table 7
- Oral SACT/Oral Anti-Cancer Medicines (OAM) is detailed in Table 8

The following points should be considered when prescribing antiemetics for patients receiving SACT drugs:

- The goal of antiemetic therapy is prevention of nausea/vomiting
- Prophylaxis is better than treatment; therefore escalate rapidly if treatment is failing
- The emetogenic potential of the SACT must be considered when deciding which antiemetics to prescribe
- For patients receiving combination SACT, antiemetic treatment should be determined according to the SACT with the greatest degree of emetogenic risk (3)
- Adult patients who are treated with multi-day SACT should be offered antiemetics before treatment that are appropriate for the emetogenic risk of the SACT administered on each day of the SACT treatment and for two days after (3)
- Antiemetics should always commence before SACT with oral doses administered at least 30 minutes before SACT is initiated
- Consideration should be given to using a H_2 blocker or proton pump inhibitor to prevent dyspepsia which can mimic nausea (2)
- Optimal emetogenic control of acute emesis is essential to prevent delayed emesis

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3 Types of Nausea and Vomiting

The types of SACT induced nausea and vomiting experienced by patients may be subdivided as detailed in Table 1 and influences the optimal treatment option.

Table 1 Types of nausea and vomiting (2)

Type of Emesis	Description
Acute	Nausea and vomiting experienced usually within a few minutes to several hours after drug administration and which commonly resolves within the first 24 hours.
Delayed-onset	Nausea and vomiting developing more than 24 hours after SACT administration and which may last for up to 6 - 7 days.
Breakthrough	Development of nausea and vomiting, despite prophylactic treatment and/or requires rescue with antiemetic agents.
Anticipatory	Nausea and vomiting that occurs prior to the beginning of a new cycle of SACT. It is primarily considered a conditioned response and typically occurs after a negative past experience with SACT.
Refractory	Nausea and/or vomiting that occur during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have not been effective in earlier cycles.

The treatment of anticipatory and refractory emesis is not dealt with in this classification document.

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4 Antiemetics to prevent and treat SACT induced nausea and vomiting

The antiemetics to prevent and treat SACT induced nausea and vomiting for:

- Parenteral SACT are detailed in Table 2 and Table 3
- Oral SACT (OAM) are detailed in Table 5

These tables should be used to choose the agent and identify the dosing for the appropriate locally approved agents.

Some medications listed on these tables may not be available on the Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes but may be used locally at hospital level with the cost borne by the hospital.

Inclusion of medications in this table does not denote NCCP endorsement of any product.

4.1 Parenteral SACT

Table 2 Emetogenic risk and associated Antiemetic Regimens Drug Classifications for parenteral SACT

Emetogenic Risk	Antiemetic Regimen*
High (>90% risk of emesis)	NK_1 Receptor Antagonist **and** 5-HT_3 Receptor Antagonist **and** Corticosteroid **and** Olanzapine[i]
Moderate (>30-90% risk of emesis)	5-HT_3 Receptor Antagonist **and** Corticosteroid
Low (10-30% risk of emesis)	5-HT_3 Receptor Antagonist **or** Corticosteroid
Minimal(<10% risk of emesis)	No routine prophylaxis required

5-HT_3, 5-hydroxytryptamine-3; NK_1, neurokinin 1;

*+/- H_2 Blocker or a proton pump inhibitor to prevent dyspepsia which can mimic nausea

[i] Unlicensed indication

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Table 3 Antiemetic Dosing* for Adults by parenteral SACT Risk Category

