SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron Orifarm 4 mg orodispersible tablet
Ondansetron Orifarm 8 mg orodispersible tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 4 mg and 8 mg ondansetron, respectively.

Excipients with known effect:
4 mg: Each orodispersible tablet contains 0.88 mg aspartame and 3 mg – 8.4 mg sorbitol.
8 mg: Each orodispersible tablet contains 1.76 mg aspartame and 6 mg – 16.9 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

4 mg: White, flat, round, 7 mm bevel-edged tablet

8 mg: White, flat, round, 10 mm bevel-edged tablet

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.

Children
Prophylaxis and treatment of nausea and vomiting induced by chemotherapy in children ≥ 6 months. Prophylaxis and treatment of postoperative nausea and vomiting in children ≥ 1 month.

4.2 Posology and method of administration

Oral use.

For the different dosage regimens appropriate strengths and formulations are available**.**
Posology

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, and individual susceptibility. The route of administration and dose of ondansetron should be flexible and selected as shown below.

Emetogenic chemotherapy and radiotherapy
For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by oral or intravenous administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron should initially be administered intravenously immediately before treatment, followed by 8 mg orally every twelve hours.

For oral administration:
Adults: 8 mg 1-2 hours before treatment, followed by 8 mg every 12th hour for a maximum of 5 days. In radiotherapy, 8 mg is given twice a day for the entire treatment period, then for a further 2 days, up to 5 days if necessary.

Highly emetogenic chemotherapy
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given by oral, IV, IM or rectal administration.

For oral administration:
24 mg ondansetron orodispersible tablets taken together with oral dexamethasone sodium phosphate 12 mg, 1 to 2 hours before treatment.

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

Paediatric Population
Children (aged ≥ 6 month) and adolescents (< 18 years)
The dose for chemotherapy induced nausea and vomiting (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 (see section 4.4).

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 mg/m². The intravenous dose must not exceed 8 mg.

Oral dosing can commence 12 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 ≥6 months and adolescents

BSA	Day 1(a,b)	Days 2-6(b)
< 0.6 m²	5 mg/m² i.v. plus	2 mg oral solution every 12 hours

	2 mg oral solution after 12 hours	
≥0.6 m^2	5 mg/m^2 i.v. plus 4 mg oral solution or tablet after 12 hours	4 mg oral solution or tablet every 12 hours
> 1.2 m^2	5 mg/m2 IV or 8 mg IV plus 8 mg oral solution or tablet after 12 hours	8 mg oral solution 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 Ondansetron orodispersible tablets cannot be used in children with a total body surface below 0.6 m^2.

Dosing by bodyweight:
Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see section 4.4 and 5.1: Clinical Studies).

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 12 hours later and may be continued for up to 5 days (Table 2).

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

Weight	Day 1 (a,b)	Days 2-6(b)
≤10 kg	Up to 3 doses of 0.15 mg/kg every 4 hours	2 mg oral solution every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hours	4 mg oral solution 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 is required.

Please refer also to ”Special populations”.

Post-operative nausea and vomiting:
Adults
Prevention of post-operative nausea and vomiting:
For the prevention of post-operative nausea and vomiting ondansetron can be administered orally or by intravenous injection.

For oral administration:
16 mg 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 post-operative nausea and vomiting:
For the treatment of established post-operative nausea and vomiting intravenous administration is recommended.

Children (aged ≥ 1 month) and adolescents (< 18 years)

For prophylaxis or in the treatment of postoperative nausea and vomiting in paediatric patients operated under general anaesthesia, a single dose of ondansetron should be administered as a slow IV injection (in not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either before, during or after induction of anaesthesia.

There are no data on the use of ondansetron in the treatment of PONV in children under 2 years of age.

No studies have been conducted on **oral** ondansetron given as prophylaxis or treatment of postoperative nausea and vomiting. In this case, slow intravenous injection is recommended.

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.

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 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 8 mg should not be exceeded.

Method of administration
The tablet should be placed on the top of the tongue where it will rapidly disperse and should then be swallowed with or without water

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant use with apomorphine (see section 4.5).

