SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Medicinal Product

OFRAN ORAL SOLUTION

2. Qualitative and Quantitative Composition

Each 5 ml solution contains Ondansetron 4 mg as Ondansetron hydrochloride USP.

For a full list of excipients, see section 6.1

3. Pharmaceutical Form

Oral Solution.
A clear colorless raspberry flavored liquid having sweet and bitter after taste, filled and sealed in an amber PET bottle with "SQUARE" printed white color PP cap. Free from any visible foreign particles.

4. Clinical Particulars

4.1 Therapeutic Indication

OFRAN ORAL SOLUTION is indicated for
1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy
2. Prevention of nausea and vomiting associated with radiotherapy
3. Prevention of post-operative nausea and vomiting

4.2 Posology and Administration

Prevention of chemotherapy induced nausea & vomiting (CINV):
In case of moderately emetogenic chemotherapy the oral dose is 10 ml of Ondansetron oral solution given twice daily.

Pediatric patients- oral solution- for pediatric patients 4 through 11 years of age the dosage is 5ml of Ondansetron solution should be administered 3 times a day for 1 to 2 days after completion of chemotherapy.

Radiotherapy induced nausea and vomiting:

Adult- oral solution: the recommended oral dosage is 10ml of Ondansetron oral solution given 3 times daily.

Post-operative nausea & vomiting (PONV):
The recommended dosage is 20 ml of Ondansetron oral solution 1hour before induction of anesthesia. Dose adjustment for patients with impaired hepatic function-

The total daily dose of 8 mg should not be exceeded.

4.3 Contraindications

Ondansetron is contraindicated in patients with known hypersensitivity to the drug.

4.4 Special Warnings and Precautions for Use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other 5- HT3 receptor antagonists.
Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of Ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

In patients treated with potent inducers of CYP3A4 (i.e., Phenytoin, Carbamazepine or Rifampicin), the oral clearance of Ondansetron was increased and Ondansetron blood
concentrations were decreased. Data from small studies indicate that Ondansetron may reduce the analgesic effect of tramadol.

4.6 Pregnancy and Lactation

In Pregnancy: Pregnancy category B. Reproduction studies at daily oral dose up to 10 and 30mg/kg/day have been performed in animals and have revealed no evidence of impaired fertility harm to the fetus due to Ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. So, the drug should be used in pregnancy only if clearly needed.

In Lactation: Ondansetron excretes in milk of lactating animals. Caution should be exercised when Ondansetron is administered to nursing mother.

4.7 Effects on ability to drive and use medicines

Ondansetron has no or negligible influence on the ability to drive and use machines.

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8 Undesirable Effects

The most common adverse effects include headache, constipation and diarrhea. In chemotherapy induced nausea and vomiting rash has occurred in approximately 1% of patients receiving Ondansetron.
Blurred vision, chest pain with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia have been rarely reported.

Reporting of suspected adverse reactions:
Healthcare professionals are requested to report any suspected adverse reactions via the national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

4.9 Overdose

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

Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg per 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.

5 Pharmacological Properties

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Serotonin (5HT3) antagonist. ATC code: A04AA01

Mechanism of action:

Ondansetron is a selective 5-HT3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT3 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-hydroxyindoleacetic acid (5-HIAA) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT3 receptors and initiate the vomiting reflex.

5.2 Pharmacokinetic Properties

Absorption

Ondansetron is absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8-mg Ondansetron, is approximately 56%. Ondansetron systemic exposure does not increase proportionately to dose. The area under curve (AUC) from a 16-mg Ondansetron was 24% greater than predicted from an 8-mg Ondansetron dose. This may reflect some reduction of first-pass metabolism at higher oral doses.

Food Effects: Bioavailability is also slightly enhanced by the presence of food.

Distribution

Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the concentration range of 10 to 500 mg/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

Age: Geriatric Population: A reduction in clearance and increase in elimination half-life are seen in patients older than 75 years compared to younger subjects [see Use in Specific Populations.

Sex: Gender differences 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.

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.

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 with 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.

5.3 Preclinical Safety Data

Embryo-foetal development studies in rats and rabbits did not show evidence of harm to the foetus when ondansetron was administered during the period of organogenesis at approximately 6 and 24 times respectively the maximum recommended human oral dose of 24 mg/day, based on body surface area. In a pre- and postnatal developmental toxicity study, there were no effects upon pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance at approximately 6 times the maximum recommended human oral dose of 24 mg/day based on body surface area.

6 Pharmaceutical Particulars

6.1 List of Excipients

1. Sucralose
2. Anhydrous Citric Acid
3. Glycerol
4. Sodium Benzoate
5. Sodium Citrate
6. Liquid Sorbitol (Non Crystalizing)
7. Raspberry Liquid Essence No.1 NA
8. Purified water

6.2 Incompatibilities

None reported.

6.3 Shelf Life

2 Years (24 Months)

6.4 Special Precautions for Storage

Store below 30°C. Protect from light. Keep out of the reach of children.

6.5 Packaging

Each PET bottle contains 50 ml solution.

6.6 Special Precautions for Disposal and Other Handling

No special precaution.

6.7 Category

POM, Recommended for using as directed by the physicians.

7. Marketing Authorization Holder:

SQUARE Pharmaceuticals Ltd
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8. Marketing Authorization Number:

H2022/CTD10171/23014

9. Date of first Authorization /renewal of the authorization:

19-07-2023

10. Date of revision of text:

19-07-2023