CCLG guideline on the management of chemotherapy induced nausea and vomiting

March 2018

CCLG does not sponsor nor indemnify the treatment detailed herein. These clinical guidelines are provided by the CCLG Supportive Care Group to inform and for use at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations are based on current best practice and not what is necessarily proposed for any forthcoming clinical trial.

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EXECUTIVE SUMMARY

The CCLG supportive care group have compiled this national framework document based on excellent international guidelines with the aim of providing a comprehensive overview which may be taken to standardize therapy across CCLG Centers for the management of chemotherapy induced nausea and vomiting.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) are said to be the most documented distressing side-effects of childhood cancer treatment, potentially influencing compliance with future treatments if not managed appropriately (Wood et al. 2015). Managed incorrectly, they can lead to physical problems such as anorexia, malnutrition and dehydration, plus psychological complications that in turn may lead to anticipatory nausea and vomiting (Rodgers et al. 2012; Dewan, Singhal and Harit, 2010).

Nausea and vomiting are reflexes initiated by the body to expel toxic substances from the stomach and intestine (Navari, 2013). Emesis is co-ordinated by the vomiting Centre situated in the medulla which receives input from the chemoreceptor trigger zone (CTZ) found in the area postrema and is outside of the blood-brain barrier. It is simulated by circulating toxins or drugs such as chemotherapy. The CTZ possesses many $5HT_3$ receptors, NK1 receptors and Dopamine receptors (D2). The vomiting Centre is stimulated by drugs, smells, sights, emotions etc. as well as G.I input. CINV may result from chemo or CSF fluid acting directly on the CTZ, in the vomiting Centre but chemotherapy may also induce the release of serotonin and substance P from cells within the gastric mucosa.

The different stages of CINV are acute (0-24hrs after 1st dose); delayed (24hrs-5 days post chemotherapy) and anticipatory (prior to the start of chemotherapy). Physiological differences exist in acute and delayed CINV. Acute is mediated by the neurotransmitter serotonin, whereas delayed is mediated by substance P. Therefore optimal management of CINV may require targeting the peripheral pathways with a $5HT_3$ receptor antagonist and the central pathway with an NK1 receptor.

The provision of adequate preventative and responsive anti-nausea and vomiting therapies is key in all centers where children and treated with chemotherapy. The different centres have traditionally used their own guidelines, but not developed according to the recommendations of the NICE Guideline Methodology. An international collaboration, centred in the Canadian POGO group, developed a series of detailed evidence-based guidelines for the management of different phases of treatment-related nausea and vomiting. This document details the recommendations and explanatory notes where necessary to explain different decisions from the Canadian-led panel. The research and main linking explanations are found in the accompanying guideline documents.

METHODS

This guideline is a national framework document for local implementation. It relies on the work undertaken by the Canadian-led POGO group who developed three clinical practice guidelines for the prevention and management of chemotherapy-induced nausea and vomiting (CINV) in children.

The POGO group convened an international guideline panel to create a clinical practice guideline based on accepted best-practice methods (similar to those used by NICE). The group undertook a series of focused systematic reviews addressing management question in the prevention of CINV, and the treatment of breakthrough, refractory and anticipatory CINV. They then summarized this evidence and debated it, placing it in clinical context and developing recommendations. The guidelines were then subject to international stakeholder review before publication.

Now all phases of the management have been completed, the CCLG Supportive Care group has undertaken to summarize and contextualize in a UK framework to provide an up to date framework for local guidelines to be developed from. This involved the summarizing of the guidelines, discussion of the recommendations made within a UK licensing context, and providing a summary guide as an example for use. Recommendations were then circulated via the CCLG Guideline Development Group panel and feedback incorporated.

The CCLG Group noted that each centre may have subtle variations on their interpretation of the evidence, some driven by local commissioning or drug procurement processes, which make cost-effectiveness decisions different and the local guideline marginally different. The CCLG Group were also vey mindful of the necessarily poor quality of evidence that underlies the banding of drugs into emetogenic potential. Such data in children are drawn from small studies, often confounded by expectation and prophylactic antiemetics. As such, centre variations may occur. Centres with experience and disagreement with a classification system (such as the POGO system) are encouraged to publish their experience to support the advancement of the knowledgebase.

CCLG GROUP

The adaptation group consisted of: Dr Bob Phillips, Prof Faith Gibson, Mr. Pritesh Patel, Mrs. Eloise Neumann, Dr Amy Mitchell, Dr Geoff Shenton, Mrs. Ghazala Javid and Dr Hugh Bishop.

RECOMMENDATIONS: OVER-RIDING PRINCIPLES

CHILDREN AND YOUNG PEOPLE ABOUT TO UNDERTAKE CHEMOTHERAPY SHOULD HAVE THEIR CHEMOTHERAPY ASSESSED FOR EMETOGENICITY

Balancing the use of antiemetic against the chance of the chemotherapy causing problems is a key principle. A number of systems have been proposed; for this guideline the POGO-developed system will be used. It divides chemotherapy into four strata

- Highly emetogenic chemotherapy (HEC) includes Very highly emetogenic chemotherapy
- Moderately emetogenic chemotherapy (MEC)
- Low emetogenicity chemotherapy
- Minimal emetogenicity

CHILDREN AND YOUNG PEOPLE SHOULD HAVE THEIR SYMPTOMS OF NAUSEA AND VOMITING ASSESSED

There are a range of assessment tools for nausea and vomiting (see 'References'). These guidelines strongly advise using them within practice in order to improve patient care. No clear data supports the use of any one system over another, and with varied age ranges two scales may be preferred.

