**Guideline for the Prevention of Acute Chemotherapy-induced Nausea and Vomiting**

**in Pediatric Cancer Patients: A Focused Update**

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**Abstract**

This update of the 2013 clinical practice guideline provides clinicians with guidance regarding the use of aprepitant and palonosetron for the prevention of acute chemotherapy-induced nausea and vomiting (CINV) in children. The recommendations were based on three systematic reviews. Substantive changes were made to the guideline recommendations including: the inclusion of palonosetron to the 5-HT3 antagonists recommended for children receiving highly emetogenic chemotherapy (HEC) and the recommendation of aprepitant for children ≥6 months of age receiving HEC. To optimize CINV control in children, future work must focus on closing critical research gaps.

**Introduction**

This focused update of the Pediatric Oncology Group of Ontario (POGO) 2013 Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients[1] was prompted by the recent publication of several pediatric randomized controlled trials evaluating aprepitant and palonosetron for the prevention of acute chemotherapy-induced nausea and vomiting (CINV). The overall aim of the guideline update is to optimize acute CINV control in children by providing guidance on the use of aprepitant and palonosetron to health care professionals who care for children with cancer. This guideline update may be of most interest to physicians, pharmacists, nurse practitioners, physician assistants and nurses. Optimal acute CINV control is defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for CINV prevention and no nausea-related change in the child’s usual appetite and diet on each day that chemotherapy is administered and for 24 hours after administration of the last chemotherapy agent of the chemotherapy block. Nausea is defined as the subjective sensation that one might vomit. The recommendations of this guideline update, like those of the previous guideline, are most applicable to chemotherapy-naïve cancer patients 1 month to 18 years of age. This update is focused on aprepitant and palonosetron and is provided pending a full guideline update.

**Methods**

Guideline Panel and Health Questions Addressed: The membership of the inter-professional POGO CINV Guideline Panel and conflict of interest (COI) declarations are provided in the online Supplementary Material Section A. No panel member had a COI that precluded participation. Health questions addressed in the 2013 guideline were reviewed and those that were relevant to this update were brought forward (Table 1).

Evidence Identification and Review: Three systematic reviews were conducted in consultation with a library scientist. The database search strategies, eligibility criteria and PRISMA flowcharts for each systematic review are provided in the online Supplementary Material Sections B-D. Two reviewers independently screened the titles and abstracts; evaluated the full-text of potentially relevant citations for eligibility and assessed risk of bias of included randomized trials using the Cochrane Collaboration tool.[2] Disagreements were resolved by a third reviewer. The three systematic reviews were:

1. Primary studies of aprepitant or palonosetron describing the rate of CINV control in children;
2. Meta-analyses evaluating palonosetron compared to other 5-hydroxytryptamine type 3 (5-HT3) antagonists for acute CINV prophylaxis in adults or children.
3. Primary studies describing palonosetron pharmacokinetic disposition.

 Evidence tables were compiled to summarize the findings of all included studies and were organized by chemotherapy emetogenicity (minimal, low, moderate and high) based on the POGO pediatric emetogenicity classification guideline[3] or, when this was not possible, by the chemotherapy emetogenicity classification used by the study authors. For studies where subjects received chemotherapy of different levels of emetogenicity (e.g. highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC)) and where study investigators did not report CINV control rates for these two groups separately, the extracted data were categorized under the lower emetogenicity level.

 Evidence summaries of adverse events were restricted to those reported in included randomized trials since adverse event reporting in these studies was more likely to be completed in a systematic fashion.

 Recommendations were developed based on the evidence identified from the systematic reviews and refined through panel discussions. The associated potential health benefits versus risks were considered for each recommendation. Strong recommendations (i.e. most individuals should receive the recommended intervention)[4] were made when the panel was certain that the potential benefits of the recommended intervention outweighed the risk of harm. Differences in opinion were resolved by consensus. The quality of evidence and strength of recommendations were assessed using the Grades of Recommendation Assessment, Development and Evaluation system[5,6] by one author and confirmed through discussion by the remaining panel members. If consensus was unable to be reached, a decision was made by the majority of panel members by a vote.

External review: A draft version of the guideline was reviewed by international experts in pediatric CINV. The committee considered the responses received before finalizing the recommendations. (Supplementary Tables S15-16).

Guideline Updates: A comprehensive update to the POGO 2013 Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients[1] is planned for 2018.

**RESULTS**

 Results of the searches for the three systematic reviews and their respective evidence tables are presented in the online Supplementary Material (Supplementary Fig. S1, Supplementary Tables S2-S8; Supplementary Fig. S2, Supplementary Table S10; Supplementary Fig. S3, and Supplementary Table 12).

