SUMMARY OF PRODUCT CHARACTERISITICS

1. NAME OF THE MEDICINAL PRODUCT

ZOPHRALEN Solution for injection 4mg/2mL
ZOPHRALEN Solution for injection 8mg/4mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOPHRALEN Solution for injection 4mg/2mL
Each ampoule contains 4mg of ondansetron (as hydrochloride dihydrate) in 2mL of aqueous solution for injection or infusion.

ZOPHRALEN Solution for injection 8mg/4mL
Each ampoule contains 8mg of ondansetron (as hydrochloride dihydrate) in 4mL of aqueous solution for injection or infusion.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:
ZOPHRALEN solution for injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
ZOMPHRALEN solution for injection is indicated for the prevention and treatment of post-operative nausea and vomiting.

Paediatric Population:
ZOPHRALEN solution for injection is indicated for the management of chemotherapy-induced nausea and vomiting in children aged ≥ 6 months, and for the prevention and treatment of post-operative nausea and vomiting in children aged ≥ 1 month.
No studies have been conducted with oral ondansetron for the prevention and treatment of post-operative nausea and vomiting. Intravenous administration is recommended in this case.

4.2 Posology and method of administration

Posology

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

For patients receiving emetogenic chemotherapy or radiation therapy, ondansetron can be given as an intravenous injection.

The recommended intravenous dose of ZOPHRALEN is 8 mg and is administered immediately before treatment.

For highly emetogenic chemotherapy, a maximum initial dose of 16 mg intravenous infusion over 15 minutes may be used. A single intravenous dose greater than 16 mg must not be given due to dose dependent increase of QT- prolongation risk.

The efficacy of ZOPHRALEN 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.

Intravenous doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50-100 mL of 0.9% Sodium Chloride or 5% Dextrose prior to administration and infused over no less than 15 minutes (see section 6.6). Doses of ZOPHRALEN 8 mg or less do not need to be diluted and may be administered by slow intravenous injection in not less than 30 seconds.

The initial dose of ZOPHRALEN may be followed by 2 additional intravenous doses (in no less than 30 seconds) of 8 mg 4 hours apart or by a constant infusion of 1 mg/h for up to 24 hours.

In order 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. ZOPHRALEN is not available for oral or rectal administration. Therefore, turn to other ondansetron products that are available in similar formulations.

Paediatric Population:

Chemotherapy induced nausea and vomiting in children aged ≥ 6 months and adolescents
The dose for CINV can be calculated based on body surface area (BSA) or weight – see below.
ZOPHRALEN Solution for injection 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 is no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged CINV. There is 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 / m^2. The single 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 dose over 24 hours must not exceed the 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 m^2	5 mg / m^2 IV plus 2 mg syrup[c] after 12 hrs	2 mg syrup[c] every 12 hrs
≥ 0.6 m^2 to ≤ 1.2 m^2	5 mg / m^2 IV plus 4 mg syrup[c] or tablet[c] after 12 hrs	4 mg syrup[c] or tablet[c] every 12 hrs
>1.2 m^2	5 mg / m^2 or 8 mg IV plus 8 mg syrup[c] or tablet[c] after 12 hrs	8 mg syrup[c] or tablet[c] every 12 hrs

[1] The intravenous dose must not exceed 8 mg.
[2] The total dose over 24 hours must not exceed the adult dose of 32 mg.
[3] ZOPHRALEN is not available as a syrup or tablet. Therefore, please refer to other ondansetron products available in these formulations.

Dosing by bodyweight:
Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see sections 4.4 and 5.1).
ZOPHRALEN 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.
Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2).

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

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 IV every 4 hrs	2 mg syrup[c] every 12 hrs
> 10 Kg	Up to 3 doses of 0.15 mg / kg IV every 4 hrs	4 mg syrup[c] or tablet[c] every 12 hrs

[1] The intravenous dose must not exceed 8 mg.
[2] The total dose over 24 hours must not exceed the adult dose of 32 mg.
[3] ZOPHRALEN is not available as a syrup or tablet. Therefore, please refer to other ondansetron products available in these formulations.

