INDICATIONS AND USAGE
Palonosetron Hydrochloride Injection is indicated for prevention of acute nausea and vomiting associated with:

- Highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) when used in combination with other antiemetics (e.g., dexamethasone, 5-hydroxytryptamine (5HT3) receptor antagonists).
- Cyclosporine associated nausea and vomiting.
- Postoperative nausea and vomiting (PONV).

DOSEAGE AND ADMINISTRATION
Palonosetron Hydrochloride Injection is supplied as a single-dose sterile, nonpyrogenic solution for dilution and injection. Each single-dose vial contains 0.25 mg (free base) per 5 mL (concentration: 0.05 mg per mL). Each patient should receive 0.25 mg of palonosetron (0.1 mg/kg) in the setting of chemotherapy-induced nausea and vomiting. For a dose of palonosetron of 0.75 mg, three times the recommended dose,湘 received palonosetron. Adverse reactions were similar in frequency and severity. No clinically relevant differences in efficacy were observed between 0.25 mg and 0.75 mg. However, the incidence of one adverse event, depressed mood, was reportedly increased at the higher dose. Therefore, the maximum recommended dose is 0.25 mg.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
In clinical trials, the most common adverse events observed with palonosetron were:

- Nausea: 1% (N=194) of patients
- Vomiting: 1% (N=194) of patients
- Fatigue: 8% (N=194) of patients
- Headache: 4% (N=194) of patients

6.2 Adverse Reactions
Serotonin syndrome (including altered mental status, autonomic instability, neuromuscular abnormalities, and/or neurologic signs such as hyperreflexia, rigidity, tremor, and incontinence) has been reported with 5-HT3 receptor antagonists. Hypersensitivity reactions, including anaphylaxis, have been reported with 5-HT3 receptor antagonists (see Warnings and Precautions). Prophylactic use of palonosetron in pediatric patients following combination chemotherapy (e.g., doxorubicin and mitomycin C) in murine tumor models.

8 USE IN SPECIFIC POPULATIONS
8.6 Pregnancy
In pregnant rats, palonosetron showed no evidence of adverse developmental effects at doses of up to 1,894 and 3,789 times the human dose for rats and mice, respectively. In pregnant mice, palonosetron showed no evidence of adverse developmental effects at doses of up to 3,000 times the human dose. In pregnant rabbits, palonosetron showed evidence of adverse developmental effects at doses of 1,600 times the human dose. There is no information on the effects of palonosetron on human pregnancy. Therefore, palonosetron should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The most common adverse reactions in chemotherapy-induced nausea and vomiting, particularly when certain agents, such as cisplatin, are used, are nausea and vomiting.

8.7 Nursing Mothers
It is not known whether palonosetron is excreted in human milk. However, the potential for clinically significant drug interactions with palonosetron is high. Therefore, palonosetron should not be used by breastfeeding women.

11 DESCRIPTION
Palonosetron hydrochloride is a white to off-white crystalline powder. It is an isoquinoline hydrochloride. Palonosetron hydrochloride exists as a single enantiomer, (S)-(+)-3-(1H-indol-3-yl)-1-phenylpropan-2-ol hydrochloride.

12.3 Pharmacokinetics
In an interaction study in healthy subjects where palonosetron 0.25 mg was administered with CYP3A4, CYP2D6, and CYP2C19 inhibitors, the mean AUC of palonosetron was increased by 10%, 9%, and 8%, respectively. In a pharmacokinetic study in healthy subjects, the AUC of palonosetron was increased by 20% following the concomitant administration of dexamethasone. The potential for clinically significant drug interactions with palonosetron is high. Therefore, palonosetron should be used only if the potential benefit justifies the potential risk to the mother. Further in vitro studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2C19, CYP3A4, or CYP2D6. Palonosetron is an inhibitor of CYP3A4. Therefore, caution should be exercised when palonosetron is used with other drugs that are primarily metabolized by CYP3A4.

12.2 Pharmacodynamics
In an interaction study in healthy subjects where palonosetron 0.25 mg was administered with CYP3A4, CYP2D6, and CYP2C19 inhibitors, the mean AUC of palonosetron was increased by 10%, 9%, and 8%, respectively. In a pharmacokinetic study in healthy subjects, the AUC of palonosetron was increased by 20% following the concomitant administration of dexamethasone. The potential for clinically significant drug interactions with palonosetron is high. Therefore, palonosetron should be used only if the potential benefit justifies the potential risk to the mother. Further in vitro studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2C19, CYP3A4, or CYP2D6. Palonosetron is an inhibitor of CYP3A4. Therefore, caution should be exercised when palonosetron is used with other drugs that are primarily metabolized by CYP3A4.