**CINV control**: The systematic review of primary papers describing the chemotherapy-induced vomiting (CIV) control rate in children receiving aprepitant or palonosetron identified 2,374 references. Of these, 70 were reviewed in full-text and 12 met the criteria for inclusion (aprepitant: [7-11]; palonosetron: 7[12-18]) (Supplementary Fig.S1). No evidence regarding the use of aprepitant or palonosetron in children receiving chemotherapy of low or minimal emetogenicity was identified.

 Between-screener agreement regarding inclusion of full-text articles was almost perfect (kappa = 90.6, 95% CI 77.7 to 100%).[19] Tables 2 and 3 summarize the characteristics of included studies. An assessment of the risk of bias in randomized studies is provided in Supplementary Table S8. Data extracted with respect to CINV control and adverse events are presented in Supplementary Tables S2-S7.

**Adverse events:** Two and four fully published, randomized controlled pediatric trials evaluating aprepitant[7,10] (202 children) and palonosetron [12,14,16,17] (421 children), respectively, were included in the adverse event summary. The incidence of drug-related adverse events reported in these trials was less than 5%; serious drug-related adverse events were reported even less frequently (Supplementary Tables S6-S7). No adverse events attributed to aprepitant or palonosetron prompted drug discontinuation. Furthermore, adverse events associated with the use of either agent resolved quickly and none were fatal. The panel therefore considered both aprepitant and palonosetron to be associated with a low risk of acute harm.

**CINV control with palonosetron versus other 5-HT3 antagonists**: A single meta-analysis of randomized trials conducted predominantly in adults met criteria for inclusion in the systematic review evaluating the efficacy of palonosetron versus other 5-HT3 antagonists for the prevention of acute CINV.[20] (Supplementary Table S10)

**Pharmacokinetic disposition of palonosetron**: Twenty articles evaluating palonosetron pharmacokinetics were included in this systematic review.[21-40] (Supplementary Table S12)

 The recommendations for the prevention of acute CINV in children receiving HEC or MEC are summarized in Table I and Fig. 1. The rationale for each revised recommendation is provided below.

**Health Question #1: What pharmacological interventions provide optimal control of acute CINV in children receiving highly emetogenic chemotherapy (HEC)?**

**Recommendation 1.1** We recommend that children ≥6 months old receiving HEC which is not known or suspected to interact with aprepitant receive:

granisetron or ondansetron or palonosetron plus dexamethasone\* plus aprepitant.

*Changes from 2013: Aprepitant recommended for children ≥6 months and inclusion of palonosetron as an alternate 5-HT3 antagonist.*

\*see recommendations 1.4, 1.5 and 1.6 for information regarding children who cannot receive dexamethasone

**Recommendation 1.2** We recommend that children <6 months old receiving HEC receive:

granisetron or ondansetron or palonosetron plus dexamethasone.

*Change from 2013: Inclusion of palonosetron as an alternate 5-HT3 antagonist.*

**Recommendation 1.3** We recommend that children ≥6 months receiving HEC which is known or suspected to interact with aprepitant receive:

granisetron or ondansetron or palonosetron plus dexamethasone.

*Change from 2013: Inclusion of palonosetron as an alternate 5-HT3 antagonist.*

Aprepitant: Three pediatric randomized trials [7,10,11] evaluating the use of aprepitant met criteria for inclusion in the evidence used to develop recommendation 1.1. The first compared acute CIV control rates provided by ondansetron plus dexamethasone plus either aprepitant or placebo (48% vs 12%; p<0.001).[10] The second described complete CIV control rates in a subset of 200 children receiving HEC and ondansetron with/without dexamethasone plus either aprepitant or placebo for CINV prophylaxis (65% versus 51%; panel calculated p = 0.047).[7] The dexamethasone dose administered in this trial was not standardized and the proportion of children in this subset who received it is unknown. The third was a small crossover study that found no difference in CIV control rates in children receiving ondansetron plus dexamethasone plus either olanzapine or aprepitant (77% vs. 79%; panel calculated p=1).[11]

Palonosetron: A meta-analysis[20] and three pediatric randomized trials [12,16,17]informed these recommendations. The meta-analysis[20] synthesized the findings of 16 randomized controlled trials involving 6,083 adults and children who received HEC or MEC. Complete acute CIV control rates observed in patients receiving dexamethasone plus palonosetron or another 5-HT3 antagonist were comparable (odds ratio: 1.14; 95% confidence interval: 0.88-1.49).

 Two of the pediatric trials evaluated palonosetron monotherapy versus ondansetron monotherapy.[16,17] One observed similar rates of complete acute CIV control between study arms (70% vs. 65%; p=0.633)[17] whereas the second observed improved CIV control in the palonosetron study arm (92% vs. 72%; panel calculated p = 0.0174).[16] The third pediatric trial used a non-inferiority design. The use of dexamethasone in this trial was discretionary and, if given, the dose was not standardized. High-dose palonosetron was found to be non-inferior to ondansetron with respect to complete acute response rates in children receiving HEC or MEC.[12] Although not a study aim, the rates of complete acute response in children receiving HEC were: high-dose palonosetron: 43%; low-dose palonosetron: 51% and ondansetron: 41%.