4.4 Special warnings and precautions for use

Impaired liver function
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner (see section 5.1). 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 ischaemia.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

Serotonin syndrome has been observed with concomitant use of ondansetron with other serotonergic medicinal products (see section 4.5). If concomitant treatment with ondansetron and other serotonergic medicinal products is clinically indicated, appropriate monitoring of the patient is recommended.

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-hourintervals, the total daily dose will be higher than if one single dose of 5mg/m^2 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 (see section 5.1).

Excipients
Ondansetron Orifarm 4 mg contains 0.88 mg aspartame in each tablet and Ondansetron Orifarm 8 mg contains 1.76 mg aspartame in each tablet. Aspartame is a source of phenylalanine. It may be harmful for patients with phenylketonuria (PKU).

Ondansetron Orifarm 4 mg contains 3 mg - 8,4 mg sorbitol in each tablet.
Ondansetron Orifarm 8 mg contains 6 mg - 16,9 mg sorbitol in each tablet.

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 coadministered 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.

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 trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhytmics (such as amiodarone) and betablockers (such as atenolol or timolol) may increase the risk of arrhythmias (see section 4.4).

Caution should be exercised when ondansetron is administered with medicinal products that may cause electrolyte abnormalities (see section 4.4).

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 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should consider the use of contraception.

Pregnancy
Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).

The available epidemiological studies on cardiac malformations show conflicting results.

Animal studies does not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Ondansetron should not be used during the first trimester of pregnancy.

Lactation
It is not known whether ondansetron passes into mother's milk. There is no data on the effects of ondansetron on breastfed infants or the effects on milk production.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.

Fertility
Ondansetron has no effect on fertility.

Women of childbearing potential should consider contraception.

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 according to organ classes and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).
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 Uncommon Rare 	Headache. Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia).[1] Muscular cramps Dizziness during rapid IV administration.
Eye disorders Rare Very rare	Transient visual disturbances (eg. blurred vision) predominantly during rapid IV administration. Transient blindness predominantly during intravenous administration.[2]

Cardiac disorders Uncommon Rare Frequency not known	 Arrhythmias, chest pain with or without ST segment depression, bradycardia. QTc prolongation (including Torsade de pointes). Cardiac arrythmia, including ventricular tachycardia (very rare) Myocardial ischemia (frequency unknown) (see section 4.4)
Vascular disorders Common Uncommon	 Sensation of warmth or flushing. Hypotension.
Respiratory, thoracic and mediastinal disorders Uncommon	 Hiccups.
Gastrointestinal disorders Common	 Constipation.
Hepatobiliary disorders Uncommon	 Asymptomatic increases in liver function tests[3].
Skin and subcutaneous tissue disorders Very rare	Toxic skin eruptions, including toxic epidermal necrolysis
General and/or administration site conditions *Common:*	Local injection site reactions during intravenous administration.

[1] Observed without definitive evidence of persistent clinical sequelae.
[2] 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.
[3] 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.

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 the national reporting system listed in Appendix V.

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 section 4.8). Manifestations that have been reported include visual disturbances, dizziness, headache, fatigue, tachycardia, bradycardia, hypotension, severe constipation, dystonia, muscle twitching, restlessness, agitation, hallucinations, convulsions,
and a vasovagal episode with transient second-degree

AV block.48 mg orally in adults and 35-48 mg i.v. in adults resulted in mild intoxication. 250 mg orally in adults and 120-150 mg i.v. in adults resulted in mild to moderate intoxication.Ondansetron prolongs QT interval in dose-dependent manner. ECG monitoring is recommended in cases of overdose. Further treatment should be as clinically required or as recommended by Poison Information Centre.

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.

Paediatric population
Paediatric cases consistent with serotonin syndrome have been reported after accidental oral overdose of ondansetron (estimated intake exceeding 4 mg/kg) in infants and children aged 12 months to 2 years).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Ondansetron is a potent, highly selective 5-HT3 receptor-antagonist. Dopaminergic receptors are not blocked.
Its precise antiemetic and antinauseal mechanism of action is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT3 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.

Clinical efficacy and safety
In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

Ondansetron does not alter plasma prolactin concentrations.

