SUMMARY OF PRODUCT CHARACTERISITICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOPHRALEN Solution for Injection 4mg/2ml:
Ampoules, each containing 4 mg of ondansetron (in the form of hydrochloride dihydrate) in 2 mL of aqueous solution for intravenous or intramuscular administration.

ZOPHRALEN Solution for Injection 8mg/4ml:
Ampoules, each containing 8 mg of ondansetron (in the form of hydrochloride dihydrate) in 4 mL of aqueous solution for intravenous or intramuscular administration.

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

Paediatric Population:
ZOPHRALEN is indicated for the treatment of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months and for the prevention and treatment of PONV in children aged ≥1 month.

4.2 Posology and method of administration

Intravenously or intramuscularly.

Nausea and vomiting associated with chemotherapy and radiotherapy:

Adults:
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. Ondansetron is administered orally, intravenously and also intramuscularly, fact that allows a flexibility in the route of administration and dosage. ZOPHRALEN dose ranging from 8 mg to 32 mg per day and is selected as shown below.

Mild emetogenic chemotherapy and radiotherapy:
For patients receiving emetogenic chemotherapy or radiotherapy, ondansetron can be used either orally (as tablets or syrup) or by intravenous or intramuscular injection.

The recommended dose of ZOPHRALEN is 8 mg and it is administered by a slow intravenous or intramuscular injection right before treatment.
For protection against delayed or prolonged emesis after the first 24 hours, ondansetron treatment must be continued with oral administration of 8 mg per 12 hours for up to 5 day.

Highly emetogenic chemotherapy:
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be used by intravenous or intramuscular injection.

A single dose of 8 mg of ZOPHRALEN may be administered by slow intravenous injection right before the chemotherapy, followed by either 8 mg every 2-4 hours for 2 more intravenous or intramuscular doses or by continuous intravenous infusion of 1 mg/h for up to 24 hours.

Alternatively, 32 mg of ZOPHRALEN may be administered by intravenous infusion for at least 15.

Doses higher than 8 mg and up to 32 mg, are administered only intravenously, diluted in 50 – 100 mL of saline or other compatible infusion fluid *(see Package Leaflet)* in not less than 15 minutes.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

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

For protection against delayed or prolonged emesis after the first 24 hours, ondansetron treatment should be continued with oral administration, with the therapeutic regimen of 8 mg every 12 hours for up to 5 days.

Children: ZOPHRALEN is administered by a slow intravenous injection of 5mg/m^2 or by continuous intravenous infusion for at least 15 minutes right before the start of the chemotherapy, followed by 4 mg per 12 hours orally for up to 5 days.

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

ZOPHRALEN should be diluted to 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid (see section 6.6) and injected intravenously for at least 15 minutes.
There are no data from controlled clinical trials on the use of ZOPHRALEN in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of ZOPHRALEN for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:

ZOPHRALEN should be administered right before chemotherapy as a single intravenous dose of 5 mg/m^2. 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 m^2	5 mg/m^2 IV followed by 2 mg syrup after 12 hours	2 mg syrup every 12 hours
≥ 0.6 m^2	5 mg/m^2 IV followed by 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours

[a]The intravenous dose must not exceed 8 mg.
[b]The total daily dose must not exceed adult dose of 32 mg.

Dosing by body weight:
Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see sections 4.4 & 5.1).

ZOPHRALEN should be administered right before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg.

Two more intravenous doses may be given in 4-hour 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

Body 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 syrup every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hours	4 mg syrup or tablet every 12 hours

[a]The intravenous dose must not exceed 8 mg.
[b]The total daily dose must not exceed adult dose of 32 mg.

Elderly patients: ZOPHRALEN is well tolerated by patients over 65 years of age, hence no alteration in dosage, dosage frequency and route of administration, is required.

Post-operative nausea and vomiting (PONV)

Adults: For the prevention of PONV ZOPHRALEN can be administered either orally (as tablets or syrup) or by intravenous or intramuscular injection.

ZOPHRALEN may be administered as a single dose of 4 mg by slow intravenous or intramuscular injection during anaesthesia induction.

For the treatment of established PONV, a single dose of 4 mg, by slow intravenous or intramuscular injection, is recommended.

Paediatric population:
PONV in children aged ≥ 1 month and adolescents:
For the prevention of PONV in paediatric patients who have undergone a surgery under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (for over at least 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to or after anaesthesia induction.

