PAEDIATRIC PUBLIC ASSESSMENT REPORT

EU-Worksharing Procedure – Assessment of Paediatric Data

ZOFRAN™

ondansetron

Suppositories 16mg

Melt 4mg

Syrup

Tablets 4mg, Tablets 8mg

Injection 2mg/ml

Flexi-amp Injection 2mg/ml

Marketing Authorisation Holder: GlaxoSmithKline

Rapporteur:	UK
Co-Rapporteur:	Sweden
Paediatric assessment Procedure start date:	2 July 2007
PdAR:	10 September 2007
Request for Supplementary Information	1 October 2007
Finalised PdAR	12 May 2008
End of Procedure	2 June 2007

INDEX

1 EXECUTIVE SUMMARY

Based on the review of the paediatric data on pharmacokinetics, safety and efficacy for Zofran™ (ondansetron) submitted as part of the EU-Worksharing Procedure, approval is recommended for the extension of the lower age range for prevention of **post-operative nausea and vomiting** (PONV) from currently 2 years to 1 month. Only a single dose PONV prophylaxis is considered acceptable. The text should be amended as follows:

Section 4.2:

Post-Operative Nausea and Vomiting

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; slow i.v. injection is recommended for this purpose.

Injection:

For prevention of PONV 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 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia.

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

Based on the review of the paediatric data on safety and efficacy of Zofran, the definition of the lower age range for **chemotherapy-induced nausea and vomiting** (CINV) is considered acceptable. Taking into consideration clinical practice in Europe and the safety profile of ondansetron, the provision of advice regarding weight-based dosing recommendations for CINV may be considered acceptable by individual member states.

The MAH is advised that the UK will require further analysis of PK data before a variation with respect to the posology for CINV and PK data for section 5.2 can be granted. All the data (1 month to 18-44 year old patients) should be analysed to disclose variability in exposure with age over a wider age range than was done before. Clearance should be assessed in relation to body weight to the power 0.75, a maturation function should be included in the model, and PONV versus CINV should be assessed as a covariate over the wider age range.

For member states who wish to implement weight-based dosing for CINV on the basis of the available data, the following amendments for the SmPC are agreed:

Section 4.2

<u>Paediatric Population:</u>

<u>Chemotherapy -induced nausea and vomiting in children aged ≥ 6 months and adolescents</u>

The dose for chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based doing results in higher total daily doses compared to BSA-based dosing – see sections 4.4.and 5.1.

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

<u>Dosing by BSA:</u>

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

Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 1 below.

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	Day1[a,b]	Days 2-6[b]
< 0.6m^2	5 mg/m^2 i.v. 2 mg syrup or tablet after 12 hours	2 mg syrup or tablet every 12 hours
> 0.6m^2	5 mg/m^2 i.v. 4 mg syrup or tablet after 12 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.

Dosing by bodyweight:

Weight-based dosing results in higher total daily doses compared to BSA-based dosing – see sections 4.4. and 5.1.

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

Two further doses 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 twelve hours later and may be continued for up to 5 days. See Table 2 below.

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

Weight	Day1[a,b]	Days 2-6[b]
≤10kg	Up to 3 doses of 0.15mg/kg at 4-hourly intervals.	2 mg syrup or tablet every 12 hours
> 10kg	Up to 3 doses of 0.15mg/kg at 4-hourly intervals.	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.

Section 4.4

Paediatric Population:

Chemotherapy -induced nausea and vomiting: When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/m^2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicate similar efficacy for both regimens – see section 5.1.

Section 5.1

Paediatric population:

Chemotherapy -induced nausea and vomiting:

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. On the days of chemotherapy, patients received either ondansetron 5 mg/m2 i.v. + after 8-12 hrs ondansetron 4 mg p.o. or ondansetron 0.45 mg/kg i.v. + after 8-12 hrs placebo p.o. 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/m2 i.v. + ondansetron 4 mg p.o.) and 41% (0.45 mg/kg i.v. + placebo p.o.). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days.

A double-blind randomised placebo-controlled trial 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 i.v. together with 2-4 mg dexamethasone p.o. and in 71% of patients when ondansetron was administered as syrup at a dose of 8mg + 2- 4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in open-label, non-comparative, single-arm study. All children received three 0.15 mg/kg doses of intravenous 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 patients.

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

Prevention of post-operative 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). 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).

The MAH is invited to propose concise text to reflect the results of the pivotal trials in the prevention and treatment of PONV in children aged 2-12 years. (S3A380, S3A381, S3GT11, S3GT09).

