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Palonosetron

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Contents

Abstract

▲ Palonosetron is a potent and highly selective serotonin 5-HT_3 receptor antagonist that has been evaluated for the prevention of chemotherapy-induced nausea and vomiting.

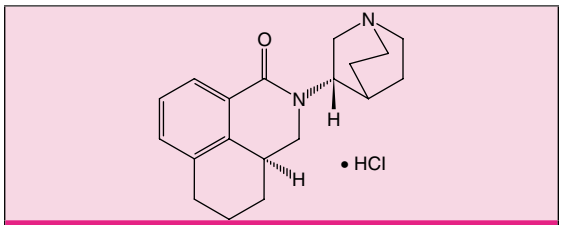
▲ Intravenously administered palonosetron has a linear pharmacokinetic profile, with a long terminal elimination half-life (≈40 hours) and moderate (62%) plasma protein binding.

▲ In two randomised, double-blind trials in 1132 cancer patients receiving moderately emetogenic chemotherapy, intravenous palonosetron 0.25mg was more effective than intravenous ondansetron 32mg in producing a complete reponse (no emesis, no use of rescue medication) during acute (0–24 hours) or delayed (24–120 hours) phases, and similar to intravenous dolasetron 100mg in acute, but more effective in delayed phase. Palonosetron 0.75mg was similar to ondansetron (acute and delayed phase) or dolasetron (acute phase), but more effective than dolasetron in delayed phase.

▲ In patients receiving highly emetogenic chemotherapy (n = 667), the complete response rates during acute and delayed phases with intravenous palonosetron (0.25 or 0.75mg) were similar to those seen in intravenous ondansetron 32mg recipients in a randomised, double-blind trial.

▲ Intravenous palonosetron was generally well tolerated in clinical trials, with few adverse events being treatment related. Palonosetron had no significant effect on the corrected QT interval or laboratory parameters.

Features and properties of palonosetron (RS-25259-197; Aloxi™, Onicit®)	
Indication	
Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, and acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy	
Mechanism of action	
Selective antagonism of serotonin 5-HT_3 receptors	
Dosage and administration (US prescribing information)	
Recommended dose	0.25mg
Route	Intravenous (IV), infused over 30 seconds
Frequency	Once, 30 minutes before administration of each course of chemotherapy
Pharmacokinetic profile (single IV infusion of 3 μg/kg in cancer patients)	
Maximum plasma concentration	5.6 ng/mL
Area under the plasma concentration-time curve from zero to infinity	35.8 ng • h/mL
Metabolism	Mainly metabolised by cytochrome P450 2D6 to inactive metabolites
Terminal elimination half-life	≈40h
Treatment-related adverse events	
Most frequent (≥5%)	Headache, constipation



Palonosetron

Cancer chemotherapy is almost invariably associated with some degree of nausea and vomiting (emesis), with an incidence as high as >99% in patients treated with cisplatin.[1] Chemotherapy-induced nausea and vomiting (CINV) are two of the most distressing and often debilitating adverse effects from a patient's perspective[2-5] and, long after the availability of effective antiemetics, still figure among the top three in the list of patient fears from chemotherapy.[6] CINV cause several medical and psychological complications in cancer patients that may significantly affect quality of life, adherence to anticancer therapy and survival.[2,5,7] Consequently, antiemetic therapy has become an integral part of supportive care in the management of cancer patients.[1,2,8]

Of the various pharmacotherapy options available, corticosteroids and serotonin 5-HT_3 receptor antagonists are the most widely used antiemetic agents, and all have high therapeutic indices.[1] The already established 5-HT_3 receptor antagonists (e.g. ondansetron, granisetron, dolasetron) are now generally accepted as being similar in terms of their antiemetic efficacy and tolerability.[1,2,8] These agents are effective in preventing the acute phase of CINV. However, they have reduced efficacy in the prevention of delayed CINV,[2,9] for which corticosteroids alone (low-risk emetogenic agent) or in combination with other agents (moderate-to-high risk) are recommended.[1-3]

Palonosetron (Aloxi™, Onicit®)[1], a new 5-HT_3 receptor antagonist with high potency and selectivity and a prolonged half-life, has shown excellent antiemetic efficacy against CINV during acute and delayed phases. The focus of this review is the use of intravenous palonosetron in the prevention of CINV associated with moderately or highly emetogenic agents.

