**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. Name of the medicinal product

Vomito 4mg (Ondansetron Orally Disintegrating Tablets USP 4 mg)

## 2. Qualitative and Quantitative composition

Each orally disintegrating tablet contains:

Ondansetron Hydrochloride USP

Eq. to Ondansetron.....4 mg

For the full list of excipients, see section 6.1

## 3. Pharmaceutical form:

Oral Disintegrating Tablets
white to off-white tablets

## 4. Clinical particulars

### 4.1 Therapeutic indications Adults:

Vomito Tablets are indicated in adults for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Vomito Tablets are indicated for the prevention of post-operative nausea and vomiting (PONV).

**Paediatric Population:**
Vomito Tablets are indicated in children aged ≥6 months for the management of chemotherapy-induced nausea and vomiting (CINV).

### 4.2 Posology and method of administration

**Chemotherapy and radiotherapy induced nausea and vomiting.**
**Adults:**
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Emetogenic chemotherapy and radiotherapy:
For oral administration: 8 mg taken 1 to 2 hours before chemotherapy or radiation treatment, followed by 8 mg every 12 hours for a maximum of 5 days to protect against delayed or prolonged emesis.

For highly emetogenic chemotherapy:
A single dose of up to 24 mg Ondansetron taken with 12 mg oral dexamethasone sodium phosphate, 1 to 2 hours before chemotherapy, may be used.
To protect against delayed or prolonged emesis after the first 24 hours, treatment with Ondansetron may be continued for up to 5 days after a course of treatment.

The recommended dose is 8 mg to be taken twice daily.

**Paediatric population:**

**CINV in children aged ≥ 6 months and adolescents.**

The dose for CINV can be calculated based on body surface area (BSA) or weight – see below.

There are no data from controlled clinical trials on the use of Ondansetron in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of Ondansetron for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:

Ondansetron Tablets oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 1).

The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

**Table 1: BSA-based dosing for Chemotherapy - Children aged ≥6 months and adolescents.**

| BSA | Day 1 (a,b) | Days 2-6 (b) |
|---|---|---|
| <0.6m$^2$ | 5mg/m$^2$ IV plus<br>2mg syrup after 12 hours | 2mg syrup every 12 hours |
| ≥0.6m$^2$ to ≤1.2m$^2$ | 5mg/m$^2$ IV plus<br>4 mg syrup or tablet after 12 hours | 4mg syrup or tablet every 12 hours |
| >1.2m$^2$ | 5mg/m$^2$ or 8mg IV plus<br>8mg syrup or tablet after 12 hours | 8mg syrup or tablet every 12 hours |

[a] The intravenous dose must not exceed 8mg.

[b] The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

Dosing by bodyweight:

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

Oral dosing can commence 12 hours after chemotherapy and may be continued for up to 5 days (Table 2).

The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

**Table 2: Weight-based dosing for Chemotherapy - Children aged ≥6 months and adolescents.**

| Weight | Day 1 (a,b) | Days 2-6 (b) |
|---|---|---|
| ≤ 10kg | Up to 3 doses of 0.15mg/kg IV every 4 hours | 2 mg syrup every 12 hours |

| | | |
|---|---|---|
| >10kg | Up to 3 doses of 0.15mg/kg IV every 4 hours | 4 mg syrup or tablet every 12 hours |

[a] The intravenous dose must not exceed 8mg.

[b] The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

**Elderly:**
No alteration of oral dose or frequency of administration is required.

**Post-operative nausea and vomiting (PONV)** Adults:
**For the prevention of PONV:**
For oral administration: 16mg taken one hour prior to anaesthesia.

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

**For both indications**
***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 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 is not altered in subjects classified as poor metabolizers 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 is required.

***Mode of administration:***
Oral use.
Do not attempt to push Emitron® Tablets through the foil backing. With dry hands, peel back the foil backing of one blister and gently remove the tablet. Immediately place the Emitron® Tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.

## 4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use with apomorphine is contraindicated.

## 4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists. Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischemia.

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

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.

## 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, propofol and thiopental.

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.

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).

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.
Caution should be exercised when ondansetron is co-administered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. 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.

## 4.6 Fertility, 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 peri- and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

**Breast-feeding**

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

- Central Nervous system: Headache, Seizures have been observed rarely.
- Cardiovascular system: Arrhythmias, hypotension, bradycardia and chest pain have been rarely reported.
- Gastrointestinal system: increase in large bowel transit time is known to be caused by ondansetron which may cause constipation in some patients.

- Hypersensitivity reactions: Immediate hypersensitivity reactions, sometimes severe (e.g. anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria) have been reported.
- Musculoskeletal: There have been rare reports of involuntary movement disorders without definitive evidence of persistent clinical sequelae.
- Other: Hiccups and transient, asymptomatic increases in aminotransferases.

**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 pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

## 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.
Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.
**Paediatric population**
Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4mg/kg) in infants and children aged 12 months to 2 years.
**Treatment**
There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.
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:** Serotonin (5HT3) antagonists, ATC code: A04AA01.

**Mode of action**

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. 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 5HT3 receptors on neurons located both in the peripheral and central nervous system. In psychomotor testing, ondansetron does not cause sedation nor impair performance.

## 5.2 Pharmacokinetic properties

Absorption

Following oral administration of ondansetron, absorption is rapid with maximum peak plasma concentrations of about 30ng/mL being attained and achieved in approximately 1.5 hours after an 8mg dose.

Distribution

The absolute oral bioavailability of the drug is approximately 60%.

Elimination

The disposition of ondansetron following oral and intravenous dosing is similar with a terminal elimination half-life of approximately 3 hours and a steady- state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%) and 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 the pharmacokinetics of ondansetron. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

**Special populations**

Renal impairment

In patients with renal impairment (creatinine clearance 15-60mL/min), systemic clearance and volume of distribution are reduced, resulting in a slight, but clinically insignificant increase in elimination half-life (5.4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged.

Hepatic impairment

In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 hours) and an oral bioavailability approaching 100% because of reduced pre-systemic metabolism.

**5.3 Preclinical safety data**

None available

## 6. Pharmaceutical particulars

**6.1 List of Excipients:**

- Dibasic calcium Phosphate
- Microcrystalline cellulose
- Colloidal anhydrous silica
- Hypromellose
- Sodium Benzoate
- Aspartame
- Magnesium Stearate
- Purified Talc
- Sodium Starch Glycolate

**6.2 Incompatibilities** Not applicable.

**6.3 Shelf life**

36 months

**6.4 Special precautions for storage**

Store below 30°C. Protect from direct sunlight, heat & moisture.

**6.5 Nature and contents of container**

1 x 10 Alu-Alu blister pack.

**6.6 Special precautions for disposal and other**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. Marketing authorization holder and manufacturing site

Sai Pharmaceuticals Limited,Kenya

**Manufactured by:**

Curis Pharmaceutical Limited

## 8. Marketing authorisation number(s)

H2022/CTD6435/2144ER

## 9. Date of first Registration/ Renewal of Registration

14 February 2022

## 10. Date of revision of text

14 February 2022