5.2. Pharmacokinetic Properties

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 month was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 74 paediatric cancer patients aged 6 to 48 months and 41 surgery patients aged 1 to 24 months following intravenous administration of ondansetron. Based on the population pharmacokinetic parameters for patients aged 1 month to 48 months, administration of the adult weight based dose (0.15 mg/kg intravenously every 4 hours for 3 doses) would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery patients (aged 5 to 24 months), paediatric cancer patients (aged 4 to 18 years), and surgical patients (aged 3 to 12 years), at similar doses, as shown in Table C. This exposure (AUC) is consistent with the exposure-efficacy relationship described previously in paediatric cancer subjects, which showed a 50% to 90% response rate with AUC values ranging from 170 to 250 ng.h/mL.

Table C. Pharmacokinetics in Paediatric Patients 1 Month to 18 Years of Age

Study	Patient Population (Intravenous Dose)	Age	N	AUC (ng.h/mL)	CL (L/h/kg)	Vd_{ss} (L/kg)	$T_{½}$ (h)
				Geometric Mean			Mean
S3A40319[1]	Surgery (0.1 or 0.2mg/kg)	1 to 4 months	19	360	0.401	3.5	6.7
S3A40319[1]	Surgery (0.1 or 0.2mg/kg)	5 to 24 months	22	236	0.581	2.3	2.9
S3A40320 & S3A40319 Pop PK[2,3]	Cancer/Surgery (0.15mg/kg q4h/ 0.1 or 0.2mg/kg)	1 to 48 months	115	257	0.582	3.65	4.9
S3KG02[4]	Surgery (2 mg or 4 mg)	3 to 12 years	21	240	0.439	1.65	2.9
S3A-150	Cancer (0.15mg/kg q4h)	4 to 18 years	21	247	0.599	1.9	2.8

1 Ondansetron single intravenous dose: 0.1 or 0.2 mg/kg

2 Population PK Patients: 64% cancer patients and 36% surgery patients.

3 Population estimates shown; AUC based on dose of 0.15 mg/kg.

4 Ondansetron single intravenous dose: 2 mg (3 to 7 years) or 4 mg (8 to 12 years)

Based on the review of the safety data, the following text is imposed. The relevant variation application must be submitted within 60 days of finalisation of this procedure.

Section 4.4:

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Paediatric Population:

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

Section 4.5

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).

There are some safety signals in the respiratory system organ class (SOC) that will need to be addressed by the MAH. As a review of the entire safety database for ondansetron would go beyond the scope of the current procedure, the MAH will have to thoroughly address this issue in the next Periodic Safety Update Report. The same applies to hepatobiliary disorders.

2 INTRODUCTION

2.1 Type of application and regulatory background

This is a paediatric data assessment for Zofran™ (ondansetron) conducted as part of the 'second wave' of the EU-Worksharing Procedure.

The EU Worksharing Procedure was set up was set up by the Mutual Recognition Facilitation Group (MRFG) in 2004. Its aim is to make information on paediatric data available for products that are approved in the EU via the either the Mutual Recognition procedure (MRP) or nationally. Companies were requested to submit the same set of data and proposals for the product information to all Member States. Two Member States (Rapporteur and CoRapporteur) prepare an assessment report, in the present case the UK and Sweden. Once a harmonised European decision is agreed, usually including the proposal for updating the Summary of Product Characteristics (SPC) with information on the use in children, the Marketing Authorisation Holder (MAH) is requested to submit, within 60 days, a type II variation to implement this proposal via national or Mutual Recognition procedures. For products approved in the MRP discussions can continue in the following type II variation. For nationally approved products it is a national decision how to update the SPC.

2.2 Background - Ondansetron

Ondansetron (Zofran™) is a 5-HT_3 antagonist, licensed for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (CINV) and the prevention and treatment of post-operative nausea and vomiting (PONV). It is available as 2mg/ml injection, 4mg and 8mg tablets, 4mg and 8mg oral lyophilisate, 4mg/5ml syrup and 16mg suppositories. The tablets, injection, oral lyophilisate and syrup are licensed in the UK for use in children as outlined in Table 1 below. Zofran suppositories are not licensed for use in children.

Table 1: Currently licensed indications, age range and dose for ondansetron in children

Indication	Age range	Dose
Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (CINV)	Not specified	Single intravenous dose of **5 mg/m^2** immediately before chemotherapy, followed by **4 mg orally twelve hours later**. 4mg orally twice daily should be continued for up to 5 days after a course of treatment.
Prevention and treatment of post-operative nausea and vomiting (PONV)	aged 2 years and over	For **prevention** of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of **0.1 mg/kg** up to a maximum of 4mg either prior to, at or after induction of anaesthesia. For **treatment** of established PONV in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of **0.1 mg/kg** up to a maximum of 4mg.