CHILDREN AND YOUNG PEOPLE ABOUT TO UNDERTAKE CHEMOTHERAPY SHOULD HAVE THEIR EMETOGENICITY-ASSESSED TREATMENT PRESCRIBED PRIOR TO CHEMOTHERAPY, ADAPTED TO THEIR OWN PERSONAL EXPERIENCE

While the evidence underpinning 'personalisation' of therapy is weak, it is common practice to use higher-level antiemetic's when a child or young person has experienced problems with nausea and/or vomiting previously. Good control is felt to reduce the chances of anticipatory, and breakthrough/refractory, nausea and vomiting in subsequent courses.

The source guidance expresses a preference for palonosetron in many areas. While this is based on current RCTs, the panel were concerned about the possible effects of recency bias (where more positive results are published more quickly) and the lack of clear cost-effectiveness. Combined with the weak evidence for the superiority of any other 5HT3 antagonist against any other, we recommendation the use of a 5HT3 antagonist (ondansetron) as in the 2012 guideline.

PROPHYLAXIS: VERY HIGHLY EMETOGENIC CHEMOTHERAPY

FOR CHILDREN AND YOUNG PEOPLE RECEIVING VERY HIGHLY EMETOGENIC CHEMOTHERAPY A COMBINATION OF 5HT3 ANTAGONIST (ONDANSETRON), DEXAMETHASONE AND APREPITANT SHOULD BE PRESCRIBED UNLESS THERE IS A CONTRAINDICATION

Contraindications include

- Age < 6 months (aprepitant, see table 4)
- Contraindication to dexamethasone (e.g. steroids included in treatment protocol). Refer to table 4.
- Drug interaction with aprepitant. Refer to table 4.

FOR CHILDREN AND YOUNG PEOPLE RECEIVING VERY HIGHLY EMETOGENIC CHEMOTHERAPY WITH A CONTRAINDICATION TO APREPITANT A COMBINATION OF 5HT3 ANTAGONIST (ONDANSETRON) AND DEXAMETHASONE SHOULD BE PRESCRIBED UNLESS THERE IS A CONTRAINDICATION

Contraindications include

- Contraindication to dexamethasone (e.g. steroids included in treatment protocol)

FOR CHILDREN AND YOUNG PEOPLE RECEIVING VERY HIGHLY EMETOGENIC CHEMOTHERAPY WITH A CONTRAINDICATION TO APREPITANT AND DEXAMETHASONE RECEIVE A) ONDANSETRON OR B) 5HT3 ANTAGONIST (ONDANSETRON) AND LEVOMEPROMAZINE OR C) 5HT3 ANTAGONIST (ONDANSETRON) AND METOCLOPRAMIDE OR D) 5HT3 ANTAGONIST (ONDANSETRON) AND NABILONE IN ADOLESCENTS.

PROPHYLAXIS: HIGHLY EMETOGENIC CHEMOTHERAPY

FOR CHILDREN AND YOUNG PEOPLE RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY A COMBINATION OF 5HT3 ANTAGONIST (ONDANSETRON) AND DEXAMETHASONE. APREPITANT SHOULD BE PRESCRIBED AT STEP 2OR 3 UNLESS THERE IS A CONTRAINDICATION

Contraindications include

- Age < 6 months (aprepitant, refer to table 4)
- Contraindication to dexamethasone (e.g. steroids included in treatment protocol). Refer to table 4.
- Drug interaction with aprepitant. Refer to table 4.

FOR CHILDREN AND YOUNG PEOPLE RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY WITH A CONTRAINDICATION TO APREPITANT A COMBINATION OF 5HT3 ANTAGONIST (ONDANSETRON) AND DEXAMETHASONE SHOULD BE PRESCRIBED UNLESS THERE IS A CONTRAINDICATION

Contraindications include

- Contraindication to dexamethasone (e.g. steroids included in treatment protocol)

FOR CHILDREN AND YOUNG PEOPLE RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY WITH A CONTRAINDICATION TO APREPITANT AND DEXAMETHASONE RECEIVE A) 5HT3 ANTAGONIST (ONDANSETRON) OR B) 5HT3 ANTAGONIST (ONDANSETRON) AND LEVOMEPROMAZINE OR C) 5HT3 ANTAGONIST (ONDANSETRON) AND METOCLOPROMIDE OR D) 5HT3 ANTAGONIST (ONDANSETRON) AND NABILONE IN ADOLESCENTS.

This group in particular have very weak evidence to guide a selection of therapies and require further research.

PROPHYLAXIS: MODERATELY EMETOGENIC CHEMOTHERAPY

FOR CHILDREN AND YOUNG PEOPLE RECEIVING MODERATELY EMETOGENIC CHEMOTHERAPY A COMBINATION OF 5HT3 ANTAGONIST (ONDANSETRON)AND DEXAMETHASONE SHOULD BE PRESCRIBED UNLESS THERE IS A CONTRAINDICATION

Contraindications include

- Contraindication to dexamethasone (e.g. steroids included in treatment protocol). See table 4.

FOR CHILDREN AND YOUNG PEOPLE RECEIVING MODERATELY EMETOGENIC CHEMOTHERAPY WITH A CONTRAINDICATION TO DEXAMETHASONE A COMBINATION OF 5HT3 ANTAGONIST AND APREPITANT SHOULD BE PRESCRIBED UNLESS THERE IS A CONTRAINDICATION

Contraindications include

- Age < 6 months
- Drug interaction with aprepitant, see table 4.

FOR CHILDREN AND YOUNG PEOPLE RECEIVING MODERATELY EMETOGENIC CHEMOTHERAPY WITH A CONTRAINDICATION TO APREPITANT AND DEXAMETHASONE RECEIVE A) ONDANSETRON OR B) 5HT3 ANTAGONIST (ONDANSETRON) AND LEVOMEPROMAZINE OR C) 5HT3 ANTAGONIST (ONDANSETRON) AND METOCLOPRAMIDE OR D) 5HT3 ANTAGONIST (ONDANSETRON) AND NABILONE IN ADOLESCENTS.

