HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZUPLENZ® safely and effectively. See full prescribing information for ZUPLENZ.

ZUPLENZ (ondansetron) oral soluble film
Initial U.S. Approval: 1991

---------- INDICATIONS AND USAGE----------

ZUPLENZ is a 5-HT_3 receptor antagonist indicated for the prevention of:

- nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m^2, in adults.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in adults and pediatric patients 4 years of age and older.
- nausea and vomiting associated with radiotherapy in adult patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen.
- postoperative nausea and/or vomiting in adults.

---------- DOSAGE AND ADMINISTRATION----------

- See full prescribing information for the recommended dosage in adults and pediatrics and preparation and administration (2)
- Patients with severe hepatic impairment: do not exceed a total daily dose of 8 mg (2.2, 8.7)

---------- DOSAGE FORMS AND STRENGTHS----------

Oral soluble film: 4 mg and 8 mg (3)

---------- CONTRAINDICATIONS----------

- Patients known to have hypersensitivity (e.g., anaphylaxis) to ondansetron. (4)
- Concomitant use of apomorphine. (4, 7)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions, including anaphylaxis and bronchospasm: Discontinue ZUPLENZ if suspected. Monitor and treat promptly per standard of care until signs and symptoms resolve. (5.1)
- QT interval prolongation and Torsades de Pointes: Avoid in patients with congenital long QT syndrome; monitor with electrocardiograms (ECGs) if concomitant electrolyte abnormalities, congestive heart failure or arrhythmias or use of other QT prolonging drugs. (5.2)
- Serotonin syndrome: Reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs. If such symptoms occur, discontinue ZUPLENZ and initiate supportive treatment. If concomitant use of ZUPLENZ with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome. (5.3)
- Masking of progressive ileus and/or gastric distension following abdominal surgery or chemotherapy-induced nausea and vomiting: Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction. (5.4)

---------- ADVERSE REACTIONS----------

The most common adverse reactions in adults for:

- prevention of chemotherapy-induced nausea and vomiting (≥5%) are: headache, malaise/fatigue, constipation, and diarrhea. (6.1)
- prevention of radiation-induced nausea and vomiting (≥2%) are: headache, constipation, diarrhea. 6.1)
- prevention of postoperative nausea and vomiting (≥9%) are: headache and hypoxia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aquestive Therapeutics at 1-877-394-5045 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved patient labeling.

Revised: 8/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZUPLENZ is indicated for the prevention of nausea and vomiting associated with:

- highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m^2, in adults
- initial and repeat courses of moderately emetogenic cancer chemotherapy in adults and pediatric patients 4 years of age and older
- radiotherapy in adult patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen

ZUPLENZ is also indicated for the prevention of postoperative nausea and/or vomiting in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage regimens for adult and pediatric patients 4 years of age and older are described in Table 1 and Table 2, respectively.

Table 1: Adult Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Highly Emetogenic Cancer Chemotherapy	A single 24-mg dose (administered successively as three 8-mg films) 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin greater than or equal to 50 mg/m^2. Allow each film to dissolve completely before administering the next film *[see Dosage and Administration (2.3)]*.
Moderately Emetogenic Cancer Chemotherapy	An 8-mg dose administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose. Then, administer 8 mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.
Radiotherapy	For total body irradiation: An 8-mg dose administered 1 to 2 hours before each fraction of radiotherapy each day. For single high-dose fraction radiotherapy to the abdomen: An 8-mg dose administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen: An 8-mg dose administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for each day radiotherapy is given.
Postoperative	A single 16-mg dose (administered successively as two 8-mg films) 1 hour before induction of anesthesia. Allow each film to dissolve completely before administering the next film *[see Dosage and Administration (2.3)]*.

Table 2: Recommended Dosage Regimen for Prevention of Nausea and Vomiting in Pediatric Patients 4 Years of Age and Older

Indication	Dosage Regimen
Moderately Emetogenic Cancer Chemotherapy	12 to 17 years of age: A 8-mg dose administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose. Then administer 8 mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy. 4 to 11 years of age: A 4-mg dose administered 30 minutes before the start of chemotherapy, with a subsequent 4-mg dose at 4 and 8 hours after the first dose. Then, administer 4 mg three times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

2.2 Recommended Dosage in Patients with Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed a total daily dose of 8 mg *[see Use in Specific Populations (8.6)]*.

2.3 Important Preparation and Administration Instructions

1. With dry hands, fold the pouch along the dotted line to expose the tear notch.
2. While still folded, tear the pouch carefully along the edge and remove the ZUPLENZ oral soluble film from the pouch.
3. Immediately place the film on top of the tongue where it dissolves in 4 to 20 seconds.
4. Once the ZUPLENZ oral soluble film is dissolved, swallow with or without liquid. ZUPLENZ may be taken with or without food *[see Clinical Pharmacology (12.3)]*.
5. Wash hands after taking ZUPLENZ.