Summary: In developing these recommendations, the trial demonstrating increased complete CIV control rates in children given aprepitant in combination with a 5-HT3 antagonist and dexamethasone was valued highly by the panel.[10] Aprepitant is not recommended for use in children less than 6 months of age because it has not been studied in this age group for the purpose of CINV prophylaxis. Aprepitant, a moderate CYP3A4 inhibitor, continues to be recommended for use in conjunction with chemotherapy which is not known or suspected to interact. A list of antineoplastic agents which are CYP3A4 substrates is included as a supplementary table in the 2013 clinical practice guideline.[1] In recommending palonosetron as a possible 5-HT3 antagonist, high value was placed on the meta-analysis which indicated that complete CIV control rates were comparable in adult and pediatric patients receiving different 5-HT3 antagonists in combination with dexamethasone.[41] The findings of non-inferiority between high-dose palonosetron and ondansetron with/without dexamethasone were also considered.[12]

**Recommendation 1.4** We recommend that children ≥6 months old receiving HEC which is not known or suspected to interact with aprepitant and who cannot receive dexamethasone for CINV prophylaxis receive:

palonosetron plus aprepitant.

*Changes from 2013: Addition of aprepitant and recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of chlorpromazine and nabilone.*

**Recommendation 1.5** We suggest that children <6 months old receiving HEC and who cannot receive dexamethasone for CINV prophylaxis receive:

palonosetron.

*Changes from 2013: Recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of chlorpromazine and nabilone.*

**Recommendation 1.6** We suggest that children receiving HEC which is known or suspected to interact with aprepitant and who cannot receive dexamethasone receive:

palonosetron.

*Changes from 2013: Recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of chlorpromazine and nabilone.*

Aprepitant: While no study that met criteria for inclusion in this systematic review specifically evaluated CINV control following prophylaxis with a 5-HT3 antagonist plus aprepitant without dexamethasone in children receiving HEC, one trial, mentioned previously, included an unknown number of children who received this regimen.[7] The higher complete CIV control rates in children receiving ondansetron with/without dexamethasone plus either aprepitant or placebo observed in this trial (65% versus 51%; panel calculated p = 0.047) indirectly supports the use of a 5-HT3 antagonist plus aprepitant.

Palonosetron: These recommendations were informed by the previously described adult-focused meta-analysis[41] and three pediatric randomized trials[12,16,17]. The meta-analysis[20] observed a greater likelihood of preventing acute CIV in patients receiving palonosetron alone compared to monotherapy with other 5-HT3 antagonists (odds ratio: 1.52; 95% confidence interval 1.15-2.02). Two of the pediatric randomized trials,[16,17] one of which was included in the meta-analysis,[16] compared palonosetron monotherapy versus ondansetron monotherapy. These trials differed substantially in their definitions of the acute phase. The trial which likely enrolled children receiving multiple day therapy[17] reported complete CIV control rates achieved during the entire acute phase (i.e. greater than 24 hours in duration). No difference was observed between study arms (palonosetron vs ondansetron: 70% vs 65%; p=0.633). In contrast, the second trial[16] compared CIV control rates in the first 24 hours of chemotherapy. Higher complete CIV control rates were observed in children who received palonosetron (92 vs 72%; panel calculated p = 0.017). Indirect support of the recommendation of palonosetron as the preferred 5-HT3 antagonist when dexamethasone cannot be given is also provided in the non-inferiority trial mentioned previously.[12] Although not a primary study aim, rates of complete acute control for the subset of children who received 1-day HEC and who did not receive dexamethasone were: low-dose palonosetron: 61%; high-dose palonosetron: 60%; and ondansetron: 42%.

Summary: In developing recommendation 1.4, value was placed on improved CIV control reported in a subset of patients within a larger randomized controlled trial who received ondansetron plus aprepitant.[7] As explained earlier, aprepitant is not recommended for children <6 months old. In recommending palonosetron as the preferred 5-HT3 antagonist in recommendations 1.4, 1.5 and 1.6, high value was placed on the meta-analysis[20] demonstrating increased acute CIV control with palonosetron versus other 5-HT3 antagonists in the absence of dexamethasone.

 The guideline panel discussed the inclusion of adjunctive antiemetic agents such as those recommended in the 2013 guideline [1] (i.e. chlorpromazine or nabilone) for children less than 6 months old, as well as for children of all ages unable to receive both aprepitant and corticosteroids. However, the absence of direct evidence to support the efficacy or safety of these agents in the younger age group or to support their efficacy in combination with a 5-HT3 antagonist in any age group dissuaded the guideline panel from making such a recommendation.