EMETOGENIC RISK	Day of SACT			Subsequent Days
HIGH	**Oral Dose**		**IV Dose**	
NK_1 Receptor Antagonist and 5-HT_3 Receptor Antagonist (plus corticosteroid)				
Netupitant /Palonosetron	300mg/0.5mg		N/A	None
NK_1 Receptor Antagonist: Choose one of the following (plus 5-HT_3 Receptor Antagonist plus corticosteroid)				
Aprepitant	125mg		N/A	80mg PO once daily on days 2 and 3
Fosaprepitant	N/A		150mg	None
Rolapitant	180mg		N/A	
+ 5-HT_3 Receptor Antagonist: Choose one of the following (plus NK_1 Receptor Antagonist plus corticosteroid)				
Granisetron	2mg	or	1mg or 0.01mg/kg	None
	OR 10mg subcutaneous			
Ondansetron	8mg twice daily **OR** 16mg once daily	or	8mg or 0.15mg/kg	
Palonosetron	0.5mg	or	0.25mg	
Other antiemetic agents				
+/- Olanzapine	**5-10mg PO (5mg if elderly or over-sedated)**			**5-10mg PO once daily on days 2-4**
+ Corticosteroid (plus NK_1 Receptor Antagonist plus 5-HT_3 Receptor Antagonist)				
Dexamethasone,[a,b]	**Dexamethasone dose**			
If netupitant/palonosetron is used	12mg	or	12mg	8mg PO or IV[c] once daily on days 2 - 4
If aprepitant is used	12mg	or	12mg	
If fosaprepitant is used	12mg	or	12mg	8mg PO or IV[c] on day 2 8mg PO or IV[c] twice daily on days 3 and 4
If rolapitant is used	20mg	or	20mg	8mg PO or IV[c] twice daily on days 2 - 4
If olanzapine is used	12mg	or	12mg	8mg PO once daily on days 2-4 None if Anthracycline and Cyclophosphamide
MODERATE	**Oral Dose**		**IV Dose**	
5-HT_3 Receptor Antagonist : Choose one of the following (Plus corticosteroid)				
Granisetron	2mg	or	1mg or 0.01mg/kg	None
	OR 10mg subcutaneous			
Ondansetron	8mg twice daily	or	8mg or 0.15mg/kg	
Palonosetron	0.50mg	or	0.25mg	
Corticosteroid (plus 5-HT_3 Receptor Antagonist)				
Dexamethasone,[a,b]	8mg	or	8mg[c]	8mg PO or IV[c] once daily on days 2 and 3
LOW	**Oral Dose**		**IV Dose**	
5-HT_3 Receptor Antagonist : Choose one of the following				
Granisetron	2mg	or	1mg or 0.01mg/kg	None
	OR 10mg subcutaneous			
Ondansetron	8mg twice daily	or	8mg or 0.15mg/kg	
Palonosetron	0.50mg	or	0.25mg	
OR				
Corticosteroid – Dexamethasone [a,b]	8mg	or	8mg[c]	None
MINIMAL				
No routine prophylaxis required				

5-HT_3, 5-hydroxytryptamine-3; IV, intravenous; NK_1, neurokinin 1; PO, oral; IV intravenous

[a]Dexamethasone dose may be modified or omitted where the SACT regimen already includes a steroid.

[B] Consider avoiding the use of corticosteroid premedications with immune checkpoint inhibitors

[C] Dose of dexamethasone IV refers to dexamethasone phosphate. Consideration of dose adjustment is required if using an alternate salt

*+/- H_2 Blocker or a proton pump inhibitor to prevent dyspepsia which can mimic nausea

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Table 4 Caution on IV Ondansetron dosing

IV ondansetron causes a dose-dependent prolongation of the QT interval. A single dose of IV ondansetron given for SACT induced nausea and vomiting in adults

- must not exceed 8mg infused in 50-100ml sodium chloride 0.9% over at least 15minutes in patients greater than 75 years
- must not exceed 16mg infused in 50-100ml sodium chloride 0.9% over at least 15minutes in patients less than 75 years
- repeat IV dosing should be given no less than 4 hours apart (8).

4.2 Oral SACT

There is a lack of clinical trials evaluating the prevention and treatment of nausea and vomiting associated with OAMs as well as divergence in the international recommendations and classifications of the emetogenic potential of OAMs. Due to the continuous administration for many OAMs, the use of steroids is not ideal.