3 DOSAGE FORMS AND STRENGTHS

Oral soluble film: 4 mg and 8 mg thin, white opaque and rectangularly shaped strips with a printed identifier in black ink of "4 mg" or "8 mg".

4 CONTRAINDICATIONS

ZUPLENZ is contraindicated in patients:

- known to have hypersensitivity (e.g., anaphylaxis) to ondansetron *[see Adverse Reactions (6.2)]*.
- receiving concomitant apomorphine due to the risk of profound hypotension and loss of consciousness *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. If hypersensitivity reactions occur, discontinue use of ZUPLENZ; treat promptly per standard of care and monitor until signs and symptoms resolve *[see Contraindications (4)]*.

5.2 QT Prolongation

Electrocardiogram (ECG) changes including QT interval prolongation have been seen in patients receiving ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ZUPLENZ in patients with congenital long QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation *[see Clinical Pharmacology (12.2)]*.

5.3 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of ondansetron alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes

(e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of ZUPLENZ and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue ZUPLENZ and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ZUPLENZ is used concomitantly with other serotonergic drugs *[see Drug Interactions (7.3), Overdosage (10)]*.

5.4 Masking of Progressive Ileus and/or Gastric Distension

The use of ZUPLENZ in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension. Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction.

ZUPLENZ is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

6 ADVERSE REACTIONS

The following serious or otherwise clinically significant adverse reactions are described elsewhere in labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- QT prolongation *[see Warnings and Precautions (5.2)]*
- Serotonin syndrome *[see Warnings and Precautions (5.3)]*
- Masking of progressive ileus and/or gastric distension *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ZUPLENZ has been established from adequate and well-controlled studies of another oral ondansetron product (ondansetron hydrochloride). Below is a display of the adverse reactions of ondansetron hydrochloride (HCl) in these studies.

Prevention of Chemotherapy-Induced Nausea and Vomiting

The most common adverse reactions reported in greater than or equal to 4% of 300 adults receiving a single 24-mg oral dose of ondansetron HCl in 2 trials for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy (cisplatin greater than or equal to 50 mg/m^2) were: headache (11%) and diarrhea (4%).

The most common adverse reactions reported in 4 trials in adults for the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy (primarily cyclophosphamide-based regimens) are shown in Table 3.

Table 3: Most Common Adverse Reactions in Adults[a] for the Prevention of Nausea and Vomiting with Moderately Emetogenic Chemotherapy [Primarily Cyclophosphamide-Based Regimens]

Adverse Reaction	Oral Ondansetron HCl 8 mg twice daily N=242	Placebo N=262
Headache	58 (24%)	34 (13%)
Malaise/fatigue	32 (13%)	6 (2%)
Constipation	22 (9%)	1 (<1%)
Diarrhea	15 (6%)	10 (4%)

[a] Reported in greater than or equal to 5% of patients treated with oral ondansetron HCl and at a rate that exceeded placebo.

Less Common Adverse Reactions

Central Nervous System: Extrapyramidal reactions (less than 1% of patients).
Hepatic: Aspartate transaminase (AST) and/or alanine transaminase (ALT) values exceeded twice the upper limit of normal in approximately 1% to 2% of 723 patients receiving oral ondansetron HCl and cyclophosphamide-based chemotherapy in US clinical trials. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur. The role of cancer chemotherapy in these biochemical changes is unclear. Liver failure and death have been reported in cancer patients receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.
Integumentary: Rash (approximately 1% of patients).
Other (less than 2%): Anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures. Except for bronchospasm and anaphylaxis, the relationship to ondansetron is

unclear.

Prevention of Radiation-Induced Nausea and Vomiting
The most common adverse reactions (greater than or equal to 2%) reported in adults receiving oral ondansetron HCl and concurrent radiotherapy were similar to those reported in patients receiving oral ondansetron HCl and concurrent chemotherapy and were headache, constipation, and diarrhea.

Prevention of Postoperative Nausea and Vomiting
The most common adverse reactions reported in adults receiving oral ondansetron HCl in trial(s) of prevention of postoperative nausea and vomiting are shown in Table 4. In these trial(s), patients were receiving multiple concomitant perioperative and postoperative medications in both treatment groups.

Table 4: Most Common Adverse Reactions in Adults[a] for the Prevention of Postoperative Nausea and Vomiting

Adverse Reaction	Oral Ondansetron HCl 16 mg as a Single Dose N=550	Placebo N=531
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Urinary retention	28 (5%)	18 (3%)
Pruritus	27 (5%)	20 (4%)

[a] Reported in greater than or equal to 5% of patients treated with oral ondansetron HCl and at a rate that exceeded placebo.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of ondansetron. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, QT/QTc interval prolongation, and ST segment depression), palpitations, and syncope. Rarely and predominantly with intravenous ondansetron HCl, transient ECG changes including QT interval prolongation have been reported.
General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron HCl.
Hepatobiliary: Liver enzyme abnormalities
Lower Respiratory: Hiccups
Neurology: Oculogyric crisis, appearing alone, as well as with other dystonic reactions
Skin: Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis
Eye Disorders: Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours.