Since direct evidence to support the preferred use of palonosetron monotherapy for children <6 months old receiving HEC is not available, recommendation 1.5 is a weak recommendation. That is, although the majority of individuals would want the suggested intervention, many would not and the decision to implement the recommendation should be based on patient, clinician and institutional values and preferences.[4] Recommendation 1.6 is also a weak recommendation since it is supported primarily by evidence in adult patients and because findings of pediatric trials are inconsistent.

**Health Question #2: What pharmacological interventions provide optimal control of acute CINV in children receiving moderately emetogenic chemotherapy (MEC)?**

**Recommendation 2.1** We recommend that children receiving MEC receive:

granisetron or ondansetron or palonosetron plus dexamethasone\*.

*Change from 2013: Inclusion of palonosetron as an alternate 5-HT3 antagonist.*

*\** see recommendations 2.2, 2.3 and 2.4 for information regarding children who cannot receive dexamethasone.

Palonosetron: The previously described meta-analysis,[41] and five pediatric studies (two randomized controlled trials,[12,14] two prospective observational studies[13,18] and one retrospective observational study[15]) informed this recommendation. The meta-analysis reported comparable complete acute CIV control rates with palonosetron plus dexamethasone versus other 5-HT3 antagonists in combination with dexamethasone (odds ratio: 1.14; 95% confidence interval: 0.88-1.49) in adults and children receiving MEC or HEC.[41] This analysis was not presented separately for patients receiving MEC.

 The previously described non-inferiority trial provided complete CIV control rates in the subset of 339 patients receiving MEC.[12] Complete acute CIV control rates of 63%, 60% and 67% were observed in these children receiving high-dose palonosetron, low-dose palonosetron or ondansetron, respectively. An unknown number of children in each study arm also received a non-standardized dose of dexamethasone. In addition, ondansetron versus palonosetron was evaluated in a randomized control trial in children receiving HEC (122 cycles) or MEC (38 cycles). However, results were not reported separately for these groups.[14] Children receiving HEC also received dexamethasone in this trial. Complete acute CIV control rates were comparable between the two study arms (70% versus 75%; p-value=0.479).

 Furthermore, results from the three single-arm observational studies also described good CIV control rates with palonosetron. The two prospective studies[13,18] reported complete acute CIV control rates in children receiving MEC and palonosetron of 84% and 98%. The retrospective review of 47 chemotherapy blocks in 43 patients receiving HEC or MEC as conditioning for hematopoietic stem cell transplant reported a complete acute CINV control rate of 68%. [15]

Summary: The recommendation to include palonosetron among the recommended 5-HT3 antagonists is based on the meta-analysis[20] and the included prospective pediatric studies [12,14] demonstrating similar CIV control rates following palonosetron versus other 5-HT3 antagonists combined with dexamethasone in children receiving MEC. Aprepitant is not included in this recommendation as there is no direct, high quality evidence demonstrating the superiority of aprepitant for CINV prophylaxis for children receiving MEC without a contraindication for corticosteroids. While a greater proportion of patients achieved CIV control with aprepitant versus placebo in the randomized controlled trial[7] included in the evidence summary, the number of patients who received dexamethasone in this subset of patients is unclear.

**Recommendation 2.2** We suggest that children ≥6 months receiving MEC who cannot receive dexamethasone for CINV prophylaxis receive:

granisetron or ondansetron or palonosetron plus aprepitant.

*Change from 2013: Addition of aprepitant and inclusion of palonosetron as an alternate 5-HT3 antagonist.*

**Recommendation 2.3** We suggest that children <6 months receiving MEC who cannot receive dexamethasone for CINV prophylaxis receive:

palonosetron.

*Change from 2013: Recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of chlorpromazine, metoclopramide and nabilone.*

**Recommendation 2.4** We suggest that children receiving MEC which is known or suspected to interact with aprepitant and who cannot receive dexamethasone receive:

palonosetron.

*Change from 2013: Recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of chlorpromazine, metoclopramide and nabilone.*

Aprepitant: The randomized trial conducted by Kang et al.[7] was considered by the panel in making this recommendation. An unknown number of children who received aprepitant in combination with ondansetron were included in this study. The proportion of complete acute CIV control with aprepitant (plus ondansetron with/without dexamethasone) vs. placebo (plus ondansetron with/without dexamethasone) for children receiving MEC was 70% vs. 55% (panel calculated p = 0.12).

