The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. In animal studies, no effects on embryo-fetal development were observed in pregnant rats given oral palonosetron at approximately 200 mg/kg (about 1200 times the recommended human dose). In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 200 mcg/kg (about 120 times the recommended human dose).

**Recommended Dosing**

- **Highly emetogenic cancer chemotherapy** -- prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.
- **Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients** Aged 1 Month to Less than 17 Years

**Pharmacokinetics**

- **Dose kittens** were calculated for 1520 adult patients in Palonosetron Hydrochloride Injection PONV clinical studies, 73 (5%) were ≥65 years old. Of the 1374 adult cancer patients in clinical studies, 316 (23%) were ≥ 65 years old, while 71 (5%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between older and younger patients (18 to 64 years).
- **Fifty adult cancer patients** were administered palonosetron at a dose of 90 mcg/kg (equivalent to 6 mg fixed dose) as a single intravenous dose. Half of the patients received palonosetron 15 minutes before chemotherapy and the other half received palonosetron 30 seconds before chemotherapy. The incidence of PONV was 32% in the pre-chemotherapy group and 23% in the 30-second group. The difference was statistically significant (p = 0.001).
- **After a single intravenous dose of 10 mcg/kg [14C]-palonosetron, approximately 80% of the dose was recovered within 3 hours, and excretion was complete within 24 hours. The area under the curve (AUC) increased with dose.**
- **The half-life of palonosetron following intravenous administration was approximately 1 hour.**
- **Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites:**
  - 3-(2-dehydro-2-(2-deoxy-D-glucopyranosylamino)-6-fluorohexyl)-1,2,3,4,5,6-hexahydro-2-oxo-1,2-diphenyl-1,2,3,4-tetrahydroisoquinoline (3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1,2,3,4-tetrahydroisoquinoline (3aR).
  - These metabolites have been isolated from urine and feces. The primary metabolites were identified by 
    nuclear magnetic resonance (NMR), high-performance liquid chromatography (HPLC), and gas chromatography-mass spectrometry (GC-MS).

**Clotagogy**

- **In vitro studies showed that palonosetron did not increase thrombocyte aggregation** compared to 5-HT3 receptor antagonists.

**Drug Interactions**

- **Palonosetron is a substrate** for CYP3A4 and is not a CYP3A4 inducer. **Race** may affect the pharmacokinetics of palonosetron. In Blacks, the area under the curve (AUC) and Cmax were increased by 22% and 14%, respectively, compared to white patients. **No differences in pharmacokinetics were observed between men and women.**
- **The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.**

**Geriatric Use**

- **The pharmacokinetics of palonosetron were not different in the 65-74 year age group compared to younger patients (18 to 64 years).**
- **No overall differences in safety or effectiveness were observed in patients ≥ 65 years of age and younger patients (18 to 64 years). Of the 1374 adult cancer patients in clinical studies, 316 (23%) were ≥ 65 years old, while 71 (5%) were ≥ 75 years old. No differences in safety or effectiveness were observed between older and younger patients (18 to 64 years).**

**Adverse Reactions**

- **The most common adverse reactions** associated with palonosetron are headache and constipation. Other adverse reactions observed include:
  - **Constipation**
  - **Diarrhea**
  - **Nausea**
  - **Pharyngitis**
  - **Anorexia**

**Breastfeeding**

- **Breastfeeding** is not recommended for patients treated with palonosetron due to the potential for serious adverse reactions in nursing infants and the potential for the drug to be excreted in human milk.

**Allergies**

- **Palonosetron Hydrochloride Injection** will be given to you in your vein during anesthesia for surgery.

**Contraindications**

- Palonosetron Hydrochloride Injection is contraindicated in patients with a history of hypersensitivity to palonosetron or any component of the product.

**Warnings and Precautions**

- **Serotonin syndrome** has been reported with 5-HT3 receptor antagonists. The risk of serotonin syndrome may be increased in the presence of other 5-HT3 receptor antagonists, selective serotonin reuptake inhibitors (SSRIs), selective serotonin reuptake inhibitors (SSNRIs), monoamine oxidase inhibitors (MAOIs), and other serotonergic drugs. The risk of serotonin syndrome may be increased in patients with pre-existing central nervous system (CNS) disorders, such as depression, anxiety, or personality disorders, or in patients concurrently receiving other serotonergic drugs.

**Adverse Effects**

- **General:** < 1%: chills.
- **Head and Face:** < 1%: non-sustained tachycardia, bradycardia, hypotension.
- **Abdominal System:** < 1%: hypertension, myocardial ischemia, constipation.
- **Respiratory System:** < 1%: breathing trouble.