7 DRUG INTERACTIONS
7.1 Apomorphine
Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contraindicated *[see Contraindications (4)]*.

7.2 Serotonergic Drugs
Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitor (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). Monitor for the emergence of serotonin syndrome. If symptoms occur, discontinue ZUPLENZ and initiate supportive treatment *[see Warnings and Precautions (5.3)]*.

7.3 Drugs Affecting Cytochrome P-450 Enzymes
Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver. Because ondansetron is metabolized by hepatic cytochrome P450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ZUPLENZ is recommended for patients on these drugs *[see Clinical Pharmacology (12.3)]*.

7.4 Tramadol
Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from two small trials indicate that when used together, ondansetron may increase patient-controlled administration of tramadol. Monitor patients to ensure adequate pain control when ZUPLENZ is administered with tramadol.

7.5 Chemotherapy
Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, intravenous ondansetron HCl did not increase systemic concentrations of high-dose methotrexate.

7.6 Temazepam
The co-administration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

7.7 Alfentanil and Atracurium
Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

Published epidemiological studies on the association between ondansetron use and major birth defects have reported inconsistent findings and have important methodological limitations that preclude conclusion about the safety of ondansetron use in pregnancy *(see Data)*. Available postmarketing data have not identified a drug-associated risk of miscarriage or adverse maternal outcomes. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Available data on ondansetron use in pregnant women from several published epidemiological studies preclude an assessment of a drug-associated risk of adverse fetal outcomes due to important methodological limitations, including the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, recall bias, and other unadjusted confounders.

Ondansetron exposure in utero has not been associated with overall major congenital malformations in aggregate analyses. One large retrospective cohort study examined 1970 women who received a prescription for ondansetron during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low birth weight or small for gestational age.

Two large retrospective cohort studies and one case-control study have assessed ondansetron exposure in the first trimester and risk of cardiovascular defects with inconsistent findings. Relative risks (RR) ranged from 0.97 (95% CI 0.86 to 1.10) to 1.62 (95% CI 1.04, 2.54). A subset analysis in one of the cohort studies observed that ondansetron was specifically associated with cardiac septal defects (RR 2.05, 95% CI 1.19, 3.28); however, this association was not confirmed in other studies.

Several studies have assessed ondansetron and the risk of oral clefts with inconsistent findings. A retrospective cohort study of 1.8 million pregnancies in the US Medicaid Database showed an increased risk of oral clefts among 88,467 pregnancies in which oral ondansetron was prescribed in the first trimester (RR 1.24, 95% CI 1.03, 1.48), but no such association was reported with intravenous ondansetron in 23,866 pregnancies (RR 0.95, 95% CI 0.63, 1.43). In the subgroup of women who received both forms of administration, the RR was 1.07 (95% CI 0.59, 1.93). Two case-control studies, using data from birth defects surveillance programs, reported conflicting associations between maternal use of ondansetron and isolated cleft palate (OR 1.6 [95% CI 1.1, 2.3] and 0.5 [95% CI 0.3, 1.0]). It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6th and 9th weeks of pregnancy

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight

gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

8.2 Lactation

Risk Summary

It is not known whether ondansetron is present in human milk. There are no data on the effects of ZUPLENZ on the breastfed infant or the effects on milk production. However, it has been demonstrated that ondansetron is present in the milk of rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZUPLENZ and any potential adverse effects on the breast fed infant from ZUPLENZ or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ZUPLENZ have been established in pediatric patients 4 years of age and older for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Use of ZUPLENZ in these age-groups is supported by evidence from adequate and well-controlled studies of ondansetron HCl in adults with additional data from 3 open-label, uncontrolled, non-US trials in 182 pediatric patients aged 4 to 18 years with cancer who were given a variety of cisplatin or noncisplatin regimens *[see Dosage and Administration (2.1), Clinical Studies (14.1)]*.

The safety and effectiveness of ZUPLENZ have not been established in pediatric patients for:

- prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy
- prevention of nausea and vomiting associated with radiotherapy
- prevention of postoperative nausea and/or vomiting.

8.5 Geriatric Use

Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and non-US-controlled clinical trials of oral ondansetron, for which there were subgroup analyses, 938 (19%) were 65 years of age and over.

No overall differences in safety or effectiveness were observed between these subjects 65 years of age and older and younger subjects. A reduction in clearance and increase in elimination half-life were seen in patients older than 75 years compared to younger subjects *[see Clinical Pharmacology (12.3)]*. There were an insufficient number of patients older than 75 years of age and older in the clinical trials to permit safety or efficacy conclusions in this age-group. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is needed in elderly patients.

8.6 Renal Impairment

No dosage adjustment is recommended for patients with any degree of renal impairment (mild, moderate, or severe. There is no experience beyond first-day administration of ondansetron *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment.