PROPHYLAXIS: LOW EMETOGENIC CHEMOTHERAPY

FOR CHILDREN AND YOUNG PEOPLE RECEIVING MODERATELY EMETOGENIC CHEMOTHERAPY A 5HT3 ANTAGONIST (ONDANSETRON) SHOULD BE PRESCRIBED

PROPHYLAXIS: MINIMALLY EMETOGENIC CHEMOTHERAPY

FOR CHILDREN AND YOUNG PEOPLE RECEIVING MINIMALLY EMETOGENIC CHEMOTHERAPY NO ROUTINE PROPHYLAXIS SHOULD BE PRESCRIBED

BREAKTHROUGH NAUSEA OR VOMITING

Breakthrough refers to the reoccurrence of significant nausea or vomiting after a period of acceptable control. Should a child or young person experience this, a 'next level up' approach to prophylaxis should be strongly considered on subsequent cycles.

FOR CHILDREN AND YOUNG PEOPLE RECEIVING MODERATE, LOW OR MINIMAL EMETOGENIC CHEMOTHERAPY, ESCALATION OF TREATMENT TO THE NEXT HIGHEST LEVEL OF INTENSITY SHOULD BE UNDERTAKEN

FOR CHILDREN AND YOUNG PEOPLE RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY, ADDITION OF A) LEVOMEPROMAZINE OR B) METOCLOPROMIDE OR C) LORAZEPAM (SEE TABLE 3 BELOW) TO THE TREATMENT SHOULD BE CONSIDERED

Refractory nausea or vomiting

Refractory refers to the continuation of significant nausea or vomiting without a period of acceptable control. Should a child or young person experience this, a 'next level up' approach to prophylaxis should be strongly considered on subsequent cycles.

For children and young people receiving moderate, low or minimal emetogenic chemotherapy, escalation of treatment to the next highest level of intensity should be undertaken

For children and young people receiving highly emetogenic chemotherapy, consider substitution of ondansetron for an alternative 5HT3 antagonist, for example granisetron (licenced iv/oral for children and patches for older children as per BNF).

For children and young people receiving highly emetogenic chemotherapy, who have previously been considered to have a contraindication to apprepitant, re-visiting that decision is strongly recommended

For children and young people who continue to suffer refractory nausea and /or vomiting, addition of a) levomepromazine infusion instead of bolus injection or b) lorazepam or c) acupressure to the treatment should be considered

Other alternative agents and approaches have been used. For example, hyoscine patches can be used for subsequent courses for refractory emesis failing to respond to other rescue therapy, applied the night before chemotherapy is due (at least 12 hours prior to chemotherapy). Others may use nabilone for refractory cinv for adolescents. Some data suggest the use of olanzapine; this is subject to ongoing study in North America.

Anticipatory nausea or vomiting

Anticipatory refers to significant nausea or vomiting prior to the delivery of chemotherapy. Research in this area is particularly weak. Lorazepam is used with good effect in centres. Refer to dosing information below in table 4. Some centers use ondansetron and / or levomepromazine up to 24hrs prior to chemotherapy.

For children and young people who develop anticipatory nausea and/or vomiting, psychological interventions such as hypnosis or systematic desensitization may be offered

For children and young people who develop anticipatory nausea and/or vomiting, low dose lorazepam refer to table 4, may be prescribed the day before, and from the first day of chemotherapy

Delayed nausea & vomiting

The above regimens are intended to prevent both acute and delayed nausea and vomiting. If additional agents are required, then aprepitant (cisplatin based regimens), granisetron and nabilone (adolescents) can be used.

Discharge medication:

For very high and high emetogenic regimes, ensure patients are discharged on at least 3 days of anti-emetics.

SOURCE GUIDELINES:

POGO Guidelines for the management of chemotherapy induced nausea and vomiting. http://www.pogo.ca/healthcare/practiceguidelines/

REFERENCES TO TOOLS:

Baxter, A., Watcha, M., Baxter, W., Leong, T. and Wyatt, M. (2011) Development and Validation of a Pictorial Nausea Rating Scale for Children. *Pediatrics*, 127(6), pp.1542–1549.

Dupuis, L.L., Taddio, A., Kerr, E., Kelly, A. and MacKeigan, L. (2006) Development and Validation of the Pediatric Nausea Assessment Tool for Use in Children Receiving Antineoplastic Agents. *Pharmacotherapy*, 26(9), pp.1221-1231.

Rhodes, V. and McDaniel, R. (1999) The Index of Nausea, Vomiting, and Retching: A New Format of the Index of Nausea and Vomiting. *Oncology Nursing Forum*, 26(5), pp.889-894.

Wood, J.M., Chapman, K. and Eilers, J.(2011) Tools for Assessing Nausea, Vomiting, and Retching. *Cancer Nursing*, 34(1), E14-E24.

OTHER REFERENCES:

Dewan, P., Singhal, S. and Harit, D. (2010) Management of Chemotherapy-Induced Nausea and Vomiting. *Indian Pediatrics,* 47, pp. 149-155.

