Active Ondansetron

Virtual SPC for PSUR Synchronisation Scheme

This Virtual SPC is based on GlaxoSmithKline's Company Core Data Sheet (CCDS) for ondansetron.

GSK does not believe that there are deficiencies in local labels, but is submitting this Virtual SPC as it contains the most recent Reference Safety Information (RSI) for the product. National labels may be subject to on-going variations to align with the CCDS, and/or may contain amendments requested by national regulatory authorities.

This document is formatted as an SPC but contains only sections 1-4. Sections 4.3, 4.4, 4.5, 4.6, 4.7, 4.8 and 4.9 of this document contain the safety information for the medicinal products and pharmaceutical forms listed below in sections 1, 2 and 3.

The safety information in this document should be used as the proposed Core Safety Profile.

4.1 Therapeutic indications and 4.2 Posology and method of administration sections are provided for information only.

Not all indications, formulations and corresponding dosage information may be registered in every country.

1. NAME OF THE MEDICINAL PRODUCT

Oral formulations:

Zofran 4 mg film-coated tablets

Zofran 8 mg film-coated tablets

Zofran 24 mg film-coated tablets

Zofran 4 mg syrup

Zofran Zydis 4 mg oral lyophilisate

Zofran Zydis 8 mg oral lyophilisate

Injection:

Zofran 2 mg injection

Zofran 4 mg pre-filled syringe

Zofran 8 mg pre-filled syringe

Suppositories:

Zofran 16 mg suppositories

2. QUALITATIVE AND QUANTITIVE COMPOSITION

Oral formulations:

Each 4 mg film-coated tablet contains ondansetron 4 mg as hydrochloride dihydrate.

Each 8 mg film-coated tablet contains ondansetron 8 mg as hydrochloride dihydrate.

Each 24 mg film-coated tablet contains ondansetron 24 mg as hydrochloride dihydrate.

Each 5 ml contains 4 mg ondansetron as hydrochloride dihydrate.

Each 4 mg oral lyophilisate contains ondansetron 4 mg.

Each 8 mg oral lyophilisate contains ondansetron 8 mg.

Injection:

Each 1 ml of aqueous solution for injection contains 2 mg ondansetron as hydrochloride dihydrate.

Each 4 mg pre-filled syringes contain 2 ml of 2 mg/ml ondansetron hydrochloride delivering a total dose of 4 mg.

Each 8 mg pre-filled syringes contain 4 ml of 2 mg/ml ondansetron hydrochloride delivering a total dose of 8 mg.

Suppositories:

Each 16 mg suppository contains 16 mg of ondansetron.

3. PHARMACEUTICAL FORM

Oral formulations:

4 mg film-coated tablet: Yellow, oval, film-coated tablet engraved with 'GX ET3'.

8 mg film-coated tablet: Yellow, oval, film-coated tablet engraved with 'GX ET5' .

24 mg film-coated tablet: Pink, oval, film-coated tablet engraved 'GXCF7' on one face and '24' on the other.

Syrup: Each bottle contains 50 ml of sugar-free strawberry flavoured syrup.

4 mg oral lyophilisate: White, round, plano-convex, freeze-dried, fast dispersing oral dosage form.

8 mg oral lyophilisate: White, round, plano-convex, freeze-dried, fast dispersing oral dosage form.

Injection:

2 mg injection: clear, colourless, sterile solution for injection or infusion.

4 mg pre-filled syringe: clear, colourless, sterile solution for injection or infusion.

8 mg pre-filled syringe: clear, colourless, sterile solution for injection or infusion.

Suppositories:

White torpedo shaped suppository.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oral Formulations:

Ondansetron oral formulations are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Ondansetron is also indicated for the prevention of post-operative nausea and vomiting.

Injection:

Ondansetron injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Ondansetron is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Suppositories:

Ondansetron suppositories are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Paediatric Population:

Ondansetron is indicated for the management 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

Ondansetron is available for oral, parenteral and rectal use to allow the route of administration and dosing to be flexible.

Oral Lyophilisate:

Place the Zydis on top of the tongue, where it will disperse within seconds, then swallow.