Elderly:
Chemotherapy (CINV) and radiotherapy (RINV) induced nausea and vomiting.

In patients 65 years of age or older, all intravenous doses should be diluted and infused over 15 minutes, and if repeated, they should be given no less than four hours apart.

In patients aged 65 to 74 years, initial intravenous doses of ondansetron 8 mg or 16 mg, infused over 15 minutes, may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart.

In patients 75 years of age or older, the initial intravenous dose of ondansetron should not exceed 8 mg 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)

Adults:
Post-operative nausea and vomiting (PONV):

For the prevention of post-operative nausea and vomiting*:* ZOPHRALEN can be administered by intravenous injection.

ZOPHRALEN solution for injection may be administered as a single dose of 4 mg given by slow intravenous injection at induction of anaesthesia.

For treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by slow intravenous injection is recommended.

Paediatric population:
Post-Operative Nausea and Vomiting *(PONV) in children aged ≥ 1 month and adolescents*

No studies have been conducted on the use of oral ondansetron for prevention or treatment of post-operative nausea and vomiting. Therefore intravenous injection (not less than 30 seconds) may be administered.

For prevention of post-operative nausea and vomiting in paediatric patients having surgery performed under general anaesthesia, a single dose of ZOPHRALEN 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 either prior to or after induction of anaesthesia or after surgery.
For the treatment of post-operative nausea and vomiting in paediatric patients having surgery performed under general anaesthesia, a single dose of ZOPHRALEN 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 oral ondansetron in the prevention or treatment of post-operative nausea and vomiting. Slow intravenous injection is recommended (not less than 15 minutes).

Elderly:
Post-Operative Nausea and Vomiting (PONV)
There is limited experience in the use of ondansetron in the prevention and treatment of PONV in the elderly, however, ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

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 intravenous or oral 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.

Mode of administration
Intravenous administration.

4.3 Contraindications

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

Based on reports of severe hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

4.4 Special warnings and precautions for use

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

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

Serotonin syndrome has been reported following concomitant use of ondansetron and other serotonergic medicinal products (see section 4.5). If concomitant administration of ondansetron and other serotonergic drugs is clinically warranted, appropriate patient monitoring is recommended.

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.

Paediatric Population:

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

<u>ZOPHRALEN injection solutions contain sodium.</u>
These medicinal products contain less than 1 mmol (23mg) sodium per ampoule, they are what we call "sodium free". However, if a common salt solution (0.9% w/v sodium chloride solution) is used to dilute ZOPHRALEN prior to administration, then the dose of sodium intake will be higher.

4.5 Interactions with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, 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 co-administered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. (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.

Serotonergic Drugs (e.g. SSRIs and SNRIs):
There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). (see section 4.4)

ZOPHRALEN should be used with caution when co-administered with serotonergic medicinal products, such as MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants, as the risk of serotonin syndrome, a potentially fatal condition, is increased (see section 4.4).
Tramadol:
Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

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

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 reproductive toxicity.

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

Safety data for ondansetron use in pregnancy are limited and findings from available pharmaco-epidemiological studies are inconsistent.

Post-marketing reports describe cases of congenital malformations with ondansetron use during pregnancy. However, the reports are not sufficient to prove causation.

Animal data
In fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in rabbits, there were no significant effects of ondansetron on maternal animals or on offspring development. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/kg/day, respectively, based on the body surface area. In a prenatal and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from day 17 to day 21 of pregnancy. With the exception of a slight reduction in maternal body weight gain, no effects were observed in pregnant rats and the pre-natal and post-natal development of their offspring, including reproductive performance of the F1 genotype. At doses of 15 mg/kg/day in rats, the maternal dose was approximately 6 times the maximum recommended oral dose of 24 mg per day based on body surface area (BSA).

Breast-feeding
It is not known if ondansetron is excreted in human breast milk. There are no data on the effects of ondansetron on the nursing child or the effects of ondansetron on milk production. Tests have shown that ondansetron is excreted in the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron should not breast-feed their babies.

Women of reproductive potential
The presence or absence of pregnancy in women of childbearing potential should be confirmed before starting treatment with ondansetron.

