

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 8mg, film-coated tablet.

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 8mg tablet contains ondansetron hydrochloride dihydrate equivalent to 8mg of ondansetron.

Excipients: Lactose monohydrate. For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Film-coated tablet.

Tablet - yellow to pale brown, oval, film-coated tablet engraved 'FW641' on one face.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

##### Adults:

Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV).

##### Paediatric Population:

Ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged  $\geq 6$  months, and for the prevention and treatment of PONV in children aged  $\geq 1$  month.

#### 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 route of administration and dose of ondansetron should be flexible in the range of 8-32mg a day and selected as shown below.

- Emetogenic Chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration. The recommended dose for oral administration is 8mg twice daily, 8mg 1-2 hours before treatment, followed by 8mg 12 hours later. To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment.
- Highly Emetogenic Chemotherapy: For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, Ondansetron can be given either by rectal, intravenous or intramuscular administration. The recommended dose for oral administration is 8mg twice daily. To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment.

Paediatric Population:

CINV in children aged  $\geq 6$  months and adolescents

The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. Weight-based dosing results in higher total daily doses compared to BSA-based dosing (sections 4.4. and 5.1).

Ondansetron injection should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid and infused intravenously over not less than 15 minutes.

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 should be administered immediately before chemotherapy as a single intravenous dose of  $5 \text{ mg/m}^2$ . 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

BSA	Day 1 <sup>(a,b)</sup>	Days 2-6 <sup>(b)</sup>
$< 0.6 \text{ m}^2$	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

a The 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 (sections 4.4. and 5.1).

Ondansetron 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

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

a The intravenous dose must not exceed 8mg.

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

### Elderly

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

## POST OPERATIVE NAUSEA AND VOMITING (PONV)

### Adults

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

For oral administration: 16mg one hour prior to anaesthesia. Alternatively, 8 mg one hour prior to anaesthesia followed by two further doses of 8 mg at eight hourly intervals.

*For the treatment of established PONV:* Intravenous or intramuscular administration 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.

Injection:

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 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 in the treatment of PONV in children below 2 years of age.

### Elderly

There is limited experience in the use of Ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly, however Ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

*For both indications:*

*Patients with renal impairment*

No special requirements.

*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 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**

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>3</sub> receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

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.

***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 (section 5.1).

Tablets only:

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

#### **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, frusemide, alfentanil, tramadol, morphine, lignocaine, 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.

##### ***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.

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias (see section 4.4 – Warnings and Precautions).

#### **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 the 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

#### 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.

### **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.

#### **Immune system disorders**

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

#### **Nervous system disorders**

Very common: Headache.

Uncommon: Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia). This was observed without definitive evidence of persistent clinical sequelae.

Rare: Dizziness during rapid IV administration.

#### **Eye disorders**

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during IV 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.

### **Cardiac disorders**

Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.

### **Vascular disorders**

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

### **Respiratory, thoracic and mediastinal disorders**

Uncommon: Hiccups.

### **Gastrointestinal disorders**

Common: Constipation.

### **Hepatobiliary disorders**

Uncommon: Asymptomatic increases in liver function tests. These events were observed commonly in patients receiving chemotherapy with cisplatin

### ***Paediatric population***

The adverse event profiles in children and adolescents were comparable to that seen in adults.

## **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 (see Undesirable effects). 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 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 (ATC code) - A04A A 01.

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.

Ondansetron does not alter plasma prolactin concentrations

Paediatric population

CINV

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m<sup>2</sup> intravenous + ondansetron 4 mg orally after 8-12 hrs or ondansetron 0.45 mg/kg intravenous + placebo orally after 8-12 hrs. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m<sup>2</sup> intravenous + ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenous + placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days.

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m<sup>2</sup> intravenous together with 2 - 4 mg dexamethasone orally
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg + 2-4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 yrs and 8 mg for children aged ≥ 12 yrs (total no. of children n= 28). Complete control of emesis was achieved in 42% of patients.

#### PONV

The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥ 44 weeks, weight ≥ 3 kg). Included subjects were scheduled to undergo elective surgery under general anaesthesia and had an ASA status ≤ III. A single dose of ondansetron 0.1 mg/kg was administered within five minutes following induction of anaesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than those receiving ondansetron ((28% vs. 11%, p < 0.0001).

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single intravenous doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg; number of patients = 735) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarised in Table 3.

Table 3 Prevention and treatment of PONV in Paediatric Patients – Treatment response over 24 hours

Study	Endpoint	Ondansetron %	Placebo %	p value
S3A380	CR	68	39	≪ 0.001
S3GT09	CR	61	35	≪ 0.001
S3A381	CR	53	17	≪ 0.001
S3GT11	no nausea	64	51	0.004
S3GT11	no emesis	60	47	0.004

CR = no emetic episodes, rescue or withdrawal

## 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 (5 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 3 hours and steady state volume of distribution of about 140L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

A 4mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25ng/ml are attained within 10 minutes of injection.

Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/ml are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.

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. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age related changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

### ***Renal impairment***

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

### ***Elderly or renal impairment***

Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance.

### ***Hepatic impairment***

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated

## **5.3 Preclinical safety data**

No additional data of relevance.

# **6 PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

### Tablet core

Lactose monohydrate

Microcrystalline cellulose

Maize starch

Magnesium stearate

### Tablet coat

Hypromellose (E464)

Titanium dioxide (E171)

Yellow iron oxide (E172)

## **6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**  
36 months.

**6.4 Special precautions for storage**  
Do not store above 25°C.  
Store in the original package.

**6.5 Nature and contents of container**  
Blister packs of 15, 30 or 60 tablets comprising PVC film and aluminium foil lidding.

**6.6 Special precautions for disposal**  
No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Goldshield Pharmaceuticals Limited

NLA Tower

12-16 Addiscombe Road

Croydon

Surrey

CR0 0XT

United Kingdom

Telephone: 0208 410 2159

Fax: 0208 686 0807

## **8 MARKETING AUTHORISATION NUMBER(S)**

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