For the treatment of PONV in paediatric patients who have undergone a surgery under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (for over at least 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 ZOPHRALEN in the treatment of PONV in children below 2 years of age.

There are no studies on oral administration of ondansetron for prevention or treatment of PONV. Slow intravenous injection is recomended (for at least 15 minutes).

Elderly patients: There is limited experience in the use of ZOPHRALEN in the prevention and treatment of PONV in elderly patients, however, ZOPHRALEN is well tolerated by patients over 65 years of age receiving chemotherapy.

Patients with renal impairment: No alteration in daily dosage, dosage frequency and route of administration, is required.

Patients with hepatic impairment: Clearance of ZOPHRALEN is significantly reduced and half-life in blood serum is significantly prolonged, in subjects with moderate or severe impairment of hepatic function. In such patients the total daily dose should not exceed 8 mg, either intravenously or orally.

Patients with poor sparteine/debrisoquine metabolism: The half-life of ondansetron is not altered, in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently, in such patients, repeated doses achieve the same levels, in blood serum, as those of the general population. No alteration in daily dosage and dosage frequency, is required.

4.3 Contraindications
Hypersensitivity to any of the components of the formulation.

4.4 Special warnings and precautions for use
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.
Respiratory adverse effects should be treated symptomatically and clinicians should pay particular attention to them, because they can be precursors of hypersensitivity reactions.
Rarely, transient ECG changes, including QT interval prolongation, have been reported in patients receiving ondansetron. Moreover, cases of torsade tachycardia (Torsade de Pointes) have been reported post-marketing, in patients using ondansetron. ZOPHRALEN should be administered with caution to patients who have or may develop QT prolongation. These cases include patients with electrolyte disorders, congenital prolonged QT syndrome, or patients receiving medicinal products known to cause QT prolongation.
As Ondansetron is known to increase colon transit time, patients with signs of subacute intestinal obstruction, should be monitored after its administration.
In patients who have undergone an adenotonsillar surgery, prevention of nausea and vomiting with ZOPHRALEN, may mask occult bleeding.

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

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, frusemide, 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.

Phenytoin, carbamazepine and rifampicin
In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, rifampicin), the oral clearance of ondansetron was increased and ondansetron concentrationsin blood were decreased.

Tramadol
Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

Use of ZOPHRALEN with QT prolonging drugs may result in additional QT prolongation. Coadministration of ZOPHRALEN with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmia (see section 4.4).

4.6 Fertility, pregnancy and lactation
Pregnancy: Ondansetron is not teratogenic in animals. The safety of ondansetron use, during human pregnancy, has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the foetus, the course of pregnacy and peri- and post-natal development. However, as animal studies are not always predictive of human response, the use of ondansetron during pregnancy is not recommended.

Lactation: Tests have shown that ondansetron passes into the milk of lactating animals. Therefore, it is recommended that mothers receiving ondansetron should not breast-feed their infants.

4.7 Effects on ability to drive and use machines
In psychomotor testing, ondansetron does not impair performance nor cause sedation. According to the pharmacology of ondansetron, harmful effects in such activities are not anticipated.

4.8 Undesirable effects
Adverse effects are listed below by system organ class and frequency.
Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

Very common, common and uncommon events were generally determined from clinical trials data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

Immune system disorders
Rare: Immediate hypersensitivity reactions, sometimes severe, including anaphylaxis.

Nervous system disorders
Very common: Headache.
Uncommon: Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia)[1].
Rare: Dizziness during rapid intravenous administration.

Eye disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during intravenous administration.
Very rare: Transitory blindness, predominantly during intravenous administration[2].

Cardiac disorders
Uncommon: Cardiac arrhythmias, chest pain with or without ST segment depression and bradycardia.

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

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Constipation.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in hepatic function tests[3].

General disorders and administration site conditions
Common: Local intravenous injection site reactions.
[1]*Have been observed without definitive evidence of persistent clinical sequelae.*
[2]*The majority of reported blindness cases were 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 effect profile in children and adolescents were comparable to that seen in adults.