OAMs have been classified as moderate-high and minimal-low in line with the NCCN classification of OAMs

Table 5 Antiemetic Dosing* for Adults by OAM SACT Risk Category

EMETOGENIC RISK	Day of SACT	Subsequent Days
Moderate-High	**Dose to be given – PO**	
5-HT_3 Receptor Antagonist: Choose one of the following		
Granisetron	1-2mg (total dose) daily	Continue daily
Ondansetron	8mg - 16mg (total dose) daily	Continue daily
Minimal-Low	**Treat with antiemetics only on "as required" basis**	
Metoclopramide	10mg three times daily	Continue as required
OR		
Prochlorperazine	10mg and then every 6 hours as needed (maximum 40mg/day)	Continue as required
OR		
5-HT_3 Receptor Antagonist: Choose one of the following		
Granisetron	1-2mg (total dose) daily PRN	Continue as required
Ondansetron	8mg - 16mg (total dose) daily PRN	Continue as required

*+/- H_2 Blocker or a proton pump inhibitor to prevent dyspepsia which can mimic nausea

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4.3 Breakthrough Emesis

For patients with breakthrough nausea and vomiting clinicians should re-evaluate emetogenic risk, disease status, concurrent illnesses and medications and ascertain that the best regimen is being administered for the emetogenic risk (3).

The general principle of treatment for breakthrough emesis is to add an additional antiemetic with a different mechanism of action than that of the current prophylactic regimen (e.g. an NK_1 receptor antagonist, a benzodiazepine, a dopamine receptor antagonist) in addition to continuing the standard antiemetic regimen (3). ASCO recommend that patients be offered olanzapine where not previously given and where already on optimal prophylaxis.

Table 6 lists antiemetic agents available for the treatment of breakthrough emesis for both parenteral SACT and OAM. These antiemetics for breakthrough emesis should be continued on a regular schedule rather than an as required schedule (2). If emesis persists, re-evaluate patients and either dose adjust or consider changing antiemetic therapy to higher level treatment for the next cycle.

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Table 6 Additional treatment options for Breakthrough SACT Induced Nausea and Vomiting (Parenteral & OAM)

Drug Class	Drug	Recommended Dose
Antihistamine	Cyclizine	50mg PO/IV three times daily
Benzodiazepine	Lorazepam	0.5-2mg PO every 6 hours
Dopamine Receptor Antagonist	[a]Domperidone	10mg PO three times daily
	or	
	Metoclopramide	10mg PO/IV three times daily
Phenothiazine	Prochlorperazine	25mg suppository every 12 hours or 10mg PO/IV every 6 hours
	Promethazine	12.5-25mg PO/IV (central line only) every 4-6hours
[b]**Other**	Haloperidol	0.5-2mg PO/IV every 4-6hours
	Scopolamine[c]	1.5mg transdermal patch every 72hours (1mg scopolamine)
Steroids, NK1 ,5HT3 receptor antagonists and olanzapine may also be added where have not been used previously, see Table 3 for details		

[a] Domperidone has been associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors. Domperidone should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting (9).

[b] This is not an exhaustive list of additional treatment options. Other options may be recommended by the patient's clinician.

[C] Unlicensed indication

5 Drug Interactions

The Summary of Product Characteristics (SmPC) and current drug interaction databases should be consulted for the most up to date information regarding drug interactions.

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6 Classification of Emetogenic Potential for SACT Drugs

Table 7 Emetogenic risk of parenteral SACT drugs[a]

High Risk (>90% frequency of emesis)		
Anthracycline/Cyclophosphamide combination	CISplatin	epiRUBicin > 90mg/m^2
CARBOplatin AUC ≥ 4	Cyclophosphamide>1500mg/m^2	Ifosfamide ≥ 2g/m^2
Carmustine > 250mg/m^2	Dacarbazine	Mechlorethamine
	DOXOrubicin ≥ 60mg/m^2	Streptozotocin

Moderate Risk (30-90% patients)		
Aldesleukin > 12-15 million IU/m^2	Cyclophosphamide ≤ 1500mg/m^2	Ifosfamide < 2g/m^2
Alemtuzumab	Cytarabine > 1000mg/m^2	Interferon alfa ≥10 million IU/m^2
Amifostine > 300mg/m^2	DACTINomycin	Irinotecan
Arsenic trioxide	DAUNOrubicin	Irinotecan (liposomal)
AzaCITIdine	Dual drug liposomal encapsulation	Melphalan[1]
Bendamustine	of cytarabine and DAUNOrubicin	Methotrexate ≥250mg/m^2
Busulfan	Dinutuximab	Oxaliplatin
CARBOplatin AUC<4	DOXOrubicin < 60mg/m^2	Thiotepa
Carmustine ≤ 250mg/m^2	epiRUBicin ≤ 90mg/m^2	Trabectedin
Clofarabine	IDArubicin	

