# Emetogenicity

This document summarises the basis for the guidance on treatment induced emesis management provided for medical oncology regimens in the ACT-NOW Systemic Anti-Cancer Therapy Regimen Library (SRL).

**Emetogenicity risk** of systemic anti-cancer therapy (SACT) is classified depending on the risk of emesis in the absence of effective antiemetic prophylaxis.

In the SRL the risk categories are grouped as follows:

Parenteral SACT:

- High greater than 90%
- Medium (Moderate) 30% to 90%
- Low 10% to 30%
- Minimal less than 10%

Overview of antiemetics included in parenteral SRL regimens.

Oral SACT:

- Medium to high greater than 30%
- Minimal to low less than 30%

## General principles

- Prevention of nausea and vomiting is the goal. Nausea and vomiting have a significant impact on quality of life and may prompt withdrawal from potentially useful and/or curative treatment. Uncontrolled vomiting can lead to dehydration, anorexia and serious metabolic imbalance.
- Adherence to antiemetic guidelines has been shown to improve emesis control.[3]
- Prophylactic antiemetics should be administered prior to systemic anti-cancer therapy (SACT). In the SRL regimens, these are all recommended for oral administration one hour prior to chemotherapy.
- On days when multiple SACT with varied emetogenic risks are scheduled, the default risk usually corresponds to the SACT with the **highest** risk, in addition to patient specific factors. However, for some combinations evidence suggests emetogenicity may be additive. In these cases, a higher category may be assigned, e.g. combinations of oxaliplatin (Medium) and irinotecan (Medium) are considered highly emetogenic.
- When a regimen includes a corticosteroid for both antiemetic use and as premedication for infusion related reactions (IRRs), the **higher** of the recommended doses should be used. When aprepitant is used as an antiemetic the dose of concomitant dexamethasone is reduced to account for the CYP3A4 interaction.
- When prescribing corticosteroids for antiemesis and/or for IRRs any corticosteroid dosing within the regimen used for other indications should also be taken into account.
- Antiemetics for multi-day parenteral regimens are tailored to the emetogenic risk of the medicines administered each day during treatment and for two days after completion of the protocol. *Except* aprepitant, which if part of the antiemetic regimen, is given on each day of the multi-day regimen only, or the usual 3-day course whichever is longer.

- Domperidone is included as the rescue antiemetic in SRL regimens unless there is a high risk of QT-interval prolongation. In highly emetogenic chemotherapy regimens that contain both olanzapine and ondansetron, cyclizine is recommended instead. The choice of rescue antiemetic may be substituted to reflect institutional policy or individual patient characteristics.
- Potential drug interactions between anti-cancer medicines, antiemetics and various other drugs, along with the individual patient's risk factors and comorbidities should always be considered in the choice of antiemesis.
- It is often difficult for patients to differentiate between nausea and dyspepsia; a trial of a proton pump inhibitor or $H_2$ antagonist may be beneficial for those with oesophageal reflux symptoms such as dyspepsia.

All antiemetic prophylaxis included in the SRL are considered a default and should be tailored to patient circumstances and institutional polices.

# Parenteral SACT

## High:

Risk of emesis in more than 90% of patients, includes:

- anthracycline plus cyclophosphamide for breast cancer
- carboplatin ≥ 5 AUC
- carmustine
- cisplatin
- cyclophosphamide ≥ 1500 mg/m$^2$
- dacarbazine
- doxorubicin ≥ 60 mg/m$^2$
- epirubicin > 90 mg/m$^2$
- ifosphamide ≥ 2 g/m$^2$ per dose
- mechlorethamine
- melphalan ≥ 140 mg/m$^2$
- sacituzumab govitecan
- streptozocin
- trastuzumab deruxtecan (Enhertu®)

## Medium:

Risk of emesis in 30% to 90% of patients, includes:

- azacitidine
- bendamustine
- busulfan
- carboplatin < 5 AUC
- cyclophosphamide < 1500mg/m$^2$
- cytarabine > 200mg/m$^2$
- dactinomycin
- daunorubicin
- daunorubin + cytarabine liposomal (Vyxeos®)
- doxorubicin < 60 mg/m$^2$
- epirubicin ≤ 90 mg/m$^2$
- idarubicin
- ifosfamide < 2g/m$^2$ per dose
- irinotecan
- melphalan < 140 mg/m$^2$
- methotrexate ≥ 250 mg/m$^2$
- oxaliplatin#
- trabectedin

# Women 50 years and under should be considered high risk for oxaliplatin-induced nausea and vomiting.[1]

## Low:

Risk of emesis in 10% to 30% of patients, includes:

