SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Medicinal Product

Ofran Injection

2. Qualitative and Quantitative Composition

Each 4 ml injection contains Ondansetron 8 mg as Ondansetron Hydrochloride USP.

For a full list of excipients, see section 6.1

3. Pharmaceutical Form

IV Injection.
A clear colorless solution having characteristic odor, filled and sealed in a 5 ml amber glass ampoule. Free from any visible foreign particles.

4. Clinical Particulars

4.1 Therapeutic Indication

Ofran Injection 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) Adult
The recommended IV dose of Ofran (Ondansetron) is a single 32 mg dose or three 0.15 mg/kg doses. A single 32 mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of Ofran.

Pediatric Patients
The dosage in pediatric patients (4 to 18 years of age) should be three 0.15 mg/kg doses.

Post-operative Nausea & Vomiting (PONV) Adult
The recommended IV dosage of Ofran for adults is 4 mg undiluted administered intravenously in not less than 30 seconds, preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Alternatively, 4 mg undiluted may be administered intramuscularly as a single injection for adults.

In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, IV dose of Ondansetron 4 mg, administration of a second IV dose of 4 mg Ondansetron postoperatively does not provide additional control of nausea and vomiting.

Pediatric Patients
The recommended IV dosage of Ofran for pediatric patients (2 to 12 years of age) is a single 0.1mg/kg dose for pediatric patients weighing 40 kg or less, or a single 4 mg dose for pediatric patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes. Little information is available about dosage in pediatric patients younger than 2 years of age.

Dosage Adjustment for Patients with Impaired Hepatic Function
A single maximal dose of 8 mg to be infused over 15 minutes beginning 30 minutes before the start of the emetogenic chemotherapy is recommended.

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 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.

4.8 Overdose

Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block. In all instances, the events resolved completely. Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose. There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate. The use of ipecacuanha to treat overdose with
ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

Paediatric Population:

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4 mg/kg) in infants and children aged 12 months to 2 years.

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.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists.

ATC Code: A04AA01

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex.

Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting. Ondansetron does not alter plasma prolactin concentrations. The role of ondansetron in opiate-induced emesis is not yet established. The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-

correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec. No significant
changes were seen in the measured electrocardiographic PR or QRS intervals.

5.2 Pharmacokinetic Properties

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. A direct correlation of plasma concentration and anti-emetic effect has not been established.

Absorption: Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (Bioavailability is about 60%). Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. A 4 mg intravenous infusion of ondansetron given over 5 minutes' results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

Distribution: The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a steady state volume of distribution of about 140 L. Equivalent systemic exposures is achieved after IM and IV administration of ondansetron. Ondansetron is not highly protein bound (70-76%).

Metabolism: Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Excretion: Less than 5% of the absorbed dose is excreted unchanged in the urine. Terminal half-life is about 3 hours.

5.3 Preclinical Safety Data

Not available.

6 Pharmaceutical Particulars

6.1 List of Excipients

Anhydrous Citric Acid
Sodium Chloride
Sodium Citrate
Water For Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Absence of Compatibility Studies

“This medicinal product must not be mixed with other medicinal products”

6.4 Shelf Life

2 Years (24 Months)

6.5 Special Precautions for Storage

Store below 30°C, protected from light and moisture.

6.6 Special Precautions for Usage

No special requirements

7. Marketing Authorization Holder:
Square Pharmaceuticals Ltd.

8. Marketing Authorization Number:
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9. Date of first Authorization /renewal of the authorization:
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10. Date of revision of text:
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