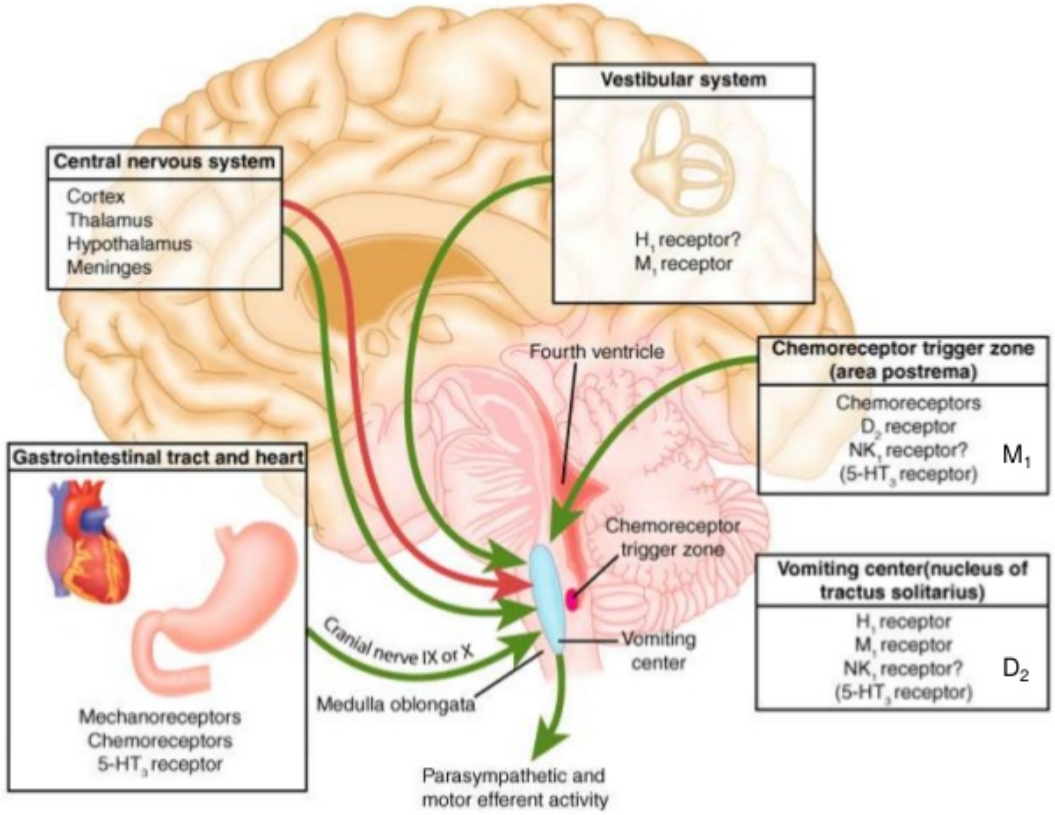
Kraukauer , E.L., Zhu, A.X., Bounds, B.C., Sahani, D., McDonald, K.R., and Brachfel, E. (2005) Case 6-2005: A 58- Year Old Man with Esophageal Cancer and Nausea and Vomiting and Intractable Hiccups. *New England Journal of Medicine,* 352(8), pp.817-825.

Navari, R. (2013) Management of Chemotherapy-Induced Nausea and Vomiting: Focus on Newer Agents and New Uses for Older Agents. *Drugs,* 73, pp.249-262.

Rodgers, C., Norville, R., Taylor, O., Poon, C., Hesselgrave, J., Gregurich, M. and Hockenberry, M. (2012) Children's Coping Strategies for Chemotherapy-Induced Nausea and Vomiting. *Oncology Nursing Forum,* 39(2), pp.202-209.

Wood, M., Hall, L., Hockenberry, M. and Borinstein, S. (2015) Improving Adherence to Evidence-Based Guidelines for Chemotherapy-Induced Nausea and Vomiting. *Journal of Pediatric Oncology Nursing,* 32(4), pp.195 –20.

FIGURE 1. SITE OF ACTIONS OF ANTI-EMETICS



Krakauer et al. (2005). New England Journal of Medicine, 352, 817.

TABLE. 1. SITE OF ACTIONS OF ANTI-EMETICS

	Dopamine$_2$-receptor antagonist (D2)	Histamine$_1$-receptor antagonist (H1)	Acetylcholine receptor antagonist	5-hydroxytryptamine receptor$_3$-receptor antagonist	5-hydroxytryptamine receptor$_2$-receptor antagonist	5-hydroxytryptamine receptor$_4$-receptor agonist	NK1 inhibitor (NK1)
Dexamethasone				+++			
Aprepitant							+++
Cyclizine		++	++				
Hyoscine hydrobromide			+++				
Levomepromazine	++	+++	++		+++		
Metoclopramide	++			+		++	
Ondansetron				+++			

Avoid Cyclizine and Metoclopramide together – Metoclopramide is a prokinetic (stimulates the gut) while Cyclizine slows it down. They can be used together in a palliative care scenario.

Levomepromazine covers actions of Metoclopramide, Cyclizine and Hyoscine but has a greater number of side effects.