4.9 Overdose
There is limited experience with ondansetron overdose. In the majority of cases, the side effects were similar to those already reported in patients receiving recommended doses (see 4.8). Effects that have been reported include, visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. Two patients who received, intravenously, 84 mg and 145 mg respectively, reported only mild side effects that did not require active treatment therapy. There is no specific antidote to ondansetron, therefore, in cases of suspected overdose there should be symptomatic and supportive treatment.
The use of ipecacuanha, to treat ondansetron overdose, is not recommended, as patients are not likely to respond, due to the very anti-emetic action of ZOPHRALEN itself.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Ondansetron is a potent and highly selective 5-HT3-receptor antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause the release of 5-HT in the small intestine by activating the vagal afferents via 5-HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of the vagal afferents may also cause a release of 5-HT in the rear area, located on the base of the fourth ventricle, resulting in promoting the emesis through a central mechanism. Thus, the effect of ondansetron in the treatment 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 in the central nervous system. The

mechanisms of action in PONV are not known but it is likely to be common with those of cytotoxic induced nausea and vomiting.

The mode of action of ondansetron in vomiting induced by opioids is not yet established. Ondansetron does not alter plasma prolactin concentrations.

Paediatric population

CINV

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 intravenous + ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/kg intravenous + placebo orally after 8 to 12 hours. Post-chemotherapy both groups received 4 mg of ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse effects between the two treatment groups.

Complete control of emesis on the worst day of chemotherapy in 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 of ondansetron syrup twice daily for 3 days.

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

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

Post-chemotherapy both groups received 4 mg of ondansetron syrup twice daily for 2 days. There was no difference in the overall incidence or nature of adverse effects 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 intravenous doses of ondansetron, administered at 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56% of the patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of a single 0.15 mg/kg intravenous dose of ondansetron followed by two 4 mg oral doses of ondansetron for children aged less than 12 years and 8 mg for children aged more than 12 years (total number of children n= 28). Complete control of emesis was achieved in 42% of the patients.

PONV

The efficacy of a single dose of ondansetron in the prevention of PONV was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age $\geq$ 44 weeks, weight $\geq$ 3 kg). Participants were scheduled to undergo elective surgery under general anaesthesia and had an ASA status $\leq$ III. A single dose of ondansetron 0.1 mg/kg was administered within 5 minutes after anaesthesia induction. The proportion of subjects who experienced at least one emetogenic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than for 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) who have undergone 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 for at least 30 seconds, right before or right after 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	End Point	Ondansetron %	Placebo %	p value
S3A380	CR	68	39	≤0.001
S3GT09	CR	61	35	≤0.001
S3A381	CR	53	17	≤0.001
S3GT11	w/o nausea	64	51	0.004
S3GT11	w/o vomiting	60	47	0.004

CR = without emetogenic episodes, use of emergency treatment or withdrawal

5.2 Pharmacokinetic properties

After oral administration of ondansetron, absorption is rapid with peak concentrations, at 26.2 ng/mL for men and at 47.72 ng/mL for women, in blood plasma to be attained in approximately 2 and 1.7 hours, respectively, after an 8 mg dose and absolute oral bioavailability of about 56%. After the oral administration of a 24 mg single dose of ondansetron, the peak concentrations, at 125.8 ng/mL for men and at 194.4 ng/mL for women, in blood plasma were attained in approximately 1.9 and 1.6 hours respectively.
4 mg and 8 mg tablets and 4 mg and 8 mg oral lyophilisates are respectively bioequivalent. At higher than 8 mg doses, C_{max} and AUC are increased more than proportionally to the dose, resulting in greater bioavailability.

5 mL of syrup are bioequivalent to a 4 mg tablet. Similarly, 10 mL of syrup are bioequivalent to an 8 mg tablet or two 4 mg tablets. A 24 mg tablet is bioequivalent to three 8 mg tablets. The average bioavailability in healthy males after the administration of a single 8 mg tablet is approximately 55% – 60%.

After oral, intramuscular or intravenous administration, similar terminal half-life, approximately 3 hours and steady volume of distribution, approximately 140 L, have been observed. After 4 mg administration of ondansetron by drip infusion, peak concentration level, at approximately 65 ng/mL, in blood serum is attained in 5 minutes. The systemic availability after the intramuscular or intravenous 4 mg administration of ondansetron is equivalent.