In patients with severe hepatic impairment, clearance is reduced, and the apparent volume of distribution is increased, resulting in a significant increase in the half-life of ondansetron. Therefore, do not exceed a total daily dose of 8 mg in patients with severe hepatic impairment (Child-Pugh score of 10 or greater) *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

10 OVERDOSAGE

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy.

In addition to the adverse reactions listed above, the following events have been described in the setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in 1 patient that was administered 72 mg of ondansetron HCl intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of oral ondansetron HCl. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the adverse reactions resolved completely.

Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg/kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

11 DESCRIPTION

The active ingredient in ZUPLENZ is ondansetron base, the racemic form of ondansetron, and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one. The structural formula is shown in Figure 1.

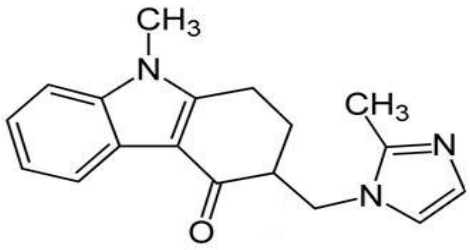

Figure 1: Structural formula of ondansetron

The empirical formula is $C_{18}H_{19}N_3O$ representing a molecular weight of 293.3.

Each 4-mg ZUPLENZ oral soluble film for oral administration contains 4 mg ondansetron base. Each 8-mg ZUPLENZ oral soluble film for oral administration contains 8 mg ondansetron base. Each ZUPLENZ oral soluble film also contains the inactive ingredients butylated hydroxytoluene, calcium carbonate, colloidal silicon dioxide, erythritol, hypromellose, monoammonium glycyrrhizinate, peppermint flavor, polyethylene oxide, sodium bicarbonate, sucralose, titanium dioxide and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

12.2 Pharmacodynamics

In healthy subjects, single intravenous doses of 0.15 mg/kg of ondansetron HCl had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

Cardiac Electrophysiology

QTc interval prolongation was studied in a double-blind, single-intravenous dose, placebo- and positive- controlled, crossover trial in 58 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 19.5 (21.8) milliseconds and 5.6 (7.4) milliseconds after 15-minute intravenous infusions of 32 mg and 8 mg of ondansetron HCl injection, respectively. A significant exposure- response relationship was identified between ondansetron concentration and ΔΔQTcF. Using the established exposure-response relationship, 24 mg infused intravenously over 15 minutes had a mean predicted (95% upper prediction interval) ΔΔQTcF of 14.0 (16.3) milliseconds. In contrast, 16 mg infused intravenously over 15 minutes using the same model had a mean predicted (95% upper prediction interval) ΔΔQTcF of 9.1 (11.2) milliseconds. In this study, the 8-mg dose infused over 15 minutes did not prolong the QT interval to any clinically relevant extent.

12. 3 Pharmacokinetics

Absorption

Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. After a single dose of ZUPLENZ 8 mg under fasting conditions (n=46), the peak plasma concentrations were achieved in 1.3 hours and the mean elimination half-life was 4.6 hours in healthy subjects. The mean (±S.D.) C_{max} and AUC were 37.28 (±14.9) ng/mL and 225 (±88.1) ng·h/mL, respectively. In the same study, mean ondansetron C_{max} and AUC following administration of 8 mg ZUPLENZ were comparable to those after 8 mg ondansetron orally disintegrating tablets. The systemic exposure after administration of ZUPLENZ 8 mg with or without water was found to be comparable *[see Dosage and Administration (2.3)]*.

In a study of oral ondansetron HCl tablets, ondansetron systemic exposure did not increase proportionately to dose. The AUC from a 16-mg tablet was 24% greater than predicted from an 8 mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses.

Food Effects

When ZUPLENZ 8 mg was administered with a high fat meal, mean time to peak plasma concentration (t_{max}) was delayed by approximately 1 hour and AUC remained similar compared to that under fasted conditions *[see Dosage and Administration (2.3)]*.

Distribution

Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes.

Elimination

Metabolism and Excretion

Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The metabolites are observed in the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination.

Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

Specific Populations

Geriatric Patients

A reduction in clearance and increase in elimination half-life are seen in patients over 75 years of age compared to younger subjects *[see Use in Specific Populations (8.5)]*.

Male and Female Patients

Differences between male and female patients were shown in the disposition of ondansetron given as a single dose. The extent and rate of absorption are greater in women than men.

Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron concentrations. These higher plasma concentrations may in part be explained by differences in body weight between men and women. It is not known whether these sex-related differences were clinically important. More detailed pharmacokinetic information is contained in Tables 5 and 6.