TABLE 2. OVERALL APPROACH FLOW-CHART

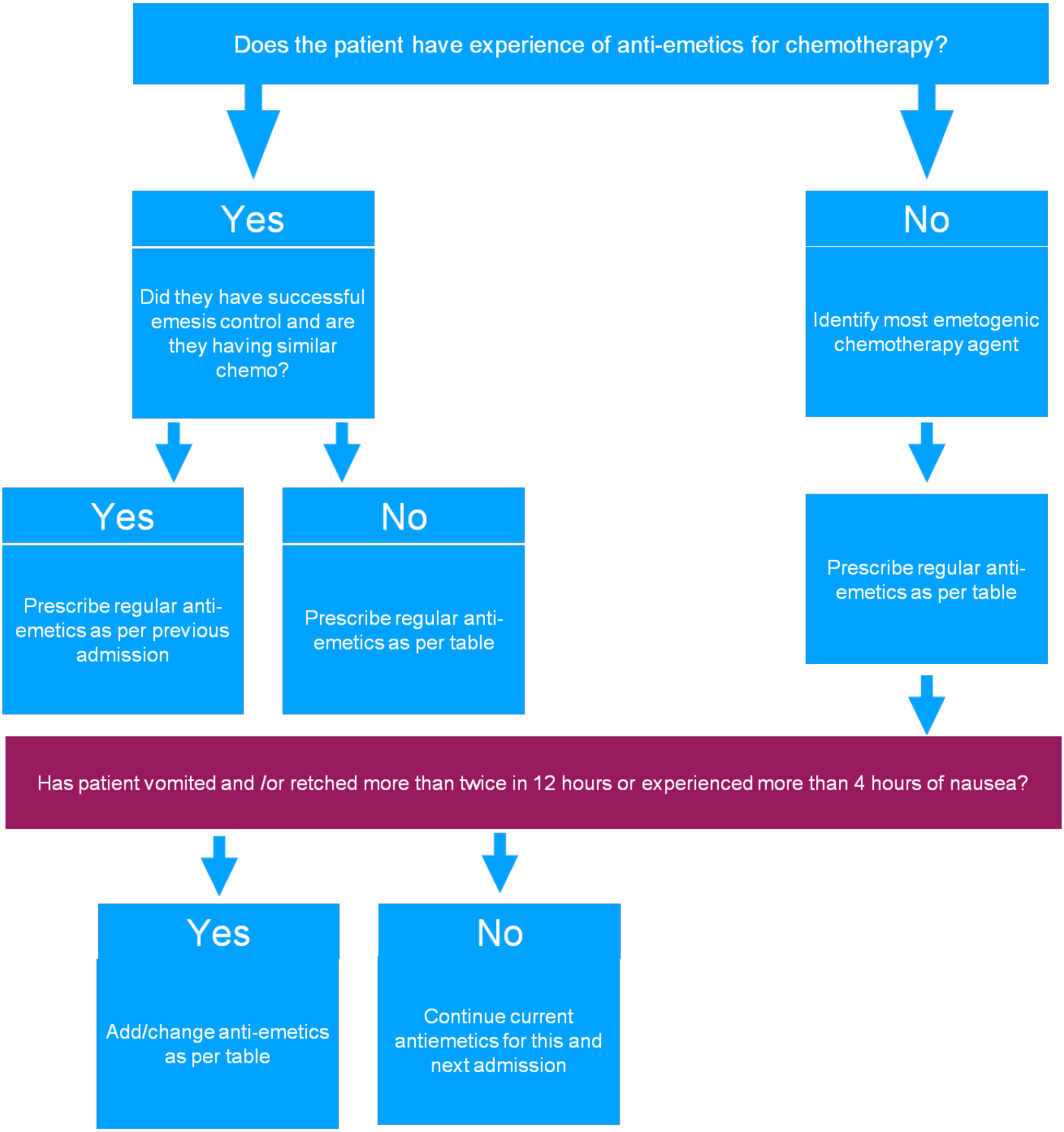


TABLE 3. EMETOGENICITY OF CHEMOTHERAPY (EXAMPLE)

Very High emetogenic potential (>90%)

Cisplatin Cyclophosphamide > 2g/m^2 Ifosfamide Melphalan Thiotepa *Combination chemotherapies:* Cyclophosphamide + anthracycline Cyclophosphamide + etoposide Etoposide + Ifosfamide Doxorubicin + Ifosfamide Cytarabine 300 mg/m^2 + etoposide Doxorubicin + methotrexate 5g/m^2	**Step 1: Cisplatin based regimen, ifosfamide or melphalan:** **Ondansetron** IV pre chemotherapy then IV/oral regularly *and* **Dexamethasone** IV/oral (if appropriate) *and* **≥6mths: Aprepitant** oral ONCE daily for 3 days. < 6 mths:levomepromazine instead of aprepitant. **Step 1: For non- cisplatin based regimen: Ondansetron and dexamethasone as above +/- levomepromazine (for <1yr to 17yrs)** **Step 2:** *Ensure all doses in step 1 have been optimised before moving onto step 2 and add* **Aprepitant** oral if not used in step 1 ***for subsequent cycles - >6mths old***]. Add levomepromazine for breakthrough if not given up front. See table 4 for aprepitant drug interactions and dexamethasone dose reduction. **Delayed**: give levomepromazine. Care with aprepitant and ifosfamide-see below in table 4. **Metoclopramide can be used instead of levomepromazine for > 1 year olds.**
High emetogenic potential (>90%)	
Dactinomycin Carboplatin Carmustine>250mg/m2 Cyclophosphamide 1g/m^2 - 2g/m^2 Cytarabine 3g/m^2/dose Dacarbazine Methotrexate ≥12 g/m^2	**Step 1:** **Ondansetron** IV pre chemotherapy then IV/oral regularly *and* **Dexamethasone** IV/oral (if appropriate) **Step 2:** *(Ensure all doses in step 1 have been optimised before moving onto step 2)* *Add* Levomepromazine IV/oral if not used in step 1 [add **Aprepitant** oral if not used in step 1 ***for subsequent cycles – > 6mths old***]. Refer to table 4 for aprepitant drug interactions and Dexamethasone dose reduction. **Step 3:** Consider levomepromazine infusion. [Add **Aprepitant** oral if not used in step 1 ***for subsequent cycles – for > 6mths olds).*** **Metoclopramide can be used instead of levomepromazine for > 1 year olds.** Delayed:Dexamethasone (if appropriate) iv/oral and metoclopramide (up to 5 days after chemotherapy completed)

TABLE 3 CONTINUED: EMETOGENICITY OF CHEMOTHERAPY

Moderate emetogenic potential (30-90%)