- amivantamab
- arsenic trioxide
- belinostat
- brentuximab vedotin (Adcetris®)
- cabazitaxel
- carfilzomib
- cytarabine (low dose) 100–200 mg/m$^2$
- docetaxel
- eribulin mesilate
- etoposide
- fluorouracil*
- gemcitabine
- gemtuzumab ozogamicin (Mylotarg®)
- inotuzumab ozogamicin (Besponsa®)
- methotrexate > 50 to < 250 mg/m$^2$
- mitomycin
- mitoxantrone
- paclitaxel
- paclitaxel nanoparticle albumin bound (Abraxane®)
- pegylated liposomal doxorubicin
- pemetrexed
- pentostatin
- teniposide[7]
- thiotepa
- topotecan
- trastuzumab-emtansine (Kadcyla®)

* fluorouracil continuous intravenous infusion (e.g. 1000 mg/m$^2$/day for 4 days) are considered minimal emetogenicity.

## Minimal

Risk of emesis in fewer than 10% of patients, includes:

- alemtuzumab
- asparaginase
- atezolizumab
- bevacizumab
- bleomycin
- blinatumomab
- bortezomib
- cemiplimab
- cetuximab
- cladribine
- cytarabine < 100 mg/m$^2$
- daratumumab
- dexrazoxane
- dostarlimab
- durvalumab
- fludarabine
- ipilimumab
- methotrexate ≤ 50 mg/m$^2$
- nivolumab
- obinutuzumab
- ofatumumab
- pegaspargase
- pembrolizumab
- pertuzumab
- polatuzumab vedotin (Polivy®)
- ramucirumab
- rituximab
- trastuzumab
- vinblastine
- vincristine
- vinorelbine

## Overview of antiemetics included in parenteral SRL regimens:

| | Acute emesis, day 1 (all orally ONE hour prior to chemotherapy) | | | | Delayed emesis (all orally ONCE daily) | | |
|---|---|---|---|---|---|---|---|
| | **Olanz** | **Aprep** | **Dex** | **Ondan** | **Olanz** | **Aprep** | **Dex** |
| **HIGH (except as specified below)** | 2.5 mg[a] + 2.5 mg prn | 125 mg | 12 mg | 8 mg[b] | 2.5 mg D2-4 + 2.5 mg daily prn | 80 mg D2,3 | 8 mg D2-4[c] |
| **HIGH – AC for breast cancer[d]** | 2.5 mg[a] + 2.5 mg prn | 125 mg | 12 mg | 8 mg[b] | 2.5 mg D2-4 + 2.5 mg daily prn | 80 mg D2,3 | NIL[e] |
| **HIGH – carboplatin AUC≥5** | | 125 mg | 8 mg | 8 mg[b] | | 80 mg D2,3 | 8 mg D2,3[f] |
| **HIGH - cisplatin ≤40mg/m² weekly[g]** | | 125 mg | 8 mg | 8 mg[b] | | 80 mg D2,3 | 4 mg D2,3[f] |
| **MEDIUM[h]** | | | 8 mg | 8 mg[b] | | | 8 mg D2,3[f] |
| **LOW[i]** | | | **Alternative:** 4 mg | **First choice:** 8 mg single dose | | | |
| **MINIMAL** | No antiemetics are included as a routine component of regimens. | | | | | | |
| **Rescue antiemetics [j]** | **domperidone** 10 mg orally THREE times daily when required for nausea and/or vomiting. **OR, if potential risk of additive QT prolongation** ***including*** **HEC regimens with olanzapine and ondansetron** **cyclIZINE** 50 mg[k] orally THREE times daily when required for nausea and/or vomiting. | | | | | | |

[a] Some centres may choose to omit pre-chemotherapy dose or advise patient to take the night before chemotherapy if patient has to drive to appointment.

[b] **AND** ondansetron 8 mg EIGHT hours after chemotherapy OR before bed.

[c] Dose and duration may be individualised at clinician's discretion.

[d] Combination of any anthracycline plus cyclophosphamide when used for breast cancer.

[e] Subsequent days of dexamethasone (days 2 to 4) are **not** included in the default regimens[1], may be given at clinician's discretion.

[f] This dose may be reduced or omitted at clinician's discretion.

[g] **HIGH – cisplatin ≤ 40 mg/m² weekly** includes weekly cisplatin, when used with radiation, and for regimens consisting of day 1 and 8 of a 21-day cycle.