Table 5: Pharmacokinetics in Male and Female Healthy Subjects after a Single Dose of an Ondansetron HCl 8-mg Tablet

Age-group (years) Sex (M/F)	Mean Weight (kg)	N	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)	Systemic Plasma Clearance L/h/kg	Absolute Bioavailability
18-40 M	69.0	6	26.2	2.0	3.1	0.403	0.483
F	62.7	5	42.7	1.7	3.5	0.354	0.663
61-74 M	77.5	6	24.1	2.1	4.1	0.384	0.585
F	60.2	6	52.4	1.9	4.9	0.255	0.643
≥75 M	78.0	5	37.0	2.2	4.5	0.277	0.619
F	67.6	6	46.1	2.1	6.2	0.249	0.747

Table 6: Pharmacokinetics in Male and Female Healthy Subjects after a Single Dose of an Ondansetron HCl 24-mg Tablet

Age-group (years) Sex (M/F)	Mean Weight (kg)	N	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)
18-43 M	84.1	8	125.8	1.9	4.7
F	71.8	8	194.4	1.6	5.8

Renal Impairment
Renal impairment is not expected to significantly influence the total clearance of ondansetron as renal clearance represents only 5% of the overall clearance. However, the mean plasma clearance of ondansetron was reduced by about 50% in patients with severe renal impairment (creatinine clearance less than 30 mL/min). The reduction in clearance was variable and not consistent with an increase in half-life *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment
In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared to 5.7 hours in healthy subjects. In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), clearance is reduced 2-fold to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours *[see Dosage and Administration (2.2), Use in Specific Populations (8.6)]*.

Drug Interaction Studies
CYP 3A4 Inducers: Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic trial of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, a reduction in AUC, C_{max}, and t½ of ondansetron was observed. This resulted in a significant increase in the clearance of ondansetron. However, this increase is not thought to be clinically relevant *[see Drug Interactions (7.2)]*.

Chemotherapeutic Agents: Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron *[see Drug Interactions (7.4)]*.

Antacids: Concomitant administration of antacids does not alter the absorption of ondansetron.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 mg/kg/day and 30 mg/kg/day, respectively (approximately 4 and 6 times the human dose of 24 mg/day, based on body surface area). Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/day (approximately 6 times the human dose of 24 mg/day, based on body surface area) did not affect fertility or general reproductive performance of male and female rats.

14 CLINICAL STUDIES

The safety and efficacy of ZUPLENZ have been established based on adequate and well-controlled adult studies of another oral ondansetron product (ondansetron HCl). Below is a display of the results of these adequate and well-controlled studies of ondansetron HCl in these conditions.

14.1 Prevention of Chemotherapy-Induced Nausea and Vomiting

Highly Emetogenic Chemotherapy

In 2 randomized, double-blind, monotherapy trials, a single 24-mg oral dose of ondansetron HCl was superior to a relevant historical placebo control in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2. Steroid administration was excluded from these clinical trials. More than 90% of patients receiving a cisplatin dose ≥50 mg/m^2 in the historical placebo comparator experienced vomiting in the absence of antiemetic therapy.

The first trial compared oral doses of ondansetron HCl 24 mg once a day, 8 mg every 8 hours for 2 doses, and 32 mg as a single dose in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin ≥50 mg/m^2. The first or single dose was administered 30 minutes prior to chemotherapy. A total of 66% of patients in the 24 mg once-a-day group, 55% in the 8 mg twice-a-day group, and 55% in the 32 mg once-a-day group completed the 24-hour study period with 0 emetic episodes and no rescue antiemetic medications, the primary endpoint of efficacy. Each of the 3 treatment groups was shown to be statistically significantly superior to a historical placebo control.

In the same trial, 56% of patients receiving a single 24-mg oral dose of ondansetron HCl experienced no nausea during the 24-hour study period, compared with 36% of patients in the 8 mg twice-a-day group ($p = 0.001$) and 50% in the 32 mg once-a-day group. Dosage regimens of ZUPLENZ 8 mg twice daily and 32 mg once daily are not recommended for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy *[see Dosage and Administration (2.1)]*.

In a second trial, efficacy of a single 24-mg oral dose of ondansetron HCl for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2, was confirmed.

Moderately Emetogenic Chemotherapy

A randomized, placebo-controlled, double-blind trial was conducted in the US study in 67 patients receiving a cyclophosphamide-based chemotherapy containing doxorubicin. The first 8-mg oral dose of ondansetron HCl was administered 30 minutes before the start of chemotherapy, with a subsequent dose 8 hours after the first dose, followed by 8 mg of ondansetron HCl twice a day for 2 days after the completion of chemotherapy. Oral ondansetron HCl was significantly more effective than placebo in preventing vomiting. Treatment response was based on the total number of emetic episodes over the 3-day study period. The results of this study are summarized in Table 7.

Table 7: Emetic Episodes: Treatment Response in Patients Receiving Moderately Emetogenic Chemotherapy (Cyclophosphamide-based Regimen Containing Doxorubicin)

	Oral Ondansetron HCl (n = 33)	**Placebo (n = 34)**	***P* Value**
Treatment response 0 Emetic episodes	20 (61%)	2 (6%)	<0.001
1 to 2 Emetic episodes	6 (18%)	8 (24%)	
More than 2 emetic episodes/withdrawn	7 (21%)	24 (71%)	<0.001
Median number of emetic episodes	0.0	Undefined[a]	
Median time to first emetic episode (hours)	Undefined[b]	6.5	

[a] Median undefined since at least 50% of the patients were withdrawn or had more than 2 emetic episodes.
[b] Median undefined since at least 50% of patients did not have any emetic episodes.