Women of childbearing potential should be advised that ondansetron is likely to cause harm to the developing embryo. Women of childbearing potential must use effective contraception (methods that result in a less than 1% chance of pregnancy) during treatment and for up to 2 days after stopping ondansetron treatment.

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

4.7 Effects on ability to drive and use machines

ZOPHRALEN has no or negligible influence on the ability to drive and handle machines.

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 <1/1000) and very rare (<1/10,000), including individual references. 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 ZOPHRALEN according to the indication and the pharmaceutical form (Table 3).

Table 3: Adverse reactions

System organ class and frequency	**Adverse reactions**
Immune system disorders	
Rare:	Immediate hypersensitivity reactions sometimes severe, including anaphylaxis
Nervous system disorders	
Very common:	Headache
Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia)
Rare:	Dizziness predominantly during rapid intravenous administration
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision) predominantly during 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.
Rare:	QTc prolongation (including Torsade de Pointes)
Vascular disorders	
Common:	Sensation of warmth or flushing.
Uncommon:	Hypotension.
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Hiccups.
Gastrointestinal disorders	
Common:	Constipation.
Hepatobiliary disorders	
Uncommon:	Asymptomatic increases in liver function tests[#].
[#] These events were observed commonly in patients receiving chemotherapy with cisplatin.	
Skin and subcutaneous tissue disorders	
Very rare:	Toxic skin rash, including toxic epidermal necrolysis
General disorders and administration site conditions	
Common:	Local IV injection site reactions.

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 continuous monitoring the benefit-risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions actions at the National Organisation for Medicines (284 Mesogeion ave., GR-15562, Cholargos, Athens, Tel: + 30 21 32040380/337, Fax: + 30 21 06549585, Website: http://www.eof.gr).

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 the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Serotonin (5-HT_3) antagonists, ATC Code: A04AA01

Mechanism of Action
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 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.

Pharmacodynamic effects
Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomised, 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.

Pediatric population and adolescents

Nausea and vomiting caused by chemotherapy
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 and ondansetron 4 mg orally after 8 to 12 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 day of chemotherapy was 49% (5 mg/m^2 intravenous and ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenous and 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 5 mg/m^2 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 years and 8 mg for children aged ≥ 12 years (total number of children n= 28). Complete control of emesis was achieved in 42% of patients.

Postoperative 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, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥ 44 weeks, weight ≥ 3 kg). The persons who participated 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). The 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 4.

Table 4 Prevention and treatment of postoperative nausea and vomiting in pediatric patients - Response to treatment within 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 pharmacodynamic properties of ondansetron remain unchanged upon repeated administration.

Absorption
Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations are attained approximately 1.5 hours after administration. 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.
Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.
Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron.

Distribution
Ondansetron is not highly protein bound (70 to 76%).

The disposition of ondansetron after oral or intravenous administration in adults is similar with a steady-state volume of distribution of approximately 140L.

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
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism. Less than 5% of the absorbed dose is excreted unchanged in the urine. The disposition of ondansetron following oral or intravenous dosing is similar to a half life of about 3 hours.

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 months 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 postoperative nausea and vomiting 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 exposure-response 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 (see section 4.2).

Special studies in elderly individuals or those with renal dysfunction have been limited to intravenous and oral administration. However, it is anticipated that the half-life of ondansetron in elderly patients will be similar to that observed in healthy volunteers, as the elimination rate of ondansetron after hypothetical administration is not determined by systematic clearance.

Renal Impairment

In patients with renal impairment (creatinine clearance 15 to 60 mL/min), both systemic clearance and volume of distribution are reduced, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 hours).

A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following intravenous administration.

Special studies in patients with renal dysfunction have been limited to intravenous and oral administration. However, it is anticipated that the half-life of ondansetron in patients with renal impairment will be similar to that observed in healthy volunteers, as the elimination rate of ondansetron after hypothetical administration is not determined by systematic clearance.

