Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondatab 4 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg Ondansetron hydrochloride dihydrate, equivalent to 4 mg Ondansetron
Excipients: Each tablet contains 46 mg lactose monohydrate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

White coloured, circular, biconvex film-coated tablets debossed with '4' on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:
Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:
Management of chemotherapy -induced nausea and vomiting in children aged ≥6 months.
Prevention and treatment of post-operative nausea and vomiting in children aged ≥1 month.

4.2 Posology and method of administration

Oral use.
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 8-32 mg 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.

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

For oral administration: 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 treatment with ondansetron should be continued for up to 5 days and rectal treatment for up to 3 days after a course of treatment.

The recommended dose for oral administration is 8 mg twice daily.

Highly Emetogenic Chemotherapy: For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, ondansetron can be given by, intravenous administration.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron should be continued for up to 5 days after a course of treatment.

The recommended dose for oral administration is 8 mg twice daily.

Paediatric Population:
Chemotherapy -induced nausea and vomiting in children aged ≥ 6 months and adolescents:
The dose for chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based doing results in higher total daily doses compared to BSA-based dosing – see sections 4.4.and 5.1.

There are no data from controlled clinical trials on the use of ondansetron in the prevention of chemotherapy-induced delayed or prolonged nausea and vomiting. 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 5mg/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. See Table 1 below.

The total daily dose 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]	Day 2-6[,b]
<0.6m^2	5 mg/m^2 i.v. 2 mg syrup or tablet after 12 hours	2 mg syrup or tablet every 12 hours
≥0.6m^2	5 mg/m^2 i.v. 4 g syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours

a The intravenous dose must not exceed 8 mg.
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 – see 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 doses 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. See Table 2 below.

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

Weight	Day 1[a,b]	Day 2-6[b]
≤10 kg	Up to 3 doses of 0.15mg/kg at 4-hourly intervals	2 mg syrup or tablet every 12 hours
>10 kg	Up to 3 doses of 0.15mg/kg at 4-hourly intervals	4 mg syrup or tablet every 12 hours

a The intravenous dose must not exceed 8 mg.
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.
Please refer also to “Special populations”.
Post operative nausea and vomiting (PONV):

Adults:

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

Treatment of established PONV
For the treatment of established PONV intravenous administration is recommended.

Paediatric population

Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents

Oral Formulations:
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.

There are no data on the use of ondansetron for the treatment of post-operative vomiting in children under 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 (PONV) in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.
Please refer also to “Special populations”.

Special populations:
Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration is 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 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 ondansetron or any of the excipients.

Hypersensitivity to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron).

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

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.

Since there is little experience to date of the use of ondansetron in cardiac patients, caution should be exercised if ondansetron is co-administered with anaesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been re-ported. Caution is advised if patients have received cardiotoxic agents and in patients with a history of prolonged QT syndrome.

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensi-tivity reactions.

Paediatric Population:

Paediatric patients receiving ondansetron with hepatotoxic chemo-therapeutic agents should be monitored closely for impaired hepatic function.

Chemotherapy -induced nausea and vomiting: 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/m2 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 indicate similar efficacy for both regimens – see section 5.1.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the 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 medicinal products commonly co-administered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lignocaine, 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.

Phenytoin, Carbamazepine and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the 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 in-crease the risk of arrhythmias. (See section 4.4).

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.

Lactation
Tests have shown that ondansetron passes into the milk of lactating animals (see section 5.3). It is therefore recommended that mothers receiving ondansetron should not breastfeed 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 (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000),

Not known (cannot be estimated from the available data)

Very common, common and uncommon events were generally deter-mined 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.
There may be cross-sensitivity with other selective 5-HT3 antagonists.

Nervous system disorders
Very common: Headache.
Uncommon: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) have been observed without definitive evidence of persistent clinical sequelae; seizures.
Rare: Dizziness during rapid IV administration

Eye disorders
Rare: Transient visual disturbances (e.g. blurred vision) predominantly during rapid 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.

Cardiac disorders

Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Very rare: Transient ECG changes including QT interval prolongation.

Vascular disorders
Common: Sensation of warmth or flushing.
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests.
These events were observed commonly in patients receiving chemo-therapy with cisplatin.

Paediatric Population
The adverse event profile in children and adolescents was comparable to that seen in adults.

4.9 Overdose

Symptoms and Signs

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 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 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: Antiemetics and antinauseants, Serotonin (5-HT3) antagonists
ATC Code: A04AA01

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist.
Its precise antiemetic and antinauseal mechanism of action 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. 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.

In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

Ondansteron does not alter plasma prolactin concentrations.

The role of ondansetron in opiate-induced emesis is not yet established.

Paediatric population:
Chemotherapy -induced nausea and vomiting:
The efficacy of ondansetron in the control of emesis and nausea in-duced by cancer chemotherapy was assessed in a double-blind ran-domised trial in 415 patients aged 1 to 18 years. On the days of che-motherapy, patients received either ondansetron 5 mg/m2 i.v. + after 8-12 hrs ondansetron 4 mg p.o. or ondansetron 0.45 mg/kg i.v. + after 8-12 hrs placebo p.o. 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/m2 i.v. + ondansetron 4 mg p.o.) and 41% (0.45 mg/kg i.v. + placebo p.o.). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days.

A double-blind randomised placebo-controlled trial 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 ad-ministered intravenously at a dose of 5 mg/m2 i.v. together with 2-4 mg dexamethasone p.o. and in 71% of patients when ondansetron was administered as syrup at a dose of 8mg + 2- 4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups re-ceived 4 mg ondansetron syrup twice daily for 2 days.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in open-label, non-comparative, single-arm study. All children received three 0.15 mg/kg doses of intravenous ondansetron, administered at 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 investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron fol-lowed by two oral ondansetron doses of 4mg 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.

Prevention of post-operative nausea and vomiting:
The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebocontrolled 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 patient 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 Post-Operative Nausea and Vomiting 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 (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. 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 given as a single dose.
The extent and rate of ondansetron's absorption is 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 levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important.

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.

The protein binding of ondansetron is 70-76%. A direct effect of plasma concentration and anti-emetic effect has not been established. 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 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.

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.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of repeated-dose toxicity, genotoxicity and carcinogenic potential.
Ondansetron and its metabolites accumulate in the milk of rats with a milk:plasma ratio of 5.2:1.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Microcrystalline cellulose
Magnesium stearate

Film-coating:
Hypromellose
Macrogol 400

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC blister with aluminium foil
Packages of 2, 4, 6, 9, 10, 15, 30, 50, 100 tablets
Hospital packs of 100 and 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1130/27/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 3 May 2011

10 DATE OF REVISION OF THE TEXT

November 2011