In a double-blind US study in 336 patients receiving a cyclophosphamide-based chemotherapy regimen containing either methotrexate or doxorubicin, oral ondansetron HCl 8 mg administered twice a day was as effective as oral ondansetron HCl 8 mg administered 3 times a day in preventing nausea and vomiting. ZUPLENZ 8 mg three times daily is not a recommended regimen for the treatment of moderately emetogenic chemotherapy *[see Dosage and Administration (2.1)]*.

Treatment response was based on the total number of emetic episodes over the 3-day study period. See Table 8 for the details of the dosage regimens studied and the results of this trial.

Table 8: Emetic Episodes: Treatment Response After Ondansetron HCl Administered Twice A Day and Three Times A Day

	Oral Ondansetron HCl	
	8 mg Twice Daily[a]	**8 mg Three Times a Day[b]**
Number of patients	**165**	**171**
Treatment response		
0 emetic episodes	101 (61%)	99 (58%)
1-2 emetic episodes	16 (10%)	17 (10%)
>2 emetic episodes/withdrawn	48 (29%)	55 (32%)
Median number of emetic episodes	0.0	0.0
Median time to first emetic episode (h)	Undefined[c]	Undefined[c]
Median nausea scores (0-100)[d]	6	6

[a] The first 8-mg dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose, followed by 8-mg administered twice a day for 2 days after completion of chemotherapy.
[b] The first 8-mg dose was administered 30 minutes before the start of emetogenic chemotherapy, with subsequent 8-mg doses 4 and 8 hours after the first dose, followed by 8-mg administered three times a day for 2 days after completion of chemotherapy.
[c] Median undefined since at least 50% of patients did not have any emetic episodes.
[d] Visual analog scale assessment: 0=no nausea, 100=nausea as bad as it can be.

Re-treatment

In single-arm trials, 148 patients receiving cyclophosphamide-based chemotherapy were re-treated with oral ondansetron HCl 8 mg three times daily during subsequent chemotherapy for a total of 396 re-treatment courses. No emetic episodes occurred in 314 (79%) of the re-treatment courses, and only 1 to 2 emetic episodes occurred in 43 (11%) of the re-treatment courses.

Pediatric Trials

Three open-label, single-arm, non-US trials have been performed with 182 pediatric patients 4 to 18 years old with cancer who were given a variety of cisplatin or non-cisplatin regimens. The initial dose of ondansetron HCl injection ranged from
0.04 mg/kg to 0.87 mg/kg (total dose of 2.16 mg to 12 mg) followed by the administration of oral doses of ondansetron HCl ranging from 4 mg to 24 mg daily for 3 days. In these studies, 58% of the 170 evaluable patients had a complete response (no emetic episodes) on day 1. In 2 trials, the response rates to ondansetron HCl 4 mg three times daily in patients younger than 12 years was similar to ondansetron HCl 9 mg three times daily in patients 12 to 18 years of age. Prevention of emesis in these pediatric patients was essentially the same as for adults.

14.2 Prevention of Radiation-Induced Nausea and Vomiting

Total Body Irradiation

In a randomized, double-blind study in 20 patients, 8 mg of oral ondansetron HCl administered 1.5 hours before each fraction of radiotherapy for 4 days was significantly more effective than placebo in preventing vomiting induced by total body irradiation. Total body irradiation consisted of 11 fractions (120 cGy per fraction) over 4 days for a total of 1,320 cGy. Patients received 3 fractions for 3 days, then 2 fractions on Day 4.

Single High-Dose Fraction Radiotherapy

In an active-controlled, double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of $\geq$80 cm^2 to the abdomen, oral ondansetron HCl was significantly more effective than oral metoclopramide with respect to complete control of emesis (0 emetic episodes). Patients received the first dose of oral ondansetron HCl (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If radiotherapy was given in the morning, 8 mg of ondansetron HCl or 10 mg of metoclopramide was administered in the late afternoon and repeated again before bedtime. If radiotherapy was given in the afternoon, patients took 8 mg of ondansetron HCl or 10 mg of metoclopramide only once before bedtime. Patients continued the doses of oral medication three times daily for 3 days.

Daily Fractionated Radiotherapy

In an active-controlled, double-blind trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses) over a field size of >100 cm^2 to the abdomen, oral ondansetron HCl was significantly more effective than prochlorperazine with respect to complete control of emesis (0 emetic episodes). Patients received the first dose of oral ondansetron HCl (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the first daily radiotherapy fraction, with subsequent 8-mg doses approximately every 8 hours on each day of radiotherapy.