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

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements

greater than 480 msec and no QTcF prolongation was greater than 60 msec. No significant changes were seen in measured ECG-PR or QRS interval.

In phase I studies in healthy elderly volunteers, no general differences in safety and efficacy were observed. In cancer patients ≥75 years of age, enrolled in clinical trials for CINV, a greater effect on QTcF has been noted in concentration-effect modelling of ondansetron. Specific dosing information is provided for elderly patients over 65 and 75 years of age, respectively, in section 4.2.

Clinical Studies
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/m² intravenous and ondansetron 4 mg orally after 8 to12 hours or ondansetron 0.45 mg/kg intravenous and placebo orally after 8 to 12 hours. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst dayof chemotherapy was 49% (5 mg/m² intravenous and ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenous and placebo orally). There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

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/m² intravenous together with 2 to 4 mg dexamethasone orally

- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg together with 2 to 4 mg dexamethasone orally on the days of chemotherapy

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days.
There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

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 4 and 8 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 years (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

Absorption
Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (bioavailability is about 60%). Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. 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).

Distribution
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 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

Metabolism
Ondansetron is mainly metabolized to 8-OH-ondansetron. However, plasma concentrations of this metabolite are not detectable due to rapid further metabolism to glucuronic and sulphate conjugates. The absence of the enzyme CYP2D6 has no effect on ondansetron's pharmacokinetics.

Elimination
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. The half-life after intravenous and oral administration is 3.3-5.4 hours (due to the fact that the half-life increases with age). Of the administered dose, 1-20% is found in unchanged form in the urine. Plasma clearance is about 500 ml/min and the half-life is about 3 hours. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Children and Adolescents (aged 1 month to 17 years)

51 children aged 1 to 24 months who were included in a clinical trial received either 0.1 or 0.2 mg/kg ondansetron before surgery. Patients aged 1-4 months showed weight-normalised clearance that was approximately 30% slower than in patients aged 5-24 months but comparable to patients aged 3-12 years. The half-life in the group 1-4 months was reported to average 6.7 hours compared to 2.9 hours for patients in the 5-24 month and 3-12 year age range. The differences in pharmacokinetic parameters in the age group of 1-4 months can be explained in part by the higher volume of distribution.

For 21 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 normalizing systemic exposure in paediatric patients.

A population pharmacokinetic analysis was performed on 74 patients aged 6 to 48 months after administration of 0.15 mg/kg ondansetron intravenously every 4 hours in three doses for treatment of chemotherapy-induced nausea and vomiting and on 41 patients aged 1 to 24 months after administration of a single dose of 0.1 mg/kg or 0.2 mg/kg ondansetron intravenously in connection with surgery. Systemic exposure (AUC) in the age of 1-24 months after intravenous administration of 0.15 mg/kg every 4 hours in three doses was comparable to what observed in children aged 5-24 months in connection with surgery and previous studies in patients with cancer (aged 4-18 years) and patients in connection with surgery (aged 3-12 years) with the same dosage.

In patients with moderate renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced, 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 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.

Elderly
Previous Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in the half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age).

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
A study of cloned human cardiac ion channels has shown that ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels.

Ondansetron and metabolites are excreted in the milk of rats dosed with radiolabelled ondansetron.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sorbitol (E420)
Crospovidone
Silica, colloidal hydrated
Microcrystalline cellulose
Crospovidone type B
Aspartame (E951)
Strawberry flavouring
Sodium stearyl fumarate
Magnesium stearate

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

4 mg, orodispersible tablet:
Blister (Alu/Alu) : 6, 7, 10, 14, 28, 30 tablets.
Unit-dose blister (Alu/Alu): 6x1, 7 x1, 10 x1, 14 x1, 28 x1, 30 x1 tablets.

8 mg, orodispersible tablet:
Blister (Alu/Alu): 6, 7, 10, 14, 28, 30 tablets.
Unit-dose blister (Alu/Alu): 6x1, 7x1, 10x1, 14x1, 28x1, 30x1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2009-11-17

10. DATE OF REVISION OF THE TEXT

2024-06-05