**Pharmacology**

- **Palonosetron** is a selective 5-HT3 receptor antagonist that acts by occupying the serotonin recognition site on the 5-HT3 receptor, thereby preventing the binding of serotonin to the receptor. It has been shown to block ion channels involved in the transmission of the neurophysiologic signal that is thought to be responsible for the initiation of nausea and vomiting. Palonosetron is rapidly absorbed and reaches peak plasma levels within 1 hour of intravenous administration. It is extensively metabolized in the liver and is excreted in the urine. Palonosetron is not significantly excreted in the feces. The half-life of palonosetron following intravenous administration is approximately 1 hour.
Palonosetron Hydrochloride Injection is supplied as a single-use sterile, clear, colorless solution in glass vials that provide:

- Palonosetron Hydrochloride Injection is indicated for prevention of acute nausea and vomiting associated with initial highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Abdominal Pain
In clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related, were reported:

- Nausea
- Vomiting
- Diarrhea
- Abdominal pain
- Stomach pain

Metabolic
- Hypokalemia
- Anorexia

Psychiatric
- Anxiety
- Euphoric mood

Other
- Headache
- Flushing
- Palpitations
- Photophobia

Abnormal Vision
- Blurred vision
- Changes in color vision

Other
- Increased appetite
- Belly pain
- Constipation
- Dry mouth
- Fatigue
- High blood pressure
- Jaundice
- Rash
- Yellowing of the skin or eyes

These adverse reactions were reported infrequently and were not considered treatment-related.

Note different dosing units in pediatrics

Risk Summary

5.2 Palonosetron Hydrochloride Injection is effective in the prevention of chemotherapy-induced nausea and vomiting when administered both before and during chemotherapy.

Chemotherapy-Induced Nausea and Vomiting
In phase 2 and 3 clinical trials, 1460 patients received a single dose of Palonosetron Hydrochloride Injection (0.075 mg) immediately before induction of anesthesia in one phase 2 and two phase 3 randomized, double-blind, placebo-controlled studies. In one phase 3 study, 961 patients received Palonosetron Hydrochloride Injection (0.075 mg) versus placebo. In these studies, the median age was 60 (range 11 to 82) years and 80% were white. Palonosetron Hydrochloride Injection was equally effective in men and women.

In the two phase 3 studies, compared to placebo, Palonosetron Hydrochloride Injection significantly reduced the incidence of chemotherapy-induced nausea and vomiting in the 0 to 24-hour post-dose interval. In two phase 3 studies, the median time to first rescue antiemetic was 21 hours in patients receiving Palonosetron Hydrochloride Injection versus 13 hours in patients receiving placebo. In addition, patients receiving Palonosetron Hydrochloride Injection reported 20% fewer days of nausea and vomiting and 25% fewer days of rescue antiemetic use compared to patients receiving placebo. These results were consistent across all individual chemotherapy agents and dose levels tested.

The median time to first rescue antiemetic use was 18 hours in patients receiving Palonosetron Hydrochloride Injection versus 13 hours in patients receiving placebo. In addition, patients receiving Palonosetron Hydrochloride Injection reported 20% fewer days of nausea and vomiting and 25% fewer days of rescue antiemetic use compared to patients receiving placebo. These results were consistent across all individual chemotherapy agents and dose levels tested.

In the post-anesthesia care unit or an infusion center, 1 (< 1%) subject experienced a single episode of allergic reaction following a single palonosetron dose of approximately 9 mg. The subject was treated with diphenhydramine hydrochloride supplementation and was discharged to home.

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.3 mg (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In a Phase 3, double-blind, randomized, non-inferiority study, compared I.V. palonosetron (1 mcg/kg, max 0.075 mg) versus I.V. ondansetron. A total of 670 patients were included in the analysis. The proportion of patients achieving a Complete Response (CR) within 24 hours was 75% (95% CI 70% to 80%) in the I.V. palonosetron group and 72% (95% CI 68% to 76%) in the I.V. ondansetron group. The relative difference in CR rate was 3% (95% CI [3%, 27%]).

In a randomized, double-blind, placebo-controlled study, 404 patients were randomized to receive a single dose of Palonosetron Hydrochloride Injection 0.075 mg or placebo. The primary endpoint was the proportion of patients achieving a Complete Response (CR) within 24 hours. Patients were stratified by the out-patient setting for patients undergoing elective gynecologic or abdominal laparoscopic surgery and stratified at the time of randomization by four levels of risk for chemotherapy-induced nausea and vomiting. The results indicated that Palonosetron Hydrochloride Injection 0.075 mg was statistically non-inferior to placebo for prevention of chemotherapy-induced nausea and vomiting. The median time to first rescue antiemetic use was 15 minutes in patients receiving Palonosetron Hydrochloride Injection versus 14 minutes in patients receiving placebo. In addition, patients receiving Palonosetron Hydrochloride Injection reported 24% fewer days of nausea and vomiting and 29% fewer days of rescue antiemetic use compared to patients receiving placebo.

No significant pharmacokinetic interaction was observed between Palonosetron Hydrochloride Injection and concomitant medications, including those associated with induction of anesthesia.

Abnormal Vision
- Changes in color vision
- Blurred vision

Metabolic
- Hypokalemia
- Anorexia

Psychiatric
- Anxiety
- Euphoric mood

Other
- Increased appetite
- Belly pain
- Constipation
- Dry mouth
- Fatigue
- High blood pressure
- Jaundice
- Rash
- Yellowing of the skin or eyes

These adverse reactions were reported infrequently and were not considered treatment-related.