Palonosetron: The evidence base described for recommendation 2.1 also informed the development of this recommendation. The meta-analysis[41] supports the preference for palonosetron over other 5-HT3 antagonists in the absence of dexamethasone. In addition, a randomized crossover trial observed similar complete CIV control rates in children receiving palonosetron or ondansetron (70% vs 75%; p=0.479). It is important to note that children who participated in this trial received either HEC or MEC and an unknown proportion also received dexamethasone for CINV prophylaxis. Furthermore, the non-inferiority trial described earlier reported complete acute CIV control rates in the very small subset of children receiving one-day MEC with dexamethasone as follows: low-dose palonosetron: 57%; high-dose: palonosetron: 88%; and ondansetron: 73%.[12] Complete acute CIV control rates reported in prospective observational studies for children receiving MEC with palonosetron monotherapy ranged from 68 to 91%.[13,15,18]

Summary: The panel developed recommendations 2.2 to 2.4 with the appreciation that children who cannot receive dexamethasone are more vulnerable to breakthrough and refractory CINV. These recommendations draw on the evidence of efficacy in children receiving HEC. Value was also placed on the large pediatric randomized controlled trials describing CIV control in the subsets of children receiving MEC and ondansetron plus aprepitant[7] and palonosetron monotherapy.[12]

 Given the broad range of emetogenicity risk classified as MEC (30 to 90%),[3] the panel recognizes that clinicians may wish to reserve palonosetron for children who cannot receive dexamethasone who are about to receive chemotherapy with an emetogenicity risk at the higher end of the MEC range.

 The panel also considered the inclusion of antiemetic agents such as chlorpromazine, metoclopramide and nabilone for use when aprepitant is not an option. However, the lack of direct evidence to support the efficacy and safety of these agents in children <6 months and the absence of high quality evidence describing their efficacy in combination with a 5-HT3 antagonist dissuaded the guideline panel from recommending their use.

 Recommendations 2.2, 2.3 and 2.4 are weak recommendations because uncertainty exists regarding the extent of the improvement in CIV control that can be achieved with the implementation of these recommendations due to the lack of direct supporting evidence.

1. **What doses of aprepitant and palonosetron are known to be effective in children receiving chemotherapy?**

**Recommendation 3.1** We suggest the following aprepitant dose for children ≥6 months:

Day 1: 3 mg/kg (max: 125 mg) PO x 1;

Days 2 and 3: 2 mg/kg (max: 80 mg) PO once daily

*Change from 2013: Inclusion of a dose for children 6 months to 12 years old. Change in dose recommended for children 12 years of age and older.*

No true aprepitant dose-finding pediatric studies have been published. Information provided within a randomized controlled trial[7] was primarily considered in the development of this recommendation (Supplementary Tables S2-S5). The aprepitant dose used in this trial was derived using data from phase I and phase III pediatric studies and was designed to achieve similar values of pharmacokinetic parameters in children as those achieved in adults after administration of recommended aprepitant doses. An aprepitant oral liquid was not administered in most other pediatric aprepitant studies; thus, doses were often assigned based on weight categories to accommodate the available capsule strengths (125mg, 80mg and 40mg). When converted to mg/kg dosing, aprepitant doses of 2 to 5.3 mg/kg/day on day 1 and 1.2 to 5.3 mg/kg/day on days 2 and 3 were given in one such trial.[10]

Summary: This recommendation places a high value on the dose simulation information discussed within a pediatric randomized control trial[7] and on evidence that this dose improves CIV control in children during the first 24 hours after receipt of HEC or MEC. The recommended dose is in agreement with the aprepitant dose approved for pediatric use by the United States’ Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[42,43] Questions, however, remain regarding the optimal aprepitant dose in children receiving multiple day chemotherapy and whether a single aprepitant dose would be sufficient for children receiving single day chemotherapy. As a result of these uncertainties, this is a weak recommendation.

**Recommendation 3.2** We suggest the following palonosetron dose for children:

1 month to <17 years: 0.02 mg/kg IV once (max 1.5 mg/dose) pre-chemotherapy

≥17 years: 0.25 mg/dose IV or 0.5 mg/dose PO once pre-chemotherapy

*Change from 2013: Inclusion of palonosetron dosing.*

No pediatric palonosetron dose-finding studies are available. The palonosetron dose recommended for children <17 years old is based on the trial that demonstrated the non-inferiority of palonosetron 0.02 mg/kg IV compared to ondansetron 0.15 mg/kg/dose IV q4h x 3 doses.[12] It is recommended that adolescents 17 to 18 years of age receive the licensed adult palonosetron dose.[44-46]

The palonosetron dose recommended for patients 17 years of age and older is based on a dose-finding study which concluded that 0.003 mg/kg was the lowest effective dose in adults.[34] It is notable that adults weighing less than 83 kg who receive the approved adult palonosetron dose (0.25 mg IV) receive more than 0.003 mg/kg.

The pediatric palonosetron dose approved by the FDA and EMA[44,46] is 6 times greater than the recommended adult dose. Since pediatric dosing is often calculated to approximate the dose intensity (e.g. area under the curve from time 0 to infinity (AUC0-inf), maximum concentration, and time above a threshold concentration) achieved in adults, a systematic review of studies which describe palonosetron pharmacokinetic disposition in adults and children was undertaken. Findings from this review confirmed that when single palonosetron doses of 0.02 mg/kg are given to children, the dose intensity achieved exceeds that achieved when palonosetron 0.003 mg/kg doses are given to adults (Supplementary Table S12).

