SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ONDANSETRON - FRESENIUS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution for injection contains 2mg Ondansetron (as hydrochloride dihydrate).

Each ampoule with 2 ml contains 4 mg ondansetron.

Each ampoule with 4 ml contains 8 mg ondansetron.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear and colorless solution, free of any visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

- For the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
- For the prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:

- For the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for prevention and treatment of PONV in children aged ≥1 month.

4.2 Posology and method of administration

For intravenous injection or for intravenous infusion after dilution. For instructions on dilution of the product before administration, see section 6.6.

Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV)

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-Fresenius should be flexible in the range of 8-32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy

For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by intravenous or oral administration. The recommended intravenous dose of ondansetron is 8 mg administered as a slow intravenous injection in not less than 30 seconds immediately before treatment.

Oral or rectal treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours. For oral or rectal administration refer to the SmPC of ondansetron tablets and suppositories, respectively.

Highly emetogenic chemotherapy e.g. high-dose cisplatin

Ondansetron-Fresenius may be administered as a single 8 mg intravenous dose immediately before chemotherapy. Doses of greater than 8 mg and up to a maximum of 16 mg of ondansetron may only be given by intravenous infusion diluted in 50 to 100 ml of saline or other compatible infusion fluid and infused over not less than 15 minutes. A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk (see sections 4.4, 4.8 and 5.1).

For management of highly emetogenic chemotherapy, a dose of 8 mg may be administered by slow intravenous injection in not less than 30 seconds, followed by two further intravenous doses of 8 mg four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

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

Oral or rectal treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours. For oral or rectal administration refer to the SmPC of ondansetron tablets and suppositories, respectively.

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. In paediatric clinical studies, ondansetron was given by intravenous infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid (see section 6.6) and infused over not less than 15 minutes.

Weight-based dosing results in higher total daily doses compared to BSA based dosing (see sections 4.4)

Ondansetron-Fresenius should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid (see section 6.6.) and infused intravenously over not less than 15 minutes.

There are no data from controlled clinical trials on the use of Ondansetron-Fresenius 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-Fresenius for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:

Ondansetron-Fresenius should be administered immediately before chemotherapy as a single intravenous dose of 5 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. See Table 1 below. 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 induced nausea and vomiting - Children aged ≥6 months and adolescents[a]

BSA	Day 1[b,c]	Days 2-6[c]
< 0.6 m^2	5 mg/m^2 i.v. plus 2 mg syrup after 12 hours	2 mg syrup every 12 hours
> 0.6 m^2 to ≤ 1.2 m^2	5 mg/m^2 i.v. plus 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours
> 1.2 m^2	5 mg/m^2 or 8 mg i.v. plus 8 mg syrup or tablet after 12 hours	8 mg syrup or tablet every 12 hours

a Not all pharmaceutical forms may be available.
b The intravenous dose must not exceed 8 mg.
c The total dose over 24 hours (given as divided doses) 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)

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The single intravenous dose must not exceed 8 mg. Two further intravenous doses may be given in 4-hourly intervals. The total dose over 24 hours (given as divided doses) 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 induced nausea and vomiting - Children aged ≥6 months and adolescents[a]

Weigth	Day 1[b,c]	Days 2-6[c]
≤ 10 kg	Up to 3 doses of 0.15 mg/kg i.v. every 4 hours	2 mg syrup every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg i.v. every 4 hours	4 mg syrup or tablet every 12 hours

a Not all pharmaceutical forms may be available.
b The intravenous dose must not exceed 8 mg.
c The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Elderly:

In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose of Ondansetron-Fresenius should not exceed 8 mg. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes.

The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart (see section 5.2).

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-Fresenius 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.

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.

Post-operative nausea and vomiting (PONV)

Adults:

Prevention of PONV

For prevention of post-operative nausea and vomiting, the recommended dose of Ondansetron-Fresenius is a single dose of 4 mg by slow intravenous injection in not less than 30 seconds administered at the induction of anaesthesia.

Treatment of established PONV

For treatment of established PONV a single dose of 4 mg given by slow intravenous injection in not less than 30 seconds is recommended.

Paediatric population:

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

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

There are no data on the use of Ondansetron-Fresenius for treatment of postoperative vomiting in children below 2 years of age.

Elderly:

There is limited experience in the use of Ondansetron-Fresenius in the prevention and treatment of post-operative nausea and vomiting (PONV) in older people, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

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 8 mg (orally or parenterally) 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 is required.