14.3 Prevention of Postoperative Nausea and Vomiting

In 2 placebo-controlled, double-blind studies (one conducted in the US and the other outside the US) in 865 females undergoing inpatient surgical procedures, oral ondansetron HCl 16 mg as a single dose or placebo was administered one hour before the induction of general balanced anesthesia (barbiturate, opioid, nitrous oxide, neuromuscular blockade, and supplemental isoflurane or enflurane), oral ondansetron HCl was significantly more effective than placebo in preventing postoperative nausea and vomiting.

No trials have been performed in males.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZUPLENZ (ondansetron) Oral Soluble Film

- 4 mg: thin, white opaque and rectangularly shaped strips printed with “4 mg” in black ink supplied in individual foil-sealed child-resistant pouches and packaged in boxes of 1 (NDC 89141-444-01) or boxes of 30 (NDC 89141-444-30).
- 8 mg: thin, white opaque and rectangularly shaped strips printed with “8 mg” in black ink supplied in individual foil-sealed child-resistant pouches and packaged in boxes of 1 (NDC 89141-448-01) and boxes of 30 (NDC 89141-448-30).

Store at controlled room temperature 20° to 25°C (68° to 77°F). Store pouches in cartons. Keep product in pouch until ready to use.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

Hypersensitivity Reactions

Inform patients that ZUPLENZ may cause hypersensitivity reactions, some as severe as anaphylaxis and bronchospasm. Instruct patients to immediately report any signs and symptoms of hypersensitivity reactions, including fever, chills, rash,

or breathing problems to their healthcare provider *[see Warnings and Precautions (5.1)]*.

QT Prolongation

Inform patients that ZUPLENZ may cause serious cardiac arrhythmias such as QT prolongation. Instruct patients to tell their healthcare provider right away if they perceive a change in their heart rate, if they feel lightheaded, or if they have a syncopal episode *[see Warnings and Precautions (5.2)]*.

Drug Interactions

- Instruct the patient to report the use of all medications, especially apomorphine, to their healthcare provider. Concomitant use of apomorphine and ZUPLENZ may cause a significant drop in blood pressure and loss of consciousness *[see Contraindications (4)]*.
- Advise patients of the possibility of serotonin syndrome with concomitant use of ZUPLENZ and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or without gastrointestinal symptoms *[see Warnings and Precautions (5.3)]*.

Masking of Progressive Ileus and Gastric Distension

Inform patients following abdominal surgery or those with chemotherapy-induced nausea and vomiting that ZUPLENZ may mask signs and symptoms of bowel obstruction. Instruct patients to immediately report any signs or symptoms consistent with a potential bowel obstruction to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Preparation and Administration

Instruct patients as follows:

1. With dry hands, fold the pouch along the dotted line to expose the tear notch.
2. While still folded, tear the pouch carefully along the edge and remove the ZUPLENZ oral soluble film from the pouch.
3. Immediately place the film on top of the tongue where it dissolves in 4 to 20 seconds.
4. Once the ZUPLENZ oral soluble film is dissolved, swallow with or without liquid. ZUPLENZ may be taken with or without food.
5. Wash hands after taking ZUPLENZ *[see Dosage and Administration (2.3)]*.

Patient Information
ZUPLENZ® (ZOO-plenz)
(ondansetron)
oral soluble film

What is ZUPLENZ?

ZUPLENZ is a prescription medicine that is used in adults to prevent nausea and vomiting:

- that happens with certain cancer chemotherapy medicines, radiation therapy to your stomach-area (abdomen), or radiation therapy to your entire body.
- that may happen after surgery.

In children 4 years of age and older, ZUPLENZ is only used to prevent nausea and vomiting that happens with certain cancer chemotherapy medicines.

It is not known if ZUPLENZ is safe and effective in children to prevent nausea and vomiting with radiation therapy, nausea and vomiting that may happen after surgery, or nausea and vomiting associated with highly emetogenic cancer chemotherapy.

Who should not take ZUPLENZ?

Do not take ZUPLENZ if you:

- have had an allergic reaction to ondansetron, the active ingredient in ZUPLENZ
- take apomorphine hydrochloride (Apokyn, Kynmobi)

What should I tell my doctor before taking ZUPLENZ?

Before you take ZUPLENZ, tell you doctor about all of your medical conditions, including if you:

- have any heart problems, including a condition called “congenital long QT syndrome”.
- take a medicine that causes heart problems (QT prolongation).
- have low blood levels of potassium or magnesium.
- have liver problems.
- have had recent stomach-area (abdomen) surgery.
- are pregnant or plan to become pregnant. It is not known if ZUPLENZ will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ZUPLENZ passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how ZUPLENZ works, and ZUPLENZ may affect how other medicines work. Taking ZUPLENZ with certain other medicines may cause serious side effects.