13.8 Other Interactions
In an interaction study in healthy subjects where palonosetron 0.25 mg was administered with CYP3A4, CYP2D6, and CYP2C19 inhibitors, the mean AUC of palonosetron was increased by 10%, 9%, and 8%, respectively. In a pharmacokinetic study in healthy subjects, the AUC of palonosetron was increased by 20% following the concomitant administration of dexamethasone. The potential for clinically significant drug interactions with palonosetron is high. Therefore, palonosetron should be used only if the potential benefit justifies the potential risk to the mother. Further in vitro studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2C19, CYP3A4, or CYP2D6. Palonosetron is an inhibitor of CYP3A4. Therefore, caution should be exercised when palonosetron is used with other drugs that are primarily metabolized by CYP3A4.

15.1 Clinical Pharmacology
In an interaction study in healthy subjects where palonosetron 0.25 mg was administered with CYP3A4, CYP2D6, and CYP2C19 inhibitors, the mean AUC of palonosetron was increased by 10%, 9%, and 8%, respectively. In a pharmacokinetic study in healthy subjects, the AUC of palonosetron was increased by 20% following the concomitant administration of dexamethasone. The potential for clinically significant drug interactions with palonosetron is high. Therefore, palonosetron should be used only if the potential benefit justifies the potential risk to the mother. Further in vitro studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2C19, CYP3A4, or CYP2D6. Palonosetron is an inhibitor of CYP3A4. Therefore, caution should be exercised when palonosetron is used with other drugs that are primarily metabolized by CYP3A4.
Table 6: Prevention of Overall Nausea and Vomiting (0 to 120 hours):

Complete Response Rates

Table 5: Prevention of Delayed Nausea and Vomiting (24 to 120 hours)

Hydrochloride Injection

On the administration of palonosetron, some patients may experience an acute increase in blood pressure. If this occurs, treat the patient with hypotensive therapy. Monitor blood pressure and pulse closely after administration of palonosetron. A lower bound than the recommended dose of 20 mcg/kg, non-inferiority criteria were met. The complete response in the acute phase of the first cycle of chemotherapy was 59.4% with palonosetron and 58.6% with ondansetron. The non-inferiority margin was 15%.

One double-blind, active-controlled clinical trial was conducted in emetogenic cancer chemotherapy. Palonosetron (maximum 1.5 mg) intravenous infusion of palonosetron hydrochloride injection demonstrated non-inferiority to the active control. These studies were designed to show non-inferiority. A lower bound of the 97.5% confidence interval for the difference in complete response rates of intravenous palonosetron minus intravenous ondansetron was larger than -15%. The non-inferiority margin was 15%.

The safety and efficacy of palonosetron in repeated cycles of chemotherapy were evaluated in Phase 3 trials. The majority of patients in these studies were women (77%), White (65%) and female rats. Palonosetron has been found to have no effect on fertility and reproductive performance of male and female rats. Female rats treated with palonosetron, 0.0024 mg/kg/day to 0.024 mg/kg/day (4-fold to 40-fold the recommended human dose), had a similar incidence of vaginal adenomas to controls. In the rat uterotrophic assay, palonosetron, up to 0.5 mg/kg, had no effect on the incidence of multiparous vaginal adenomas.

Palonosetron hydrochloride injection showed no effect on fertility and male reproductive performance in the hamster model. Male rats treated with palonosetron, 0.00044 mg/kg/day to 0.0044 mg/kg/day (2-fold to 20-fold the recommended human dose), had a similar incidence of seminiferous tubule adenomatous hyperplasia to controls. In the rat uterotrophic assay, palonosetron, up to 0.5 mg/kg, had no effect on the incidence of spermatocytic seminiferous tubule adenomas.

In a 12-month, carcinogenicity study in dogs and 2-year, carcinogenicity study in rats, palonosetron was found to have no effect on the incidence of spontaneous tumors in either species. The tumors found in the study included thyroid C-cell adenoma and combined adenoma and carcinoma, hepatic adenoma and carcinoma and increased incidences of thyroid follicular cell adenomas and carcinomas. A Phase 2, double-blind, dose-ranging study evaluated the efficacy of palonosetron in the prevention of nausea and vomiting associated with highly emetogenic chemotherapy. This study was conducted in 161 chemotherapy-naive adult cancer patients. The safety and efficacy of palonosetron in repeated cycles of chemotherapy were evaluated in Phase 3 trials. The majority of patients in these studies were women (77%), White (65%) and female rats. Palonosetron has been found to have no effect on fertility and reproductive performance of male and female rats. Female rats treated with palonosetron, 0.0024 mg/kg/day to 0.024 mg/kg/day (4-fold to 40-fold the recommended human dose), had a similar incidence of vaginal adenomas to controls. In the rat uterotrophic assay, palonosetron, up to 0.5 mg/kg, had no effect on the incidence of multiparous vaginal adenomas.

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