1. Pharmacodynamic Properties

- Palonosetron is a highly selective, competitive, high-affinity antagonist of the 5-HT_3 receptor.[10] The negative logarithm of the inhibitory constant (pKi) for the drug was 10.4 using [^{3}H]-quizapine as a radioligand in NG108-15 cells, with low affinities (pKi all <6.0) for 28 other receptors including other serotonin subtypes.[10] Similarly, palonosetron also lacked activity at several ion channels.[10]
- The affinity of palonosetron for the 5-HT_3 receptor (pKi >10) was higher than that of all other known 5-HT_3 receptor ligands tested, including ondansetron (pKi = 8.4) and tropisetron (pKi = 8.7), in saturation binding studies in NG108-15 cells.[10]
- Parenteral palonosetron dose-dependently inhibited 2-methyl serotonin-induced bradycardia associated with the von Bezold-Jarisch reflex in rats.[11] Intraduodenal or intravenous palonosetron was up to 15 times more potent than granisetron and up to 55 times more potent than ondansetron in inhibiting the von Bezold-Jarisch reflex.[11]
- Oral or intravenous palonosetron produced dose-dependent inhibition of emetic episodes induced by cisplatin, dacarbazine, dactinomycin or chlormethine in animal models, with a potency 2–93 times higher than that of ondansetron or granisetron.[11]
- Importantly, a complete inhibition of the emetic response was seen against three of the four emetogens in the oral dosage range (1–100 μg/kg) tested in dogs, with the dose required for complete inhibition being at least ten times lower for palonosetron than that for ondansetron.[11] Against cisplatin-induced emesis, the duration of antiemetic effect of palonosetron (30 μg/kg orally) was 7 hours compared with 4 hours for that of an equieffective dose of ondansetron (300 μg/kg orally).[11]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

2. Pharmacokinetic Properties

The pharmacokinetic properties of palonosetron (intravenous[12-15] or oral[12,13]) have been evaluated in several studies in healthy volunteers (five studies available in a single poster[12] or abstracts[13,14]) and a dose-ranging study in cancer patients (fully published) [see section 3].[15] Additional information has been taken from the US prescribing information.[16] Discussion focuses on the pharmacokinetic profile of intravenous palonosetron in cancer patients. The pharmacokinetic parameters in these patients[15] were generally similar to those in healthy volunteers.[12]

Absorption and Distribution

- Palonosetron exhibited linear, dose-proportional pharmacokinetics over the dose range 1–90 μg/kg in healthy subjects[12] and in patients with cancer.[15] In cancer patients receiving single intravenous doses of palonosetron in this dose range, the mean maximum plasma concentration (C_{max}) ranged from 0.89 to 336 ng/mL and the area under the plasma concentration-time curve from zero to infinity (AUC_∞) ranged from 13.8 to 957 ng • h/mL.
- In six cancer patients,[15] the mean C_{max} and AUC_∞ values were 5.6 ng/mL and 35.8 ng • h/mL after a single intravenous dose of palonosetron 3 μg/kg (equivalent to a fixed dose of 0.21mg for a 70kg adult; see section 5).[16]
- Palonosetron is moderately bound to plasma proteins (62%).[12] The volume of distribution of palonosetron was approximately 8.3 L/kg after administration of a single intravenous dose of 10 μg/kg.[12]
- Following intravenous administration, palonosetron follows a biexponential pharmacokinetic profile, with an initial rapid distribution phase followed by a slower elimination phase.[12,15]