No palonosetron pharmacokinetic parameter is predictive of CINV outcomes in adults.[47] However, a logistical regression exposure-relationship model developed using pediatric data noted increased CIV control (no emetic episode and no use of rescue medication during the first 24 hours after the start of emetogenic chemotherapy) with increasing palonosetron AUC0-inf. This effect plateaued at an AUC0-inf of approximately 100 µg∙h/L which approximates the AUC0-inf achieved after administration of 0.02 mg/kg/dose in children.[48] Since the emetogenicity of the chemotherapy received by the patients included in the model was not reported, it is not possible to determine if the association between CIV control and palonosetron AUC applies to both MEC and HEC.

 Flat or non-weight based palonosetron doses have been shown to be effective in children (Supplementary Table S14). In two pediatric randomized controlled trials that evaluated single IV palonosetron doses of 0.25 mg, it was possible to calculate the weight-based palonosetron dosing range.[16,17] One found acute CIV control to be comparable in patients receiving either palonosetron (dose range: 0.03 mg/kg to 0.09 mg/kg) or ondansetron (70% vs 65%; p=0.633).[17] In the other trial, CIV control in the palonosetron arm (dose range: 0.003 to 0.019 mg/kg/dose) was superior to that of the ondansetron study arm (92% vs 72%; p=0.0092).[16] Another pediatric randomized trial[14] and three single arm studies[13,15,18] evaluated a single palonosetron dose of 0.005 mg/kg. The randomized trial noted similar CIV control rates in patients receiving HEC or MEC and palonosetron or ondansetron (70% vs 75%; p=0.479).[14] The three single arm studies reported CIV control rates ranging from 68% to 98%.[13,15,18]

Summary: This recommendation places value on the results of a large randomized trial demonstrating the non-inferiority of ondansetron and palonosetron 0.02 mg/kg,[12] the current pediatric IV palonosetron dose licensed by the FDA and EMA and the current adult oral palonosetron dose licensed by Health Canada.[44,46] While a 0.02 mg/kg dose is safe and effective, it may be unnecessarily high. Since other pediatric studies have demonstrated significant CIV control in patients receiving palonosetron 0.005 mg/kg and 0.01 mg/kg,[13-16,18] it is unclear if palonosetron 0.02 mg/kg is required to achieve optimal acute CIV control in children or if a lower dose could achieve comparable outcomes. In addition, optimal palonosetron dosing in children receiving multiple day chemotherapy is unknown and is an important research gap.

This is a weak recommendation because the panel is not certain that a palonosetron dose of 0.02 mg/kg is warranted for MEC and HEC.

**Implementation Considerations**

While motivated by CINV control optimization and safety, the panel recognized that the cost of aprepitant and palonosetron may be a barrier to the implementation of these recommendations. In jurisdictions where cost is a barrier to using palonosetron 0.02 mg/kg/dose and compliance with the dose approved by regulatory authorities is not a concern, it may be reasonable to initiate palonosetron at the recommended dose with a patient’s first chemotherapy block and, depending on the patients’ CINV control, to administer a lower dose with a future chemotherapy block. Administration of ondansetron or granisetron may also be reasonable.

**Conclusions**

Recommendations for the prevention of acute CINV in children have been updated. (Table 1 and Supplementary Table S17) Significant changes have been made to the recommendations in light of new evidence supporting the use of aprepitant and palonosetron in children. However, extensive evidence gaps remain. (Table 4) Continual appraisal of the evidence and prospective evaluation of patient outcomes that are achieved with the implementation of these recommendations are required. Furthermore, to ensure that control of acute CINV in children is optimized future work must address critical evidence gaps.

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**TABLE 1 Health Questions and Summary of Recommendations for the Prevention of Acute Chemotherapy-Induced Nausea and Vomiting in Pediatric Cancer Patients**