Aldesleukin Arsenic trioxide Azacitidine Cladribine Clofarabine Cyclophosphamide < 1g/m^2 Cytarabine >200mg/m^2 to <3g/m^2	Daunorubicin Daunorubicin liposomal Docetaxel Doxorubicin Etoposide Epirubicin Idarubicin Imatinib Inotuzumab	Irinotecan Lomustine Methotrexate ≥1g/m^2 to <12g/m^2 Mitoxantrone Oxaliplatin> 75mg/m2 Procarbazine Temozolomide Treosulfan	**Step 1:** **Ondansetron** IV pre chemo then IV/oral regularly +/- dexamethasone. If c/I to steroids prescribe levomepromazine instead/metoclopramide. **Step 2:** *Add* Dexamethasone (if appropriate) mostly at step 2 than step1). Then add l**evomepromazine** IV/oral if not already added or metoclopramide [Consider **Dexamethasone IV/oral** for subsequent courses if appropriate) **Delayed:** Dexamethasone(if appropriate) and metoclopramide

Low emetogenic potential (<30%)

Amsacrine ATG Bortezomib Busulfan Capecitabine CH14.18 Antibodies Cyclophosphamide <300 mg/m^2 Cytarabine <200 mg/m^2 Fludarabine 5-fluorouracil Gemcitabine	Gemtuzumab Hydroxyurea Intrathecals Nilotinib Paclitaxel Topotecan Vinblastine/ Vincristine Vindesine Vinorelbine	**Step 1:** Use prn **Ondansetron** **Step 2:** **Ondansetron** oral/IV regularly

TABLE 3 CONTINUED: EMETOGENICITY OF CHEMOTHERAPY		
Minimal emetogenic potential (min) <10%		
Alemtuzumab Asparginase Bevacizumab Bleomycin Chlorambucil Dasatinib Lenalidomide Mercaptopurine	Methotrexate< 1g/m^2 Nelarabine Rituximab Sorafenib Sunitinib Temsirolimus Thalidomide Thioguanine	**Step 1** : No antiemetics required unless previous history of emesis. If previous history, use **Ondansetron**.
Anticipatory Nausea and Vomiting		
Anticipatory refers to significant nausea or vomiting prior to the delivery of chemotherapy.		**Lorazepam oral:** Give one dose evening before and one dose 1 hr before starting chemotherapy

Very High

Step 1:

Cisplatin based regimen or melphalan:

Ondansetron IV pre chemotherapy then IV/PO regularly *and*

Dexamethasone IV/oral (if appropriate) *and*

<1yr-5yrs: levomepromazine

≥6mths: Aprepitant oral; ONCE daily for 3 days.

For non- cisplatin based regimen:

Ondansetron and dexamethasone as above +- levomepromazine

Step 2:

Ensure all doses in step 1 have been optimised before moving onto step 2.

add **Aprepitant oral** if not used in step 1 ***for subsequent cycles – all age groups***].

Add levomepromazine for breakthrough if not given up front.

Delayed: give levomepromazine. Care with aprepitant and ifosfamide-see table 4 below.

High

Step 1:

Ondansetron IV pre chemotherapy then IV/oral regularly *and*

Dexamethasone IV/oral (if appropriate)

Step 2:

(Ensure all doses in step 1 have been optimised before moving onto step 2)

Add Levomepromazine IV/PO if not used in step 1

[add **Aprepitant oral** if not used in step 1 ***for subsequent cycles – all age groups***]

Step 3:

Consider levomepromazine infusion. [Add **Aprepitant oral** if not used in step 1 ***for subsequent cycles – all age groups***

Moderate

Step 1:

Ondansetron IV pre chemotherapy then IV/oral regularly +/- dexamethasone. If c/I to steroids prescribe levomepromazine instead.

Step 2:

Add l**evomepromazine** IV/oral if not already added. Dexamethasone (if appropriate) mostly at step 2 than step1

[Consider **Dexamethasone IV/oral** for subsequent courses if appropriate)

Low/Minimum

Step 1:

No anti-emetics for minimum otherwise ondansetron prn for low

Step 2:

Ondansetron oral/IV regularly

TABLE 4. ANTI-EMETICS RECOMMENDED DOSAGES AND USAGE INSTRUCTIONS *(ALPHABETICAL)*

DRUG : Aprepitant

Drug class:

NK1 receptor antagonist

Formulations:

125mg, 80mg capsule, 125mg powder for oral suspension

INDICATION:

Treat and prevent acute and delayed CINV for cisplatin regimens

Drug dose and route:

Administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, administer in the morning

Weight	Day 1	Day 2	Day 3
<6kg	Not recommended for <6 months old		
6kg–7.9kg	25mg	15mg	15mg
8kg–9.9kg	30mg	20mg	20mg
10kg–11.9kg	35mg	25mg	25mg
12kg–14.9kg	45mg	30mg	30mg
15kg–19.9kg	60mg	40mg	40mg
20kg–24.9kg	75mg	50mg	50mg
25kg–29.9kg	90mg	60mg	60mg
30 kg and above	125mg	80mg	80mg

Side effects:

Hiccups, headache, decreased appetite, cough, neutropenia (slightly prolonged compared to without aprepitant).

Comments:

NB: Can increase **Ifosfamide** mediated neurotoxicity and **Irinotecan** toxicity. Monitor closely.

Caution in patients receiving concomitant substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range. Also p450 2c9 inducer.

Avoid aprepitant with the following:pimozide, terfenadine and St John's Wort.

Caution with the following as they may affect the aprepitant level and efficacy: ketoconazole, Itraconazole, voriconazole, posaconazole, ciclosporin,tacrolimus, sirolimus, everolimus, irinotecan and clarithromycin.