Metabolism and Elimination

- Approximately 50% of an intravenously administered dose of palonosetron is metabolised in the liver via multiple routes.[13,14,16] The two primary metabolites, *N*-oxide-palonosetron and 6-(*S*)-hydroxy-palonosetron, are essentially inactive as 5-HT_3 receptor antagonists (<1% of the activity of palonosetron).[16]
- In *in vitro* studies,[16] palonosetron was metabolised primarily by cytochrome P450 (CYP) 2D6 and, to a lesser extent, by CYP3A and CYP1A2.[16] However, clinical pharmacokinetic studies showed no difference in the metabolism of palonosetron between poor and extensive metabolisers of CYP2D6 substrates.[16]
- Within 144 hours of administration of a single intravenous dose of palonosetron 10 μg/kg, approximately 80% of the dose was recovered in the urine, half of which was unchanged drug (40% of the dose).[16] The total body and renal clearance of palonosetron were 160 and 66.5 mL/h/kg in healthy subjects.[16] Slow elimination of palonosetron from the body results in a long terminal elimination half-life of ≈40 hours.[14,16]

Special Populations

- Age, hepatic dysfunction or mild-to-moderate renal impairment have no clinically significant effect on the pharmacokinetics of palonosetron,[16] although total systemic exposure increases by 28% in patients with severe renal impairment compared with that in healthy subjects.[16]

Drug Interactions

- The potential for drug interactions with palonosetron appears to be low, because the drug does not interact with any other clinically important CYP isoenzyme.[16] There was no significant pharmacokinetic interaction following concomitant administration of single-dose palonosetron (0.75mg intravenously) with steady-state metoclopramide (10mg four times daily orally) in healthy volunteers.[16]

3. Therapeutic Efficacy

The efficacy of single doses of intravenously administered palonosetron in preventing CINV has been evaluated in three randomised, double-blind, parallel group, multicentre phase III clinical trials in adult patients (≥18 years) with malignant disease.[17-20]

Patients naive or non-naive to chemotherapy with a Karnofsky index ≥50%[17,18] or ≥60%[20] were randomised to receive a single, fixed dose of one of the antiemetic agents. The drugs were administered intravenously over 30 seconds (palonosetron[17,18,20] and dolasetron[18]) or over 15 minutes (ondansetron)[17,20] 30 minutes prior to administration of the primary chemotherapeutic agent. At the discretion of the investigator, a single dose of a corticosteroid administered before chemotherapy[18,20] and/or rescue medication for the treatment of nausea and emesis after chemotherapy[17,18,20] was permitted. Patient diaries were used to record emetic episodes, use of rescue medication, severity of nausea, patient satisfaction and the impact of nausea and emesis on daily functioning and quality of life.[17,18,20]

Exclusion criteria included the use of drug(s) with antiemetic properties from 24 hours before to 5 days after treatment, emesis or National Cancer Institute Common Toxicity Criteria grade 2 or 3 nausea within 24 hours preceding chemotherapy, and baseline corrected QT (QTc) >500ms.[17,18,20]

The primary efficacy endpoint was the proportion of patients with a complete response (no emetic episode, no use of rescue medication) during the first 24 hours after chemotherapy administration (acute phase).[17,18,20] Secondary endpoints included the proportion of patients with a complete response during the delayed (24–120 hours; days 2–5) and the overall (0–120 hours; days 1–5) phases, and the proportion of patients with complete control (defined as no emetic episode, no need for rescue medication and no more than mild nausea). Data regarding the severity of nausea, patient satisfaction and quality of life in these patients have not been published to date. An intent-to-treat analysis was performed for all efficacy evaluations.[17,18,20]