|  |  |
| --- | --- |
| Health Questions and Recommendations | Strength of Recommendation andLevel of Evidence[5,6] |
| Health question #1: What pharmacological interventions provide optimal control of acute CINV in children receiving highly emetogenic chemotherapy (HEC)? |
| Recommendation 1.1: We recommend that children ≥6 months old receiving HEC which is not known or suspected to interact with aprepitant receive: granisetron or ondansetron or palonosetron + dexamethasone + aprepitant.*Changes from 2013: Aprepitant recommended for children ≥6 months and inclusion of palonosetron as an alternate 5-hydroxytryptamine type 3 (5-HT3) antagonist.* | Strong recommendationModerate quality evidence |
| Recommendation 1.2: We recommend that children <6 months old receiving HEC receive: granisetron or ondansetron or palonosetron + dexamethasone.*Change from 2013: Inclusion of palonosetron as an alternate 5-HT3 antagonist.* | Strong recommendationModerate quality evidence |
| Recommendation 1.3: We recommend that children ≥6 months receiving HEC which is known or suspected to interact with aprepitant receive: granisetron or ondansetron or palonosetron + dexamethasone.*Change from 2013: Inclusion of palonosetron as an alternate 5-HT3 antagonist.* | Strong recommendationModerate quality evidence |
| Recommendation 1.4: We recommend that children ≥6 months old receiving HEC which is not known or suspected to interact with aprepitant and who cannot receive dexamethasone for CINV prophylaxis receive: palonosetron + aprepitant.*Changes from 2013: Addition of aprepitant and recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of nabilone and chlorpromazine.* | Strong recommendationModerate quality evidence |
| Recommendation 1.5: We suggest that children <6 months old receiving HEC and who cannot receive dexamethasone for CINV prophylaxis receive: palonosetron.*Changes from 2013: Recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of nabilone and chlorpromazine.* | Weak recommendationModerate quality evidence |
| Recommendation 1.6: We suggest that children receiving HEC which is known or suspected to interact with aprepitant and who cannot receive dexamethasone receive: palonosetron.*Changes from 2013: Recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of nabilone and chlorpromazine.* | Weak recommendationModerate quality evidence |
| Health Question #2: What pharmacological interventions provide optimal control of acute CINV in children receiving moderately emetogenic chemotherapy (MEC)? |
| Recommendation 2.1: We recommend that children receiving moderately emetogenic chemotherapy (MEC) receive: granisetron or ondansetron or palonosetron + dexamethasone.*Change from 2013: Inclusion of palonosetron as an alternate 5-HT3 antagonist.* | Strong recommendationModerate quality evidence |
| Recommendation 2.2: We suggest that children ≥6 months receiving MEC who cannot receive dexamethasone for CINV prophylaxis receive: granisetron or ondansetron or palonosetron + aprepitant.*Change from 2013: Addition of aprepitant and inclusion of palonosetron as an alternate 5-HT3 antagonist.*  | Weak recommendationModerate quality evidence |
| Recommendation 2.3: We suggest that children <6 months receiving MEC who cannot receive dexamethasone for CINV prophylaxis receive: palonosetron.*Change from 2013: Recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of chlorpromazine, metoclopramide and nabilone.* | Weak recommendationModerate quality evidence |
| Recommendation 2.4: We suggest that children receiving MEC which is known or suspected to interact with aprepitant and who cannot receive dexamethasone receive: palonosetron.*Change from 2013: Recommendation of palonosetron as the preferred 5-HT3 antagonist. Deletion of chlorpromazine, metoclopramide and nabilone.* | Weak recommendationModerate quality evidence |
| Health Question #3: What doses of aprepitant and palonosetron are known to be effective in children receiving chemotherapy? |
| Recommendation 3.1: We suggest the following aprepitant dose for children ≥6 months:Day 1: 3 mg/kg (max: 125 mg) PO x 1;Days 2 and 3: 2 mg/kg (max: 80mg) PO once daily.*Change from 2013: Inclusion of a dose for children 6 months to 12 years old. Change in dose recommended for children 12 years of age and older.*  | Weak recommendationModerate quality evidence |
| Recommendation 3.2: We suggest the following palonosetron dose for children:1 month to < 17 years: 0.02 mg/kg IV once (max 1.5 mg/dose) pre-chemotherapy≥17 years: 0.25 mg/dose IV or 0.5 mg/dose PO once pre-chemotherapy*Change from 2013: Inclusion of palonosetron dosing.* | Weak recommendationModerate quality evidence |

A recommendation summary table that includes the remarks for each recommendation is presented in Supplementary Table S17.

**TABLE 2 Summary of Included Studies Evaluating Aprepitant**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Year | Antiemetics evaluated | Emetogenicity(No. of patients; %) | No. of patients | No. of chemo-therapyblocks | Mean age(range), years | No. ofChemo-therapy-naïve patients (%) |
| Randomized trials |  |  |  |
| Parallel group design |
| Bakhshi | 2015 | Ondansetron + dexamethasone + **aprepitant** vs.Ondansetron + dexamethasone + placebo | HEC: 93 (100%)  | 93 | NA | Aprepitant: 12.7 (6-18) Placebo: 13.1 (5-18) | 93 (100%) |
| Kang | 2015 | Ondansetron + **aprepitant** +/- dexamethasone vs.Ondansetron + placebo +/- dexamethasone | VHECa: 200 (66%)HEC/MECb: 102 (34%) | 302 | NA | 7.5c (0.5-17.8)  | 123 (41%) |
| Crossover group design |
| Long  | 2015 | Ondansetron + dexamethasone + **aprepitant** vs.Ondansetron + dexamethasone + olanzapine | HEC: 13 (100%) | 13 | 27 | 13a (5-18)  | NR |
| Observational studies  |
| Prospective design |
| Bodge | 2014 | Ondansetron + dexamethasone + **aprepitant** | HEC/MEC: 18 blocks (100%) | 11 | 18 | 9.6 (1-17) | NR |
| Retrospective design |
| Bauters | 2013 | [Ondansetron or tropisetron or granisetron] + dexamethasone + **aprepitant** | HEC/MEC: 18 blocks (100%) | 104 | 20 | 14 (8-16) | 0 (0%) |

a included in evidence base for recommendations regarding HEC;  b included in evidence base for recommendation regarding MEC; c median age;