Aprepitant may reduce the efficacy of warfarin. Also reduces the efficacy of hormonal contraception during and for 28 days after its use.

Dose of oral dexamethasone must be reduced by 50% .

Drug: Cyclizine

Drug class:

Antihistamine

Formulations:

50mg tablets, IV injection

INDICATION:

For the purpose of this guidelines use for emesis of raised intracranial pressure. Palliative care, irradiation sickness and opiate induced vomiting.

Drug dose and route:

IV/Oral:

1 month–5 years	**500microgram-1mg/kg up to 3 times daily (Max 25mg/dose)** **Prescribe to the nearest 5mg.**
6–11 years	**25mg up to 3 times daily**
12 years+	**50 mg up to 3 times daily**

Continuous IV or SC Infusion:

1–23 months	**3mg/kg over 24 hours**
2–5 years	**50mg over 24 hours**
6–11 years	**75mg over 24 hours**
12–17 years	**150mg over 24 hours**

Side effects:

Drowsiness, Dry mouth

Blurred vision

Urinary retention

Restlessness

Insomnia, Tachycardia

Drug induced rash

Extrapyramidal side effects rare

Comments:

Avoid using with Hyoscine and Levomepromazine

For continuous IV or SC infusion – dilute with Glucose 5%, water for injection or normal saline0.9%.

Crush the tablets and disperse in water prior to administration.

<table>
<tr>
<td><u>Drug: Dexamethasone</u>

Drug class:

Corticosteroid

Formulations:

2mg tablets/2mg soluble tablet

0.5mg tablets

2mg/5mL liquid

IV injection

Indication:

Effective for delayed emesis and acute CINV</td>
<td><u>Drug dose and route:</u>

IV/Oral:

Loading dose 8mg/m² (Max single dose 12mg). Then:

<table>
<tr><th>SA m²</th><th>IV/Oral Dose</th></tr>
<tr><td>≤ 0.6m²</td><td>2mg TWICE a day</td></tr>
<tr><td>> 0.6m²</td><td>4mg TWICE a day</td></tr>
<tr><td>>1.2m2</td><td>8mg TWICE a day</td></tr>
</table>
Or prescribe 2.5mg-5mg/m2 up to Three times a day

Prescribe TWICE daily doses early morning and afternoon to reduce insomnia

(E.g. 5am and 4pm). Frequency can be increased to TDS.</td>
<td><u>Side effects:</u>

Adrenal suppression

Gastric irritation

Osteoporosis

Weight gain, insomnia

Mood and behavioural problems</td>
<td><u>Comments:</u>

Give 1st dose with Ondansetron, before chemotherapy. For maximum of 5 days

IV Dose should be infused.

Dose of dexamethasone must be halved when used in combination with Aprepitant.

Contra-indicated: Brain tumour patients and those already on steroids (allogenic BMT, SCT, and ALL) & those on mifamurtide. Caution in osteosarcoma patients (discuss with the consultant).</td>
</tr>
<tr>
<td><u>Drug:Granisetron patch</u> 3.1mg/24 hours

Indication: treat and prevent acute and delayed CINV</td>
<td><u>Drug dose and route:</u>

12 years -18yrs

Apply 1 patch 24-48 hrs. Before chemotherapy due.

Iv and oral doses for granisetron for those trusts still able to prescribe as per BNFc</td>
<td><u>Side effects:</u>

Constipation, headache, rash.

Transient increase in liver enzymes.</td>
<td><u>Comments:</u>

Patch can be kept on for 7 days

Remove at least 24 hours after chemotherapy has been completed.

Not licensed in children Only consider for nausea and vomiting induced by cytotoxic chemotherapy for planned duration of 3–5 days where oral antiemetics cannot be used.</td>
</tr>
</table>

<table>
<tr>
<td><u>Drug:</u>

<u>Hyoscine Hydrobromide</u>

Drug class:

Anticholinergic/Antimuscarinic

Formulations:

Transdermal Patch 1mg/72 hrs.

Indication: refractory CINV</td>
<td><u>Drug dose and route:</u>

Topically:

Will take up to 6 hours to work

<table>
<tr><td>1 month – 2 years</td><td>1/4 of a patch every 72 hours</td></tr>
<tr><td>3 – 9 years</td><td>1/2 of a patch every 72 hours</td></tr>
<tr><td>10 years+</td><td>1 patch every 72 hours</td></tr>
</table>
</td>
<td><u>Side effects:</u>

Drowsiness

Dry mouth

Dizziness

Blurred vision

Difficulty with micturition</td>
<td><u>Comments:</u>

Avoid using with Cyclizine, metoclopramide and Levomepromazine

Apply to a clean, dry, hairless area of skin behind the ear, avoiding any cuts or irritation. Wash hands after applying and the skin area after removal.

Scopaderm® patches can be cut.</td>
</tr>
</table>

Drug:

Levomepromazine

Drug class:

Phenothiazine

Formulations:

6mg tablet, 25mg Tablets

(tablets may be halved and dispersed)

IV Injection

Indication:

Delayed emesis, refractory and breakthrough CINV

Useful in vomiting due to raised intracranial pressure

Drug dose and route:

Oral

1 month – 11 years	**50-200microgram/kg once or twice a day.** Dose may be increased as necessary and as tolerated. Max 1mg/kg/dose once or twice a day (max 25mg/dose)
12-17 years	**3- 6.25 mg once or twice a day.** Dose may be increased as necessary and as tolerated. Max 25 mg twice daily.
Dose rounding Important as no liquid formulation available	**Dose doses less than 3mg** – Prescribe to the nearest 0.5mg. Disperse one 6mg tablet in 6mL of water and give proportion. **Doses greater than 3mg** – round to nearest 3mg or 12.5mg. Liquid can be manufactured in some centers.