While standard doses of ondansetron (32mg) and dolasetron (100mg) were used, the doses of palonosetron (0.25 and 0.75mg) were based on the results of a randomised, double-blind, dose-ranging study.[15] In this phase II study (n = 161), complete response rates were 46% or 40% with palonosetron 3 or 10 μg/kg (approximately corresponding to fixed doses of 0.25 and 0.75mg) during the 24-hour period after highly emetogenic chemotherapy that included cisplatin >70 mg/m^2 and cyclophosphamide >1100 mg/m^2.[15]

In addition to the above trials, a noncomparative trial (n = 875)[21] has evaluated the efficacy of intravenous palonosetron 0.75mg in preventing CINV with repeated cycles of moderately or highly emetogenic chemotherapy in patients who had earlier participated in one of the phase III trials.[17,18,20] Results of this trial have indicated that the efficacy of palonosetron 0.75mg, with or without concomitant corticosteroids, was generally maintained over repeated cycles (up to four) of chemotherapy in acute, delayed and overall phases (complete response rates ≥55%, >58% and >45%, respectively).[21]

Moderately Emetogenic Chemotherapy

Two double-blind trials (n = 563[17] and 569[18]) have compared palonosetron (0.25 and 0.75mg) with ondansetron 32mg[17] or dolasetron 100mg[18] in preventing CINV in patients receiving moderately emetogenic agents, including methotrexate >250 mg/m^2, cyclophosphamide <1500 mg/m^2, doxorubicin >25 mg/m^2, cisplatin ≤50 mg/m^2 or any dose of carboplatin. In these trials, 42%[17] and 67%[18] of patients were naive to chemotherapy, and a majority (72%[17] and 82%[18]) were female, with an even distribution across the treatment groups. Only 5% of patients received corticosteroids in the trial that allowed their concomitant use.[18] Efficacy criteria required palonosetron to show non-inferiority to the comparators at a 97.5% confidence level and a maximum delta of 15%.[17,18]

Complete Response

- Recipients of single intravenous doses of palonosetron 0.25 or 0.75mg consistently achieved high complete response rates during the acute phase (0–24 hours) after moderately emetogenic chemotherapy (primary endpoint) [figure 1].[17,18]
- The complete response rate in acute phase in patients receiving palonosetron 0.25mg was significantly higher than that in ondansetron 32mg recipients[17] and similar to that in dolasetron 100mg