Hepatic Impairment

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15 to 32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

5.3 Preclinical safety data

A study on cloned ion channels of the human heart demonstrated that ondansetron has the potential to influence cardiac repolarization by blocking hERG-type potassium channels at clinically relevant concentrations. Dose-dependent QT interval prolongation has been observed in a comprehensive QT study involving healthy volunteers (see paragraph 5.1 - QT Prolongation).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate, Sodium citrate, Sodium chloride, Water for injections

6.2 Incompatibilities

ZOPHRALEN solution for injection must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at a temperature below 25°C.

6.5 Nature and contents of container

ZOPHRALEN solution for injection is packaged in glass or polypropylene ampoules and placed in a cardboard box.All packages may not be available on the market.

Each pack contains:

1 ampoule of 2 mL or 4 mL
or
20 ampoules of 2 mL or 4 mL
or
50 ampoules of 2 mL or 4 mL

6.6 Special precautions for disposal and other handling

ZOPHRALEN injectable ampoules should not be placed in an autoclave for sterilization.

Compatibility with intravenous fluids

ZOPHRALEN should not be administered in the same syringe or intravenous line with any other drug.

ZOPHRALEN injection should only be mixed with recommended infusion solutions.

For the purpose of compliance with good pharmaceutical practice, intravenous solutions for injection should be prepared at the time of infusion. However, ondansetron solution for injection has been found to be stable for seven days at room temperature (below 25°C) exposed to fluorescent lighting or in a refrigerator with the following intravenous fluids used for infusion:

Sodium chloride 0.9% w/v for intravenous infusion.
Glucose 5% w/v for intravenous infusion.
Mannitol 10% w/v for intravenous infusion,
Ringer's solution for intravenous infusion.
Potassium chloride 0.3% w/v and sodium chloride 0.9% w/v for intravenous infusion.
Potassium chloride 0.3% w/v and glucose 5% w/v for intravenous infusion.

Compatibility studies of ondansetron have been performed with polyvinyl chloride bags and devices used for infusions. Satisfactory stability is also provided by using polyethylene bags or type 1 glass vials.

Solutions of ondansetron in sodium chloride 0.9% w/v or glucose 5% w/v are stable in polypropylene syringes.

Ondansetron solution for injection when mixed with other compatible infusion fluids is considered stable in polypropylene syringes.

Note: The preparation must be kept in suitable aseptic conditions when an extension of its preservation time is required.

Compatibility with other drugs:
ZOPHRALEN solution for injection may be administered by intravenous infusion at 1 mg/hour, from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of an infusion set for ZOPHRALEN concentrations of 16 to 160 micrograms/mL (e.g. 8 mg/500 mL and 8 mg/50 mL respectively):

Cisplatin:
Concentrations up to 0.48 mg/mL (e.g. 240 mg in 500 mL) administered over one to eight hours.

5-Fluorouracil:
Concentrations up to 0.8 mg/mL (e.g. 2.4 g in 3 litres or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (500 mL per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045%w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin:
Concentrations in the range 0.18 mg/mL to 9.9 mg/mL (e.g. 90 mg in 500 mL to 990 mg in 100 mL), administered over ten minutes to one hour.

Etoposide:
Concentrations in the range 0.14 mg/mL to 0.25 mg/mL (e.g. 72 mg in 500 mL to 250 mg in 1L), administered over thirty minutes to one hour.

Ceftazidime:
Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5 mL for 250 mg and 10 mL for 2 g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide:
Doses in the range 100 mg to 1 g, reconstituted with Water for Injections BP, 5 mL per 100 mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin:
Doses in the range 10 – 100 mg reconstituted with Water for Injections BP, 5 mL per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

Dexamethasone:
Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2 – 5 minutes via the Y-site of an infusion set delivering 8 or 16 mg of ondansetron diluted in 50 – 100 mL of a compatible infusion fluid over approximately 15 minutes.
Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 micrograms – 2.5 mg/mL for dexamethasone sodium phosphate and 8 micrograms – 1 mg/mL for ondansetron.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Solution for injection 4mg/2mL: 40893/09/19-02-2010
Solution for injection 8mg/4mL: 40895/09/19-02-2010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Solution for injection 4mg/2ml: 8-12-2004
Solution for injection 8mg/4ml : 8-12-2004

10. DATE OF REVISION OF THE TEXT

October 2023