Slow IV Infusion: over 30 minutes

25-100microgramg/kg TWICE daily or daily

Continuous IV or SC Infusion:

1 month – 11 years	Continuous infusion 100-400microgram/kg in 24 hrs. Maximum 25mg/24 hours
12-17 years	**5mg to 25mg over 24 hours** increasing as necessary to a max of 25mg/24 hours

Side effect:

Somnolence

Asthenia

Dry mouth

Hypotension

Sedation

Site reaction

constipation

Comments:

Avoid using with Cyclizine, Hyoscine and metoclopramide

Avoid use in hepatic impairment.

Reduce dose in renal impairment.

Care in patients receiving ifosfamide since sedation may mask signs of encephalopathy.

Drug: **Lorazepam** Drug class: *Benzodiazepine* Formulations: 1mg &2mg tablets (tablets may be halved), IV Injection **Indication:** Anticipatory nausea and vomiting. Breakthrough and refractory CINV.	**Drug dose and route:** **Slow IV bolus/Oral:** **50micrgram-100microgram/kg (max 4mg) every 8–12 hours** For anticipatory nausea and vomiting, give one dose evening before and one dose 1 hour before starting chemotherapy.	Side effects: Drowsiness Amnesia Confusion and ataxia Pain with IV injection	Comments: Care in patients receiving ifosfamide since sedation may mask signs of encephalopathy

Drug:

Metoclopramide

Drug class:

Dopamine antagonist

Formulations:

10mg Tablets

5mg/5mL liquid

10mg/2ml Injection

Indication:

Prevent delayed nausea and vomiting. Effective for severe intractable vomiting due to radiotherapy.

Drug dose and route:

IV/Oral: Prevention of delayed chemotherapy-induced nausea and vomiting

150microgram/kg THREE times a day – dose banded as per below

Prescribe for as short a duration as possible and review regularly

Contraindicated in children <1 year Maximum 10mg per dose TDS. See MHRA alert 2013. Consultant decision.

Weight	Oral Dose	IV Dose
10–14.9kg	1mg	1mg
15–19.9kg	2mg	2mg
20–29.9kg	2.5mg	2.5mg
30–60kg	5mg	5mg
>60kg	10mg	10mg

Side effects:

Extrapyramidal effects

Hyperprolactinemia

Drowsiness

Restlessness

Comments:

Should be used after levomepromazine failed for maximum 5-days. **Review with consultant before using.**

Reduce dose in renal and hepatic impairment

Use with caution with cyclizine and hyoscine – will reduce prokinetic effects

Treat dystonic reactions with IV bolus of **PROCYCLIDINE:**

<2 yrs.	0.5-2mg as a single dose
2–10 yrs.	2-5mg as a single dose
>10 yrs.	5-10mg as a single dose

Usually effective in 5-10 min but may take up to 30min

Drug: **Nabilone** **Preparations:** Capsule 1mg **Indication**: For delayed and refractory CINV in adolescents.	Drug dose and route: Oral >30kg 1mg three times a day	Side effects: dizziness, drowsiness, behavioral alterations, dry mouth, ataxia, postural hypotension. Hallucinations, euphoria and other psychotic reactions in some patients. Patients and carers should be made aware of possible changes in mood and other adverse behavioural effects.	Comments: A cannabinoid drug with central action. Used in adolescents when refractory to dexamethasone and ondansetron. It is used for acute, delayed and refractory emesis. Used for high & very high when 1st, 2nd & 3rd line failed for subsequent cycles. Start the night before, duration of chemo and until 48 hours after chemo. Do not use with levomepromazine and lorazepam.

Drug:

Ondansetron

Drug class:

$5HT_3$ antagonist

Formulations:

4mg tablets

8mg tablets

4mg/8mg orodispersible film*

4mg/5mL liquid

IV 2mg/ml

Sublingual melts:4mg&8mg

Drug dose and route:

IV/Oral:

5mg/m^2 TWICE TO THREE times a day (Max 8mg per dose) – dose banding can be used in your trust as per below

Weight	SA m^2	Oral Dose	IV Dose
4–4.9kg	0.26–0.29	1mg	1.5mg
5–6.9kg	0.30–0.37	2mg	1.5mg
7–8.9kg	0.38–0.45	2mg	2mg
9–11.9kg	0.46–0.55	2mg	2.5mg
12–16.9kg	0.56–0.70	4mg	3mg
17–23.9kg	0.71–0.89	4mg	4mg
24–29.9kg	0.9–1.09	4mg	5mg
30–38.9kg	1.1– 1.2	6mg	6mg
>39	>1.2	8mg	8mg

Side effects:

Constipation

Headache

Flushing

Occasional diarrhea

Comments:

*Use **Orodispersible film** if possible as it is cheaper than liquid ondansetron for patients with SA >0.56m^2 or wt. >12kg.

Each film is a 4mg dose and it cannot be halved.

Reduce dose in moderate or severe hepatic impairment

Do not use with drugs that prolong QT interval

Less effective for delayed emesis use metoclopramide

Drug: **Procyclidine** Anticholinergic Prevent & treat acute dystonic reactions Preparation: 5mg/ml injection 5mg/5ml liquid SF, 2.5mg/5ml 5mg tablet	**Drug dose and route:** Dystonias: 7-12 years 1.25mg 8hourly >12-18yrs 2.5mg 8 hourly **Acute dystonia doses: single doses** < 2yrs 500microgram to 2mg 2-10 yrs. 2-5mg >10 yrs. 5-10mg	Side effects: Anti-cholinergic	Comments: Effective in 5-10mins but may take up to 30 mins Contra-indicated in Gastro-intestinal obstruction; myasthenia gravis. Caution in liver impairment