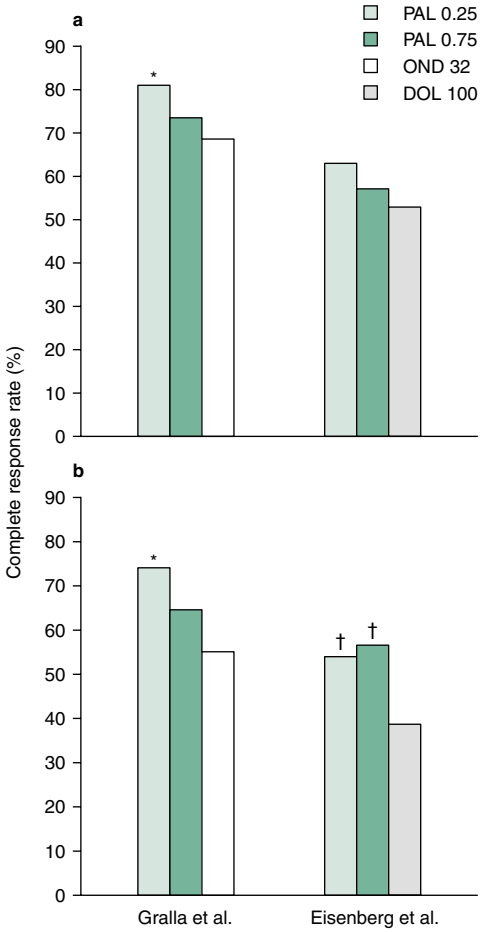


Fig. 1. Antiemetic efficacy of palonosetron (PAL) against moderately emetogenic chemotherapy (MEC). Complete response rates (no emesis, no use of rescue medication) during (**a**) acute (0–24h) and (**b**) delayed (24–120h) phases obtained with PAL (0.25 or 0.75mg; n = 189 in each group in both trials),[17,18] ondansetron (OND, 32mg; n = 185)[17] or dolasetron (DOL, 100mg; n = 191)[18] in two randomised, double-blind, parallel-group, multicentre clinical trials (conducted by Gralla et al.[17] and Eisenberg et al.[18]). In these studies, patients scheduled to receive MEC were given one of the antiemetic agents intravenously 30 minutes before administration of the primary chemotherapeutic agent (see text for details). * $p < 0.01$ vs OND; † $p < 0.005$ vs DOL.

recipients[18] (figure 1). The proportion of patients showing a complete response with palonosetron 0.75mg was similar to that with ondansetron 32mg[17] or dolasetron 100mg.[18]

- Importantly, in both of these trials,[17,18] the lower bounds of the 97.5% CI of the difference in complete response rate in acute phase between palonosetron (0.25 and 0.75mg) and the comparators were greater than the preset threshold of −15%, indicating that both doses of palonosetron were non-inferior to ondansetron[17] or dolasetron.[18]
- The efficacy of palonosetron against nausea/emesis induced by moderately emetogenic agents was maintained during the delayed phase (24–120 hours) [secondary endpoint].[17,18] Palonosetron 0.25mg was significantly more effective than ondansetron 32mg[17] or dolasetron 100mg[18] in preventing delayed CINV (figure 1). Complete response rate with palonosetron 0.75mg was similar to that with ondansetron 32mg[17] and significantly higher than that with dolasetron 100mg.[18]
- During the overall phase (0–120 hours), complete response rates with palonosetron 0.25mg were significantly higher than those observed with ondansetron 32mg (69% vs 50%; $p < 0.001$)[17] or dolasetron 100mg (46% vs 34%; $p = 0.021$);[18] complete response rates in the respective palonosetron 0.75mg groups were 59%[17] and 47% ($p = 0.012$ vs dolasetron).[18]

Other Efficacy Parameters

- In general, other secondary endpoints showed that palonosetron was at least as effective as ondansetron or dolasetron.[17,18] For example, although there were no between-group differences in complete control rates during the acute phase, these rates were significantly (all $p \leq 0.03$) higher during the delayed and overall phases with palonosetron 0.25 or 0.75mg (42–67%) than with comparators (31–50%).[17,18]
- There were also significantly fewer emetic episodes with palonosetron 0.25mg than with ondansetron 32mg (all $p \leq 0.05$)[17] or dolasetron 100mg (all $p < 0.02$) during acute, delayed and overall phases.[18] Palonosetron 0.75mg was more effective than dolasetron 100mg[18] during delayed and overall phases only ($p < 0.002$ for both) [quantitative data not reported].
- The antiemetic effect of single doses of palonosetron (0.25 or 0.75mg) persisted for >120 hours, as shown by the median time to treatment failure (time to first emetic episode/use of rescue med-

ication, whichever occurred first)[17] or median time to first emetic episode.[18] A Kaplan-Meier analysis showed that the time to treatment failure with palonosetron 0.25mg was significantly longer than that with ondansetron 32mg ($p = 0.0003$)[17] or dolasetron 100mg ($p < 0.02$)[18]

Highly Emetogenic Chemotherapy

A single phase III trial (n = 667) has evaluated the efficacy of palonosetron in preventing CINV with highly emetogenic chemotherapy, including cisplatin ≥60 mg/m^2, cyclophosphamide >1500 mg/m^2 and dacarbazine.[19,20] The efficacy criteria required palonosetron to show non-inferiority to ondansetron during the acute phase at the 97.5% confidence level and a maximum delta of 15%.[20]