Pre-filled Syringe:

Ondansetron pre-filled syringes are not graduated. Therefore, the entire contents of the pre-filled syringe must be administered to ensure the correct dose of ondansetron is received.

Individuals for whom the 4 mg dose (or multiples thereof) is inappropriate must not be treated using the pre-filled syringes.

Chemotherapy And Radiotherapy Induced Nausea And Vomiting (CINV and RINV)

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Populations - Adults

Emetogenic Chemotherapy And Radiotherapy

Oral Formulations:

The recommended oral dose is 8 mg 1 to 2 hours before treatment, followed by 8 mg orally 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg to be taken twice daily.

Injection:

The recommended intravenous (IV) or intramuscular (IM) dose of ondansetron is 8 mg administered as a slow 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.

Suppositories:

The recommended dose of ondansetron suppositories is one 16 mg suppository given 1 to 2 hours before treatment.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended daily dose of ondansetron suppositories is one 16 mg suppository.

Highly emetogenic chemotherapy e.g. High-dose cisplatin

Ondansetron can be given by oral, IV, IM or rectal administration.

Oral Formulations:

The recommended oral dose is 24 mg taken together with oral dexamethasone sodium phosphate 12 mg, 1 to 2 hours before treatment.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg to be taken twice daily.

Injection:

Ondansetron may be administered as a single 8 mg IV or IM 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 IV 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 should not be given. (See Special warnings and precautions for use)

For management of highly emetogenic chemotherapy , a dose of 8 mg of ondansetron may be administered by slow IV in not less than 30 seconds, or IM injection immediately before chemotherapy, followed by 2 further IV or IM doses of 8 mg 2 to 4 hours apart, or by a constant infusion of 1 mg/h for up to 24 hours.

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

Oral or rectal treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Suppositories:

The recommended dose of ondansetron suppositories is one 16 mg suppository given 1 to 2 hours before treatment.

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

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended daily dose of ondansetron suppositories is one 16 mg suppository.

Paediatric Population -– Chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months and adolescents

Oral Formulations and Injection:

The dose for chemotherapy induced nausea and vomiting (CINV) can be calculated based on body surface area (BSA) or weight – see below. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid (see Instructions for Use and Handling) and infused over not less than 15 minutes.

Weight-based dosing results in higher total daily doses compared to BSA-based dosing (*see Special Warnings and Precautionsfor Use*).

Ondansetron injection should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid (*see Use and Handling*) and infused intravenously over not less than 15 minutes.

There are no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of ondansetron for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m². The intravenous dose must not exceed 8 mg.

Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 1). The total daily dose must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for Chemotherapy - Children aged ≥6 months and adolescents

BSA	Day 1(a,b)	Days 2-6(b)
< 0.6 m²	5 mg/m² i.v. plus 2 mg syrup after 12 hours	2 mg syrup every 12 hours
≥0.6 m²	5 mg/m² i.v. plus 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours
> 1.2 m2	5 mg/m2 IV or 8 mg IV plus 8 mg syrup or tablet after 12 hours	8 mg syrup or tablet every 12 hours

a. The intravenous dose must not exceed 8 mg.

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

Dosing by bodyweight:

Weight-based dosing results in higher total daily doses compared to BSA-based dosing (*see Special Warnings and Precautions for Use and Pharmacodynamics: Clinical Studies*).

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

Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2).

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

Weight	Day 1 (a,b)	Days 2-6(b)
≤10 kg	Up to 3 doses of 0.15 mg/kg every 4 hours	2 mg 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 8mg.
b. The total daily dose must not exceed adult dose of 32 mg.

Suppositories:

The use of ondansetron suppositories in children is not recommended. The usual methodof administration is IV followed by oral therapy (*see Children - Oral Formulations and Injection above*).

Populations - Elderly

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Populations - Renal Impairment

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Populations - Hepatic Impairment

Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients, a total daily dose of 8 mg should not be exceeded.

Populations - 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)

Populations - Adults

Oral Formulations:

For prevention of post-operative nausea and vomiting, the recommended oral dose is 16 mg given 1 hour prior to anaesthesia.

For treatment of established post-operative nausea and vomiting ondansetron, administration by injection is recommended.