Especially tell your doctor if you take:

- medicines called selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or monoamine oxidase inhibitors (MAOIs). Ask your doctor if you are not sure if you take these medicines.
- tramadol hydrochloride (Ultram, Ultram ER, Ryzolt, ConZip, Rybix ODT).
- any other medicine for nausea and vomiting.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take ZUPLENZ?

- Read the Instructions for Use at the end of this Patient Information for information about the right way to take ZUPLENZ.
- Take ZUPLENZ exactly as your doctor tells you to take it.
- If you take too much ZUPLENZ, call your doctor or go to the nearest hospital emergency room right away.
- An adult should help a young child use ZUPLENZ.

What should I avoid while taking ZUPLENZ?

ZUPLENZ may cause dizziness. Do not drive, operate machinery, or do other dangerous activities until you know how ZUPLENZ affects you.

What are the possible side effects of ZUPLENZ?

ZUPLENZ may cause serious side effects, including:

- **severe allergic reactions**. Stop taking ZUPLENZ and get medical help right away if you have any of these signs or symptoms of an allergic reaction to ZUPLENZ:
  - o fever
  - o chills
  - o chest tightness or chest pain
  - o rash
  - o itching
  - o swelling of your mouth, face, lips or tongue
  - o hives
  - o trouble breathing
- **heart rhythm changes**. ZUPLENZ can cause a change in the electrical activity in your heart called QT prolongation, which can cause irregular heartbeats. Tell your doctor right away if you get any symptoms of heart rhythm changes such as feeling as if your heart is beating fast, irregular or slow, if you feel lightheaded or you faint.
- **serotonin syndrome.** A possible life-threatening problem called serotonin syndrome can happen with medicines called 5-HT_3 receptor antagonists, including ZUPLENZ, especially when used with medicines to treat migraine headaches and depression called selective serotonin **reuptake inhibitors** (SSRIs), serotonin and

norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and certain other medicines. Get medical help right away if you have any of these signs or symptoms of serotonin syndrome:

o agitation	o seeing things that are not there	o confusion
o coma	o rapid pulse	o high or low blood pressure
o dizziness	o sweating	o flushing
o fever	o tremors	o stiff muscles
o muscle twitching	o become unstable	o seizures
o nausea	o vomiting	o diarrhea

- **ZUPLENZ may make it more difficult to recognize the signs and symptoms of a blockage in the intestine (bowel obstruction) in people who have had stomach-area (abdomen) surgery or nausea and vomiting after chemotherapy**. Tell your doctor right away if you have had stomach-area (abdomen) surgery or nausea and vomiting after chemotherapy and you have any signs or symptoms of a blockage in your intestine while taking ZUPLENZ, including: stomach pain or swelling of your stomach-area (abdomen).

The most common side effects of ZUPLENZ in adults include:

- headache
- tiredness and body discomfort
- constipation
- diarrhea
- low oxygen in the blood (hypoxia)

These are not all the possible side effects of ZUPLENZ. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZUPLENZ?

- Store ZUPLENZ at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep ZUPLENZ in the foil pouch until ready to use. Keep foil pouches in the carton.
- Use ZUPLENZ right after you take it out of the pouch.

Keep ZUPLENZ and all medicines out of the reach of children.

General information about the safe and effective use of ZUPLENZ.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZUPLENZ for a condition for which it was not prescribed. Do not give ZUPLENZ to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your doctor or pharmacist for information about ZUPLENZ that is written for health professionals.

What are the ingredients in ZUPLENZ?
Active ingredient: ondansetron
Inactive ingredients: butylated hydroxytoluene, calcium carbonate, colloidal silicon dioxide, erythritol, hypromellose, monoammonium glycyrrhizinate, peppermint flavor, polyethylene oxide, sodium bicarbonate, sucralose, titanium dioxide and xanthan gum.

Manufactured by:
Aquestive Therapeutics
Warren, NJ 07059
For more information call 1-877-394-5045.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: August 2021

Instructions for Use
ZUPLENZ® (ZOO-plenz)
(ondansetron)
oral soluble film

Step 1. Keep the ZUPLENZ film in the foil pouch until ready to use. Use ZUPLENZ film right away after you take it out of the pouch.

Step 2. Make sure your hands are dry.

Step 3. Fold the pouch along the dotted line to expose the tear notch. See Figure A.

Figure A

Step 4. While still folded, tear the pouch carefully along the edge. See Figure B.

Figure B

Step 5. Take the ZUPLENZ film out of the pouch. See Figure C.

Figure C

Step 6. Put the ZUPLENZ film on top of your tongue. It will dissolve in 4 to 20 seconds. See Figure D.

Figure D

Step 7. Do not chew or swallow the film whole.

Step 8. Swallow after the ZUPLENZ film dissolves. You may swallow the dissolved film with or without food or liquid.

Step 9. Wash your hands after taking ZUPLENZ.

How should I store ZUPLENZ?

- Store ZUPLENZ at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep ZUPLENZ in the foil pouch until ready to use. Keep foil pouches in the carton.
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