Following administration of an ondansetron suppository, the concentrations of ondansetron in blood plasma are detected in between 15 and 60 minutes after dosing. The concentrations are substantially increased in a linear way until they reach the peak concentration in the range of 20 ng/mL to 30 ng/mL usually in 6 hours after dosing. Then, the concentrations in blood plasma are being reduced but at a slower rate than that observed after oral administration, due to the continuing absorption of ondansetron. The half-life of extratory phase, depends on the absorption rate of ondansetron and not on the systemic clearance and is approximately 6 hours.

Females show a small, clinically insignificant, increase in half-life compared to males. The absolute bioavailability of ondansetron from a suppository is approximately 60% and is unuffected by gender.

Ondansetron blood plasma proteins binding is ranging from 70% to 76%. Ondansetron clearance is performed by the systemic circulation, mostly through multiple enzymatic pathways of hepatic metabolism. Less than 5% of the dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (debrisoquine polymorphism) has no effect on ondansetron pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged
with repeated dosing.

Gender

It has been observed that ondansetron availability is different in two genders, with females to show a higher degree and duration of absorption after a single oral dose as well as reduced systemic clearance and volume of distribution (adjusted to body weight).

Special Patient Populations

Children and Adolescents (aged 1 month to 17 years)
In paediatric patients aged 1 to 4 months (n=19) who have undergone a surgery, weight-based clearance was approximately 30% lower than in patients aged 5 to 24 months (n=22) but comparable to that of patients aged 3 to 12 years. The average half-life in patient population aged 1 to 4 month was reported to be 6.7 hours compared to 2.9 hours for patients in the 5 to 24 months and 3 to 12 year age range. The differences in pharmacokinetic parameters in the patient population aged 1 to 4 months can be partly explained by the higher percentage of total body water in neonates and infants and the higher volume of distribution for water soluble drugs like ondansetron.

In paediatric patients aged 3 to 12 years who have undergone a selective surgery with general anaesthesia, the absolute values for both clearance and volume of distribution of ondansetron were reduced in comparison to those in adult patients. Both parameters were increased linearly with the weight and by the 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, they were similar among the several population age groups. Use of weight-based dosing compensates for age-related changes and is effective in normalising the systemic exposure in paediatric patients.

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

Elderly
Studies in healthy elderly volunteers have showned the bioavailability of ondansetron to be slightly increased but clinically insignificant (65%) when administered orally and a half-life of 5 hours.

Renal Impairment
In patients with moderate renal impairment (creatinine clearance from 15 mL/min to 60 mL/min) both systemic clearance and volume of distribution are reduced resulting in a slight, but clinically insignificant, increase in half-life (5.4 hours).
A study in patients with severe renal impairment who had undergone regular haemodialysis (studied were performed between dialyses) showed ondansetron pharmacokinetics to be unchanged.

Hepatic Impairment
In patients with severe hepatic impairment, the systemic clearance is remarkably reduced with prolonged half-lives (15 – 32 hours) and the oral bioavailability is approaching 100% due to reduced pre-systemic metabolism.
Ondansetron pharmakokinetics after the administration of a suppository have not been evaluated in patients with hepatic impairment.

5.3 Preclinical safety data

From 2-year carcinogenicity studies in rats and mice, there were no evidence of carcinogenicity at doses up to 10 mg/mL and 30 mg/mL per day, respectively. Ondansetron has not been proved to be mutagenic in mutagenicity tests.

Moreover, for the Solution for Injection:
A study, on cloned ion channels of the human heart, has shown that ondansetron has the potential to affect cardiac repolarization, via blockade of type hERG potassium channels, at clinically relevant concentrations. QT prolongation has been observed in vivo, in cats anesthetized by intravenous administration but at doses exceeding by 100 times those that are pharmacologically effective. Similar effects were observed in monkeys of the species cynomolgus. Transient ECG changes have been reported in clinical practice (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Citric acid monohydrate, sodium citrate dihydrate, sodium chloride and water for injections.

6.2 Incompatibilities
ZOPHRALEN should not be administered in the same syringe or by drip infusion with any other medication (see section 6.6).

ZOPHRALEN should be admixed only with the recommended, for intravenous infusion, fluids (see section 6.6).

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 25ºC.

6.5 Nature and contents of container
ZOPHRALEN is packed in glass or polypropylene ampoules and in carton box.

6.6 Special precautions for disposal and other handling
ZOPHRALEN ampoules should not be placed in autoclave.

Instructions on the correct way of opening the ampoule.