[1]Melphalan is generally regarded as being moderately emetogenic. When used in high doses as part of conditioning regimens for autologous bone marrow transplant, it is regarded as being highly emetogenic in clinical practice (5)

Low Risk (10-30% patients)		
Aflibercept	eriBULin	PACLitaxel
Aldesleukin < 12million IU/m^2	Etoposide	Panitumumab
Amifostine ≤ 300mg/m^2	5-Fluorouracil	Pegylated liposomal DOXOrubicin
Axicabtagene ciloleucel	Gemcitabine	PEMEtrexed
Bortezomib	Gemtuzumab ozogamicin	Pentostatin
Brentuximab vedotin	Inotuzumab ozogamicin	Pertuzumab
Cabazitaxel	Interferon alfa >5 -<10 million IU	Tamlimogene laherparepvec
Carfilzomib	Ipilimumab	Temsirolimus
Cetuximab	Methotrexate <250mg/m^2	Tisagenlecleucel
Copanlisib	MitoMYcin	Topotecan
Cytarabine ≤ 1000mg/m^2	MitoXANTRONE	Trastuzumab emtansine
DOCEtaxel	Nab-PACLitaxel	

Minimal (<10% patients)		
Asparaginase	Fludarabine	Ramucirumab
Atezolizumab	Interferon alfa ≤ 5 million IU	riTUXimab
Avelumab	Nelarabine	Siltuximab
Bevacizumab	Nivolumab	Trastuzumab
Bleomycin	Obinutuzumab	VinBLAStine
Blinatumomab	Ofatumumab	VinCRIStine
Cladribine	Pegaspargase	VinCRIStine (liposomal)
Daratumumab	Peginterferon	Vinorelbine
Decitabine	Pembrolizumab	
Dexrazoxane	Pixantrone	

[a] Potential drug interactions between antineoplastic/antiemetic therapies and various other drugs should always be considered

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Table 8 Emetogenic risk of oral SACT drugs [a] (OAMs)

Moderate to High ≥30 %	
Busulfan ≥ 4mg/day	Mitotane
Ceritinib	Olaparib
Crizotinib	Procarbazine
Cyclophosphamide ≥ 100mg/m^2/day	Temozolomide ≥ 75mg/m^2/day
Lenvatinib	Trifluridine/tipracil
Lomustine (single day)	

Minimal to Low <30%	
Acalabrutinib,	Lapatinib
Afatinib	Larotrectinib
Alectinib	Lenalidomide
Axatinib	Lorlatinib
Binimetinib	Melphalan
Bosutinib	Mercaptopurine
Busulphan (<4mg/day)	Methotrexate
Cabozantinib	Nilotinib
Capecitabine	Osimertinib
Chlorambucil	Palbociclib
Cobimetinib	Panobinostat
Cyclophosphamide<100mg/m2/day	PAZOPanib
Dabrafenib	Pomalidomide
Dacomitinib	PONATinib
Dasatinib	Regorafenib
Duvelisib	Ruxolitinib
Encorafanib	SORAfenib
Erlotinib	SUNitinib
Etoposide	Talazoparib tosylate
Everolimus	Temozolomide (<75 mg/m^2/day)
Fludarabine	Thalidomide
Gefitinib	Thioguanine
Gilteritinib	Topotecan
Glasdegib	Trametinib
Hydroxyurea	Tretinoin
Ibrutinib	Vandetanib
Idelalisib	Vemurafenib
Imatinib	Venetoclax
Ivosidenib	Vismodegib
Ixazomib	Vorinostat

[a] Potential drug interactions between antineoplastic/antiemetic therapies and various other drugs should always be considered

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