HEC: highly emetogenic chemotherapy; VHEC: very highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; No.: number; NA: Not applicable; NR: Not reported

**TABLE 3 Summary of Included Studies Evaluating Palonosetron**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Year | Antiemetics evaluated | Emetogenicity(No. of patients (%) | No. of patients | No. of chemo-therapyblocks | Mean age(range), years | No. ofChemo-therapy-naïve patients (%) |
| Randomized trials |  |  |
| Parallel group design |
| Kovacs | 2016 | **Palonosetron** (10 µg/kg) +/- corticosteroid vs.**Palonosetron** (20 µg/kg) +/- corticosteroid vs.Ondansetron | HEC: 154 (31%)MEC: 339 (69%) | 493 | NA | Palonosetron 10 µg/kg:  8.1 (0.2-16.9)Palonosetron 20 µg/kg:  8.4 (0.2-16.9)Ondansetron:  8.2 (0.2-16.9) | 105 (21%) |
| Tang | 2013 | **Palonosetron** vs.Ondansetron  | HEC: 80 (100%) | 80 | NA | Palonosetron: 13.9 (6-27)Ondansetron: 14.3 (5-26) | NR |
| Sepulveda-Vildosola | 2008 | **Palonosetron** vs.Ondansetron | HEC: 100 (100%) | 100 | NA | Palonosetron: 14.1 (2.2-15)Ondansetron: 7.7 (1.7-10.5) | 14 (14%) |
| Crossover group design |
| Patil | 2015 | **Palonosetron** [+ dexamethasone for HEC]vs.Ondansetron [+ dexamethasone for HEC] | HECa: 122 blocks (76%)MEC: 38 blocks (24%) | 37 | 160 | 7.6 (2.2-17) | 37 (100%) |
| Observational studies |  |  |
| Prospective design |
| Nadaraja | 2011 | **Palonosetron** | MEC: 138 blocks (100%) | 53 | 138 | 6.6 (2-18) | NR |
| Varrasso | 2013 | **Palonosetron** | MEC: 44 blocks (100%) | 8 | 44 | 6-18 | NR |
| Retrospective design |
| Ripaldi | 2010 | **Palonosetron** | HEC/MECa: 47 blocks (100%) | 43 | 47 | 10b (1-18) | NR |

a included in evidence base for recommendation regarding MEC; b median age

HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; NA: Not applicable; NR: Not report

**TABLE 4 Aprepitant and Palonosetron for the Prevention of Acute Chemotherapy-Induced Nausea and Vomiting in Children: Examples of Evidence Gaps**

|  |
| --- |
| **APREPITANT**  |
| * Aprepitant dosing and safety in children <6 months
 |
| * Aprepitant dosing in children receiving multiple day chemotherapy
 |
| * Fosaprepitant dosing in children of all ages
 |
| * Evaluation of the extent of aprepitant pharmacokinetic drug interactions with commonly used pediatric chemotherapy agents
 |
| * Evaluation of the efficacy and safety of adjunctive antiemetics such as chlorpromazine nabilone and metoclopramide in children
 |
| * Evaluation of the efficacy of a 5-HT3 antagonist plus aprepitant in children receiving moderately emetogenic chemotherapy who cannot receive dexamethasone
 |
| **PALONOSETRON** |
| * Palonosetron dosing in children receiving moderately emetogenic chemotherapy or multiple day chemotherapy
 |
| * Oral palonosetron dosing
 |
| * Effectiveness of palonosetron IV doses lower than 0.02 mg/kg/dose in children receiving highly emetogenic chemotherapy
 |
| * Efficacy of palonosetron monotherapy in children receiving moderately or highly emetogenic chemotherapy
 |
| * Comparison of the efficacy of palonosetron in conjunction with aprepitant in children
 |
| * Comparison of the efficacy of palonosetron versus other 5-HT3 antagonists as monotherapy and in conjunction with dexamethasone in children
 |

**FIGURE 1 Summary of Recommendations Regarding Antiemetic Agent Selection for Prevention of Acute Chemotherapy-Induced Nausea and Vomiting in Children**

|  |
| --- |
|  |
|  |