Compatibility with intravenous fluids:
ZOPHRALEN should be admixed only with the recommended, for intravenous infusion, fluids. In order to be in compliance with good pharmaceutical practice, intravenous solutions should be prepared at the time of the infusion. However, it has been demonstrated that ZOPHRALEN is stable for 7 days at room temperature (below 25°C) with fluorescent lighting or in a refrigerator with the following intravenous fluids used for infusion:

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

Compatibility studies, of ZOPHRALEN with PVC bags and devices used for infusion, have been performed. Satisfactory stability also provided by using polyethylene bags or Type I glass ampoules. ZOPHRALEN solutions, in sodium chloride 0.9% w/v or glucose 5% w/v, are stable in polypropylene syringes. ZOPHRALEN is considered stable in polypropylene syringes, when admixed with other compatible infusion fluids.
Note: The product should be kept in appropriate aseptic conditions, when the extension of its shelf life is required.

Compatibility with other drugs:
ZOPHRALEN can be administered by intravenous infusion at 1 mg/h, via an infusion bag or pump. The following drugs may be administered along with ZOPHRALEN via the Y-site of an infusion set for ondansetron concentrations of 16 – 160 mcg/ mL (e.g. 8 mg/500 mL & 8 mg/50mL respectively):

Cisplatin:
Concentrations up to 0.48 mg/mL (e.g. 240 mg/500 mL), administered for over 1 – 8 hours.

5-Fluorouracil:
Concentrations up to 0.8 mg/mL (e.g. 2.4 g/3 L or 400 mg/500 mL), are administered at a rate of at least 20 mL/h (500 mL/24 h) Higher concentrations of 5-fluorouracil may cause precipitation of ZOPHRALEN. The 5-fluorouracil infusion may includemagnesium chloride up to 0.045% w/v along with other compatible excipients.

Carboplatin:
Concentrations ranging from 0.18 mg/mL to 9.9 mg/mL (e.g. from 90 mg/500 mL to 990 mg/100 mL), are administered for a period of 10 minutes to 1 hour.

Etoposide:
Concentrations ranging from 0.14 mg/mL to 0.25 mg/mL (e.g. from 72 mg/500 mL to 250 mg/L), are administered over for a period of 30 minutes to 1 hour.

Ceftazidime:
Doses ranging from 250 mg to 2000 mg are reconstituted with bis-distilled water for injection according to the manufacturer's instructions (e.g. 2.5 mL for 250 mg and 10 mL for 2 g of ceftazidime) and administered by an intravenous injection for about 5 minutes.

Cyclophosphamide:
Doses ranging from 100 mg to 1 g, are reconstituted with bis-distilled water for injection, 5 mL per 100 mg of cyclophosphamide, as recommended by the manufacturer and administered by an intravenous injection for about 5 minutes.

Doxorubicin:
Doses ranging from 10 mg to 100 mg, are reconstituted with bis-distilled water for injection, 5 mL per 10 mg of doxorubicin, as recommended by the manufacturer and administered by an intravenous injection for about 5 minutes.

Dexamethasone:
20 mg of dexamethasone sodium phosphate are administered by slow intravenous injection for over 2 – 5 minutes via the Y-site of an infusion set, together with 8 mg or 32 mg of ZOPHRALEN, diluted in 50 – 100 mL of a compatible infusion fluid and injected for about 15 minutes.

Compatibility between dexamethasone sodium phosphate and ZOPHRALEN has been demonstrated by the administration of these drugs through the same device in concentrations from 32 mcg/mL to 2.5 mg/mL of dexamethasone sodium phosphate and from 8 mcg/mL to 1 mg/mL of ZOPHRALEN.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBERS

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

ZOPHRALEN Solution for Injection 4 mg/2 mL: 8-12-2004 (first authorisation)
ZOPHRALEN Solution for Injection 8 mg/4 mL: 8-12-2004 (first authorisation)

ZOPHRALEN Solution for Injection 4 mg/2 mL: 19-02-2010 (renewal)
ZOPHRALEN Solution for Injection 8 mg/4 mL: 19-02-2010 (renewal)

10. DATE OF REVISION OF THE TEXT

September 2012

*Based on the circular 20285/11/4-9-2012 issued by the **National Organisation** for **Medicines (EOF)** and on the current QRD template version 3.0, 04/2013*