- During the first 24 hours (acute phase) following highly emetogenic chemotherapy, a complete response was achieved in ≥57% of patients in all treatment groups without any significant difference between palonosetron (0.25 or 0.75mg) and ondansetron 32mg (figure 2).[19,20] The lower limit of the 97.5% CI for the difference between palonosetron (0.25 and 0.75mg) and ondansetron was above the preset threshold of −15%, thus showing non-inferiority of both doses of palonosetron to ondansetron.[20]
- In patients receiving concomitant corticosteroids (≈67% in each group),[22] a complete response during the acute phase was seen in 65% and 56% of patients treated with palonosetron 0.25mg or ondansetron 32mg.
- The complete response rate during the delayed phase was >45% with palonosetron (0.25 or 0.75mg), with either dose being similar to ondansetron 32mg in producing a complete response (figure 2).[20]
- Compared with ondansetron 32mg, the median time to first emetic episode was significantly longer with palonosetron 0.25 or 0.75mg (42.7 vs >120 hours for each palonosetron dose; both $p < 0.03$),[19] and the number of emetic episodes during the acute phase was significantly lower with palonosetron 0.75mg ($p = 0.008$) [data not reported].[20]

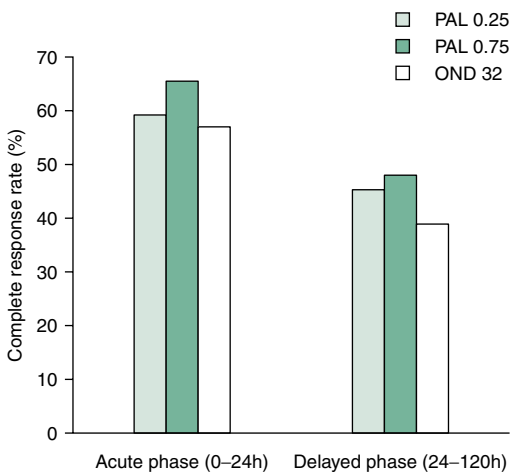


Fig. 2. Antiemetic efficacy of palonosetron (PAL) against highly emetogenic chemotherapy (HEC). Complete response rates (no emesis, no use of rescue medication) during acute (0–24h) and delayed (24–120h) phases obtained with PAL (0.25 or 0.75mg; n = 223 in each group) or ondansetron (OND, 32mg; n = 221) in a randomised, double-blind, parallel-group, multicentre clinical trial.[19,20] Patients scheduled to receive HEC were given one of the antiemetic agents intravenously 30 minutes before administration of the primary chemotherapeutic agent (see text for details).

4. Tolerability

- Palonosetron, administered as single intravenous doses prior to chemotherapy, was generally well tolerated in patients receiving moderately[17,18] or highly[15,19] emetogenic chemotherapy in the clinical trials discussed in section 3. As expected in cancer patients undergoing chemotherapy, who have a high rate of complications and comorbid illness, the incidence of adverse events was high (up to 67% with palonosetron 0.75mg in one trial[17]) and ascertaining their causality was difficult. However, most adverse events were mild in intensity (up to 84%)[17] and/or unrelated to palonosetron treatment (>80%).[18]
- In general, adverse events with palonosetron were similar in nature, frequency, duration and intensity to those of the comparator agents.[17-19,22] Among the adverse events judged by the investigators as at least possibly treatment related or with cause unknown, headache and constipation were the most frequent in all treatment groups across all trials.[15,17,18,22] Figure 3 summarises adverse events reported by ≥2% of patients in any treatment group