[h] In addition to the inclusion of the above antiemetics for MEDIUM emetogenicity chemotherapy (MEC), the following statement is included in MEC regimens containing oxaliplatin: Women 50 years and under should be considered high risk for oxaliplatin-induced nausea and vomiting, so antiemetic prophylaxis regimen should include an NK1 (e.g. aprepitant 125 mg day 1 and 80 mg days 2 and 3) based on trial evidence.[1]

[i] Ondansetron 8 mg (single oral dose ONE hour prior to chemotherapy) is included as the default option for LOW SRL regimens to promote steroid-sparing. Given only a minor decrement in efficacy of 5-HT3 receptor antagonists compared with dexamethasone the consensus of the supportive care workshop members was that either option is appropriate. If a corticosteroid is required as part of premedication to prevent infusion related reactions (IRRs), it is included instead of ondansetron. The dose of dexamethasone is 4 mg unless higher is recommended for IRRs.

[j] The choice of rescue antiemetic may be substituted to reflect institutional policy or individual patient characteristics.

[k] Consider starting dose at 25 mg and increasing as tolerated/required.

## Oral SACT

- Evidence for emetogenic risk potential and the most appropriate nausea and vomiting prophylaxis for oral SACT is limited. The continuous administration of many oral SACT further complicates this and precludes the use of steroids.
- Consequently, no precise recommendations for antiemetic prophylaxis are available.
- All antiemetic prophylaxis included in SRL regimens for oral SACT should be considered in conjunction with patient characteristics, and on-going antiemesis prophylaxis should be individualised as appropriate.

### Medium to high

Risk of emesis in greater than 30% of patients, includes:

- avapritinib
- busulfan ≥ 4 mg/day
- cabozantinib
- crizotinib
- cyclophosphamide > 100 mg/m$^2$/day
- dabrafenib
- etoposide
- imatinib > 400 mg/day
- lenvatinib > 12 mg/day
- lomustine
- midostaurin
- mitotane
- niraparib
- olaparib
- procarbazine
- temozolomide > 75 mg/m$^2$/day
- vinorelbine

**Antiemetics are included as a routine component of Medium to high SRL regimens, as**

**ondansetron** 8 mg orally TWICE daily
***Either,*** ONE hour prior to chemotherapy and 8 to 12 hours after chemotherapy.
***Or,*** when required for nausea and/or vomiting.

***AND/OR***
**domperidone** 10 mg orally THREE times daily when required for nausea and/or vomiting.
***OR, if potential risk of additive QT prolongation***
**cyclIZINE** 50 mg* orally THREE times daily when required for nausea and/or vomiting.
*Consider starting dose at 25 mg and increasing as tolerated/required.

**The following statement/s is included under the Supportive Care Factors section of the regimen:**

**Either,** if *routine* ondansetron premedication is included in the SRL regimen definition:
"Emetogenicity: MEDIUM to HIGH—Routine antiemetic premedication may initially be required; an individualised approach is appropriate."

**OR,** if *no* routine antiemetic premedication is included in the SRL regimen definition:
"Emetogenicity: MEDIUM to HIGH—As required antiemetics may be recommended initially; an individualised approach is appropriate."

And for regimens containing **mitotane**:
"If daily antiemetics are required inadequate glucocorticoid replacement may be the likely cause of nausea and increased hydrocortisone replacement is warranted".

**Note:** Laxatives are included in regimens if appropriate as prophylaxis for $5HT_3$ constipation.

## Minimal to low

Risk of emesis in less than 30% of patients, includes (Note: hormone agents are not included):

- abemaciclib
- acalabrutinib
- afatinib
- alectinib
- axatinib
- binimetinib
- brigatinib
- busulfan < 4 mg/day
- capecitabine
- chlorambucil
- cobimetinib
- cyclophosphamide < 100 mg/m$^2$/day
- dasatinib
- encorafenib
- entrectinib
- erlotinib
- everolimus
- fludarabine
- gefitinib
- gilteritinib
- hydroxyurea
- ibrutinib
- imatinib ≤ 400mg/day
- ixazomib
- lapatinib
- lenalidomide
- lorlatinib
- melphalan
- mercaptopurine
- methotrexate
- neratinib
- nilotinib
- osimertinib
- palbociclib
- pazopanib
- pomalidomide
- ponatinib
- pralsetinib
- regorafenib
- ribociclib
- ripretinib
- ruxolitinib
- sorafenib
- sunitinib
- temozolomide ≤ 75 mg/m$^2$/day
- thalidomide
- tioguanine
- trametinib
- tretinoin
- tucatinib
- vemurafenib
- venetoclax
- vismodegib

No antiemetics are included as a routine regimen component of Minimal to low regimens.

The following statement is included under the Supportive Care Factors section of the regimen: "Emetogenicity: Minimal to low—Routine antiemetic premedication is not usually required; an individualised approach is appropriate."

Each cancer type working group chair has the final decision as to the requirement of antiemetics within an SRL regimen.

## References


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