

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. Name of the Medicinal Product

**OBEREM**(Ondansetron Oral Solution USP 2mg/5ml)

## 2. Qualitative and Quantitative Composition

Composition:

Each 5ml contains:

Ondansetron Hydrochloride USP

Equivalent to Ondansetron 2.0mg

Flavoured Syrupy Base q.s.

Excipient(s) with known effect Each ml contains Propylene Glycol, Methyl Paraben, Propyl Paraben and Ponceau 4R.

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM: Oral Solution.

**Product Description:** Pink colour clear liquid having sweet taste and pleasant flavor.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications:

1) OBEREM is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

2) OBEREM is also indicated for the prevention and treatment of post-operative nausea and vomiting. Routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and vomiting will occur.

3) For the short-term treatment of nausea/vomiting associated with acute gastroenteritis.

### 4.2 Posology and method of administration:

Chemotherapy and Radiotherapy

Adults: The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of Ondansetron hydrochloride should be flexible in the range of 8-32mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy: Ondansetron hydrochloride can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron hydrochloride 8mg should be administered as a slow intravenous or intramuscular injection immediately before treatment, followed by 8 mg orally twelve hourly.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron Hydrochloride should be continued for up to five days after a course of treatment.

Highly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g.. high-dose cisplatin, Ondansetron hydrochloride can be given either by rectal, intravenous or intramuscular administration.

Ondansetron hydrochloride has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy.
- A dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8mg two to four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.
- A single dose of 32mg diluted in 50-100ml of saline or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

The efficacy of Ondansetron hydrochloride in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20mg administered prior to chemotherapy.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron hydrochloride should be continued for up to five days after a course of treatment.

#### Paediatric Population

CINV in children aged  $\geq 6$  months and adolescents. Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

#### Dosing by BSA

Ondansetron hydrochloride should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m<sup>2</sup>. The intravenous dose must not exceed 8 mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 1).

The total daily dose must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for Chemotherapy - Children aged  $\geq 6$  months and adolescents

<b>BSA</b>	<b>Day 1 <sup>(a,b)</sup></b>	<b>Days 2-6 <sup>(b)</sup></b>
$<0.6\text{m}^2$	5 mg/m <sup>2</sup> i.v. plus 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
$\geq 0.6\text{m}^2$	5 mg/m <sup>2</sup> i.v. plus 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet every 12 hrs

aThe intravenous dose must not exceed 8mg.

b The total daily dose must not exceed adult dose of 32 mg

#### Dosing by bodyweight

Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

Ondansetron hydrochloride should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg.

Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 2).

Table 2: Weight-based dosing for Chemotherapy - Children aged  $\geq 6$  months and adolescents

<b>Weight</b>	<b>Day 1 <sup>(a,b)</sup></b>	<b>Days 2-6 <sup>(b)</sup></b>
$\leq 10 \text{ Kg}$	Up to 3 doses of 0.15mg/kg every 4 hrs	2 mg syrup every 12 hrs
$>10 \text{ Kg}$	Up to 3 doses of 0.15mg/kg every 4 hrs	4 mg syrup or tablet every 12 hrs

aThe intravenous dose must not exceed 8mg.

b The total daily dose must not exceed adult dose of 32 mg.

Elderly: Ondansetron hydrochloride is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Patients with Renal Impairment: No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic Impairment: Clearance of Ondansetron hydrochloride is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

Post-operative nausea and vomiting (PONV):

Adults: For the prevention of PONV Ondansetron hydrochloride can be administered orally or by intravenous or intramuscular injection.

Ondansetron hydrochloride may be administered as a single dose of 4mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV a single dose of 4mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population

PONV in children aged  $\geq 1$  month and adolescents

Oral formulation:

No studies have been conducted on the use of orally administered Ondansetron in the prevention or treatment of post-operative nausea and vomiting; slow i.v. injection is recommended for this purpose.

For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of Ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia.

For the treatment of PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of Ondansetron hydrochloride may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg.

There are no data on the use of Ondansetron hydrochloride in the treatment of PONV in children below 2 years of age.

Elderly: There is limited experience in the use of Ondansetron hydrochloride in the prevention and treatment of PONV in the elderly, however Ondansetron hydrochloride is well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment: No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment: Clearance of Ondansetron hydrochloride is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe

impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism: The elimination half-life of Ondansetron hydrochloride is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

### ***4.3 Contraindications***

Concomitant use with apomorphine (see section 4.5). Hypersensitivity to any component of the preparation.

### ***4.4 Special warnings and precautions for use***

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT<sub>2</sub> receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving Ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using Ondansetron. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, with congenital long QT syndrome, or patients taking other medicinal products that lead to QT prolongation. Therefore, caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with antiarrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

As Ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

In patients with adenotonsillar surgery prevention of nausea and vomiting with Ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after Ondansetron.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric Population

Paediatric patients receiving Ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

#### CINV

When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/m<sup>2</sup> followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicates similar efficacy for both regimens.