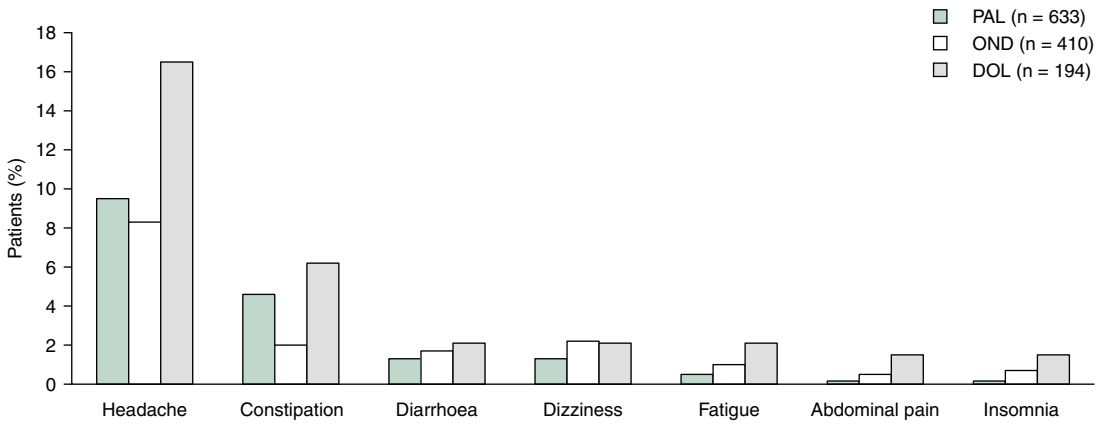


Fig. 3. Tolerability profile of palonosetron (PAL) 0.25mg compared with that of ondansetron (OND) 32mg or dolasetron (DOL) 100mg. Pooled data[16] on adverse events (occurring in ≥2% of patients in any treatment group) at least possibly related to the antiemetic therapy or with cause unknown that was reported in four randomised, double-blind, parallel-group, multicentre clinical trials in patients receiving moderately[17,18] or highly[15,19] emetogenic chemotherapy. Patients were given a single dose of one of the antiemetic agents intravenously 30 minutes before administration of the primary chemotherapeutic agent (see section 3 for further details).

in a pooled analysis of data from these trials that is reported in the US prescribing information. Only headache (9%) and constipation (5%) occurred with an incidence of ≥2% in palonosetron 0.25mg recipients.[16]

- Serious adverse events occurred with low (≤5%)[17,18] and similar frequency in palonosetron and comparator groups.[17,18] None of the serious events was assessed as being related to the study medication.[17,18] Two patients discontinued treatment due to adverse events: one non-serious, treatment related (palonosetron 0.75mg group), the other serious, not treatment related (ondansetron 32mg group).[17] No other treatment discontinuations were reported in palonosetron clinical trials.
- No significant treatment-related abnormalities in laboratory values or ECG recordings were observed, and palonosetron was similar to the comparators with respect to these parameters.[17,18] Importantly, the increases from baseline in QTc (Fridericia correction) interval with palonosetron 0.25 or 0.75mg (1–3.4ms) were nonsignificant and were similar to those seen with ondansetron (5ms) or dolasetron (5.4ms).[17,18]
- Results of a large, noncomparative trial (section 3)[21] showed that palonosetron 0.75mg administered prior to repeated cycles of chemotherapy was well tolerated, with no unexpected treatment-related adverse events occurring in the later cycles.

5. Dosage and Administration

In the US, the recommended dosage of palonosetron for the prevention of CINV is 0.25mg administered as a single, 30-second intravenous infusion approximately 30 minutes before the start of chemotherapy.[16]

6. Palonosetron: Current Status

Palonosetron is the first, and currently the only, 5-HT_3 receptor antagonist approved for the prevention of delayed CINV with initial and repeat courses of moderately emetogenic chemotherapy in the US.[23] It is also approved for the prevention of acute CINV caused by initial and repeat courses of moderately or highly emetogenic agents. Palonosetron has recently been included in the antiemesis guidelines of the National Comprehensive Cancer Network as the preferred 5-HT_3 antagonist in patients receiving moderately emetogenic chemotherapy.[3] In clinical trials, palonosetron 0.25 or 0.75mg was similar to or more effective than the comparator 5-HT_3 receptor antagonists in preventing CINV with moderately or

highly emetogenic chemotherapy, with a good tolerability profile.

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