Injection:

For prevention of post-operative nausea and vomiting, the recommended dose of ondansetron injection is a single dose of 4 mg by IM or slow IV injection administered at the induction of anaesthesia.

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

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

Oral Formulations:

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting (PONV); slow IV injection (in not less than 30 seconds) is recommended for this purpose.

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

Injection:

For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow IV injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For treatment of PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron 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 in the treatment of PONV in children under 2 years of age.

Populations - Elderly

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly, however ondansetron is well tolerated

in patients over 65 years receiving chemotherapy.

Populations - Renal Impairment

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Populations - Hepatic Impairment

Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients, a total daily dose of 8 mg should not be exceeded.

Populations - Patients with Poor Sparteine/Debrisoquine Metabolism

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently, in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

4.3. Contraindications

Concomitant use with apomorphine (see Interactions with other medicinial products).

Hypersensitivity to any component of the preparation.

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.

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 ~~4 hourly~~ intervals, the total daily dose will be higher than if one single dose of 5mg/m2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicates similar efficacy for both regimens (see Pharmacodynamics).

Oral Lyophilisate only:

Ondansetron Zydis formulation contains aspartame and therefore should be taken with caution in patients with phenylketonuria.

Pre-filled Syringe only:

The tip cap of the pre-filled syringe contains dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

Tablets only:

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 coadministered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, frusemide, alfentanil, tramadol, morphine, lignocaine, thiopental or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of

metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

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

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 Special warnings and precautions for use)

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

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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. Pregnancy and Lactation

Pregnancy

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Lactation

Tests have shown that ondansetron passes into the milk of lactating animals. It is

therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7. Ability to perform tasks that require judgement, motor or cognitive skills

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) and very rare (<1/10,000). 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. . The adverse event profiles in children and adolescents were comparable to that seen in adults.

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 IV administration.

Eye disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.

Very rare: Transient blindness predominantly during intravenous administration[2].

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.

Local burning sensation following insertion of suppositories.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests[3]

General disorders and administration site conditions

Common: 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.

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 Undesirable effects*). 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.

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.

5.1 Pharmacodynamics

Oral Formulations and Injection:

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, 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.

Clinical Studies

Paediatric population

CINV

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 intravenous and ondansetron 4 mg orally after 8 to12 hours or ondansetron 0.45 mg/kg intravenous and placebo orally after 8 to 12 hours. Post-chemotherapy both groups received4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst dayof 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 received4 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/m² intravenous together with 2 to 4 mg dexamethasone orally

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

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

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at 4 and 8 hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 yrs and 8 mg for children aged ≥ 12 years (total no. of children n= 28). Complete control of emesis was achieved in 42% of patients.

PONV

The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥ 44 weeks, weight ≥3 kg). Included subjects were scheduled to undergo elective surgery under general anaesthesia and had an ASA status ≤ III. A single dose of ondansetron 0.1 mg/kg was administered within five minutes following induction of anaesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than those receiving ondansetron ((28% vs. 11%, p <0.0001).

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single intravenous doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg; number of patients = 735)) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarised in Table 3.

Table 3 Prevention and treatment of PONV in Paediatric Patients – Treatment response over 24 hours

Study	Endpoint	Ondansetron %	Placebo %	p value
S3A380	CR	68	39	≤ 0.001
S3GT09	CR	61	35	≤ 0.001
S3A381	CR	53	17	≤ 0.001
S3GT11	no nausea	64	51	0.004
S3GT11	no emesis	60	47	0.004

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetics

Special Populations

Children and Adolescents (aged 1 month to 17 years)

Oral formulations and Injection:

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 1 to 4 month patient population 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 watersoluble 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 agerelated 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.

6.2 Incompatibilities

Injection:
Ondansetron injection should not be administered in the same syringe or infusion as any other medication.

Ondansetron injection should only be mixed with those infusion solutions that are recommended.

6.4 Special precautions for storage

Syrup:

Store upright below 30ºC. Do not refrigerate.

Injection:

Protect from light.

6.6 Special precautions for disposal and other handling

Injection:

Ondansetron injection ampoules should not be autoclaved.

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