#### ***4.5 Interaction with other medicinal products and other forms of interaction***

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. (See section 4.4)

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias. (See section 4.4).

*Serotonergic Drugs (e.g. SSRIs and SNRIs):* There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs). (See section 4.4)

*Apomorphine:* Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

*Phenytoin, Carbamazepine and Rifampicin:* In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

*Tramadol:* Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

#### ***4.6 Pregnancy and lactation***

##### **Pregnancy**

The safety of Ondansetron for use in human pregnancy has not been established.

Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and pre- and post-natal development. However as animal studies are not always predictive of human response the use of Ondansetron in pregnancy is not recommended.

##### **Lactation**

Tests have shown that Ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron should not breast-feed their babies.

#### ***4.7 Effects on 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***

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1000$ ) and very rare ( $< 1/10,000$ ). Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of Ondansetron according to indication and formulation.



<b>Immune system disorders</b>	
Rare:	Immediate hypersensitivity reactions, sometimes severe including anaphylaxis.
<b>Nervous system disorders</b>	
Very common:	Headache.
Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia), observed without definitive evidence of persistent clinical sequelae.
Rare:	Dizziness during rapid intravenous administration.
<b>Eye disorders</b>	
Rare:	Transient visual disturbances (e.g. blurred vision), predominantly during intravenous administration.
Very rare:	Transient blindness, predominantly during intravenous administration. The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.
<b>Cardiac disorders</b>	
Uncommon:	Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Very rare:	Transient ECG changes including QT interval prolongation, predominantly with intravenous administration of Ondansetron.
<b>Vascular disorders</b>	
Common:	Sensation of warmth or flushing.
Uncommon:	Hypotension.
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon:	Hiccups.
<b>Gastrointestinal disorders</b>	
Common:	Constipation.
<b>Hepatobiliary disorders</b>	
Uncommon:	Asymptomatic increases in liver function tests. These events were observed commonly in patients receiving chemotherapy with cisplatin.
<b>Pediatric population</b>	
The adverse event profiles in children and adolescents were comparable to that seen in adults.	

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at <https://primaryreporting.who-umc.org/ET> or toll free call 8482 to Ethiopian food and drug authority (EFDA).

#### **4.9 Overdose**

##### Symptoms and Signs

There is limited experience of Ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block.

##### Treatment

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.

### **5. Pharmacological properties**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: selective 5-HT<sub>3</sub> receptor antagonist

ATC code:-A04AA01

##### Mode of action

Ondansetron is a potent, highly selective 5HT<sub>3</sub> 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 5HT<sub>3</sub> receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. 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 5HT<sub>3</sub> 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.

#### **5.2 Pharmacokinetic Properties**

Following oral administration, Ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of

about 30ng/ml are attained approximately 1.5 hours after an 8mg dose. For doses above 8mg 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. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (five hours) of Ondansetron. Gender differences were shown in the disposition of Ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight). The disposition of Ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a terminal half life of about three hours and steady state volume of distribution of about 140L. Equivalent systemic exposure is achieved after IM and IV administration of Ondansetron.

Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on Ondansetron's pharmacokinetics. The pharmacokinetic properties of Ondansetron are unchanged on repeat dosing.

#### Special Patient Populations

##### Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 month was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like Ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of Ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults.

### ***5.3 Preclinical safety data***

There are no pre-clinical data of relevance

## **6. PHARMACEUTICAL PARTICULARS**

### ***6.1 List of Excipients***

Sucrose

Propylene Glycol

Methyl Paraben

Propyl Paraben

Sodium Citrate

Citric acid (Monohydrate)

Colour Ponceau 4R

Flavour Fruit Mixed (Vital)

Purified Water

### ***6.2 Incompatibilities:***

Not applicable

### ***6.3 Shelf Life:*** 24 Months

### ***6.4 Special Precautions for Storage:***

Store below 30°C. Protect from Light.

Keep away from the reach of Children.

### ***6.5 Nature and Contents of Container:***

Primary: 30 ml Amber coloured Pet Bottle sealed with 25 mm EPE WAD Cap

Secondary: 10 ml Measuring cups & Sticker Label as per text matter.

Such one bottle in a printed carton along with Pack insert.

### ***6.6 Special precautions for disposal:*** Not applicable

## **7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURER'S NAME AND ADDRESS**

**Marketing Authorization Holder**

**Cachet Pharmaceuticals Pvt. Ltd**

415, Shah Nahar Industrial Estate,  
Dr. E. Moses Road, Worli, Mumbai-400 018,  
Maharashtra, India.

**Manufacturer's Name and Address:**

**Cachet Pharmaceuticals Private Limited**

Address: Village: Thana, Baddi, Himachal Pradesh-173 205, India.

**8. MARKETING AUTHORIZATION NUMBER**

05621/07548/REN/2020

**9. DATE OF FIRST <REGISTRATION> / RENEWAL OF THE <REGISTRATION>**

Date of first authorisation: 10.11.2016

Date of latest renewal: 01.02.2021

**10. DATE OF REVISION OF THE TEXT**

05.07.2023