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

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ 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 Clinical Pharmacology). 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

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

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 selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

As ondansetron is known to increase large bowel transit time, patients with signs of sub-acute 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-hour intervals, the total daily dose will be higher than if one single dose of 5 mg/m^2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimes has not been investigated in clinical trials. Cross trial comparing indicate similar efficacy for both regimes (see section 5.1) This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule (2 ml, 4 ml), that is to say essentially ‘sodium- free‘.

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.

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

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

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 do not indicate direct or indirect harmful effects with respect to reproducive toxicity.

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

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.

Fertility

There is no information on the effects of ondansetron on human fertility.

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥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.

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	**Not known**
Immune system disorders					
			Immediate hypersensitivity reactions sometimes severe, including anaphylaxis		
Nervous system disorders					
Headache		Seizures, movement disorders (including extrapyramidal reactions such	Dizziness during rapid IV administration		

		as dystonic reactions, oculogyric crisis and dyskinesia)[1]			
Eye disorders					
			Transient visual disturbances (e.g. blurred vision) predominantly during IV administration	Transient blindness predominantly during intravenous administration [2]	
Cardiac disorders					
		Arrhythmias, chest pain with or without ST segment depression, bradycardia	QTc prolongation (including Torsade de pointes)		Myocardial ischemia (see section 4.4)
Vascular disorders					
	Sensation of warmth or flushing	Hypotension			
Respiratory, thoracic and mediastinal disorders					
		Hiccups			
Gastrointestinal disorders					
	Constipation				
Hepatobiliary disorders					
		Asymptomatic increases in liver function tests[3]			
General disorders and administration site conditions					
	Local IV injection site reactions				

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/ and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

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, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block.

Ondansetron prolongs QT interval in a dose-dependent manner. 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 4 mg/kg) in infants and children aged 12 months to 2 years.

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: Antiemetics and antinauseants, Serotonin ($5HT_3$) antagonists
ATC Code: A04AA01

Ondansetron is a potent, highly selective $5HT_3$ 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 $5HT_3$ 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 $5HT_3$ 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. The role of ondansetron in opiate-induced emesis is not yet established.

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 the measured electrocardiographic PR or QRS intervals.

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^2 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^2 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. 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 5mg/m^2 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 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 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

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. A direct correlation of plasma concentration and anti-emetic effect has not been established.

Absorption

A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml.

Distribution

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron. Ondansetron is not highly protein bound (70-76%).

Biotransformation

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Elimination

Less than 5% of the absorbed dose is excreted unchanged in the urine. Terminal half life is about 3 hours.

Special Patient Populations

Gender differences

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).

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.

Elderly

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in 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) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly. Based on more recent ondansetron plasma concentrations and exposureresponse modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for IV dosing (see section 4.2).

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 (5.4 h). 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

In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h).

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma-ratio was 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. The clinical relevance of this finding is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium citrate dihydrate

Citric acid monohydrate

Water for injections

6.2 Incompatibilities

Ondansetron-Fresenius should not be administered in the same syringe or infusion as any other medication.

Ondansetron-Fresenius should only be mixed with those infusion solutions that are recommended in section 6.6.

6.3 Shelf life

Unopened:

The expiry date of the product is indicated on the packaging materials.

After first opening:

After first opening the medicinal product should be used immediately.

Infusion:

Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C with the solutions given in section 6.6.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

The diluted solutions should be stored protected from light.

6.4 Special precautions for storage

Store below 30^0C. Keep the ampoules in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear glass ampoules

2 ml: Pack sizes: 1, 5,10 and 50 ampoules.

4 ml: Pack sizes: 1, 5,10 and 50 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Ondansetron-Fresenius may be diluted with the following solutions for infusion:

Sodium chloride 9 mg/ml (0.9 % w/v)

solution Glucose 50 mg/ml (5 % w/v) solution

Mannitol 100 mg/ml (10 % w/v) solution

Ringer's lactate solution

The diluted solutions should be stored protected from light.

Note: Ondansetron-Fresenius ampoules should not be autoclaved.

7 MANUFACTURER

LABESFAL - LABORATORIOS ALMIRO S.A, FRESENIUS KABI GROUP,

Lagedo, Santiago de Besteiros, 3465-157, Portugal.

8 MARKETING AUTHORISATION HOLDER

NEOPHARM (ISRAEL) 1996 LTD

Hashiloach 6, POB 7063 Petach Tiqva 4917001.

9 MARKETING AUTHORISATION NUMBER(S)

148-94-33550-00

Revised in November 2023 according to MOHs guidelines.