The FDA approved use of ondansetron for CINV in children aged 6 months to 18 years and PONV in children aged 1 month to 12 years in March 2005. The posology for PONV is the same as the one proposed for the EU licence. The dose for CINV is only given on an mg/kg, not on a body surface area basis. The US label states that for CINV, ondansetron should be infused intravenously over 15 minutes. No such recommendation is made in the proposed EU SmPC. For PONV, the US label states that the recommended rate of administration is not to be less than 30 seconds, preferably over 2 to 5 minutes. The proposed EU SmPC recommends slow intravenous injection.

2.3 Submitted Documentation

The supporting data were submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) on 22 February 2006. They include a Clinical Overview, 3 complete study reports (S3A40319, S3A40320, S3A40323), 12 summary trial reports (S3AP47, S3AP48, S3GK02, S3A-380, S3A-381, S3GT11, S3GT09, S3AM20, GLZOF008, S3A-239, S3AB3006, S3AB4003), a safety review dated 20 May 2005, line listings of adverse reactions reported in children aged <2 years from postmarketing and cited literature references. In addition, proposals for amended product information were submitted, see section 2.4 below.

In response to requests for supplementary information, further data were received on 21 December 2006 and 31 March 2008. These included:

- One response documents each
- Periodic Safety Update Report (PSUR) March 2005 – 28 February 2006
- copies of published papers of clinical trials
- Summary of a worldwide literature search of Zofran use in paediatric patients, dated May 2004
- Paediatric adverse event review update, data lock point 30 September 2007
- Hepatobiliary system safety review, dated 13 November 2007
- Respiratory system safety review, dated 13 November 2007
- Study report S3GK02.

2.4 Proposed changes to the SmPC

The text proposed at submission is outlined below (annotations as compared to the presently licensed UK SmPC, new text *italics underlined*, deleted text ~~strikethrough~~)

Section 4.2:

CINV:

Children *and Adolescents (aged 6 months to 17 years):*

Oral Formulations and Injection:

In children with a body surface area of less than 0.6 m^2 an initial i.v. dose of 5 mg/m^2 is administered immediately before chemotherapy, followed by a 2 mg oral dose of ondansetron syrup 12 h later. 2 mg orally twice daily can be continued for up to 5 days after a course of treatment.

In children with a body surface of 0.6 to 1.2m² Zofran ~~may be~~ *is* administered as a single intravenous dose of 5mg/m² immediately before chemotherapy, followed by 4mg orally ~~twelve~~ *12* hours later. 4mg orally twice daily ~~should~~ *can* be continued for up to 5 days after a course of *treatment.*

For children with a body surface area of greater than 1.2 m² an initial i.v. dose of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later. 8mg orally twice daily can be continued for up to 5 days after a course of treatment.

Alternatively, in children aged 6 months or older, ondansetron is administered as a single i.v. dose of 0.15 mg/kg (not to exceed 8mg) immediately before chemotherapy. This dose may be repeated every 4 hours for a total of three doses. 4 mg orally twice daily can be continued for up to 5 days after a course of treatment. Adult doses must not be exceeded.

Assessor's comment:
The proposed dose recommendations changed throughout the procedure, see below.

PONV:

Children ~~(aged 2 years and over):~~ and Adolescents (aged 1 month to 17 years):

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; slow i.v. injection is recommended for this purpose.

Injection:

For prevention *and treatment* of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia, *or after surgery.*

~~For treatment of established PONV in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of 0.1mg/kg up to a maximum of 4mg.~~

~~There is limited data on the use of Zofran in the prevention and treatment of PONV in children under 2 years of age.~~

Section 5.1:

Special Patient Populations

Children and Adolescents (aged 1 month to 17 years)

Oral formulations and Injection:In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg/kg ondansetron prior to undergoing surgery. Patients aged 1 to 4 months had a clearance when normalised to body weight that was approximately 30% slower than in patients aged 5 to 24 months 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. No dose adjustment is necessary for patients aged 1 to 4 months as only a single i.v. dose of ondansetron is recommended for the treatment of postoperative nausea and vomiting. The differences in pharmacokinetic parameters can be explained in part by the higher volume of distribution in the 1 to 4 month patient population.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old) were reduced *in comparison to values with adult patients*. ~~The magnitude of the change was age related, with clearance falling from about 300mL/min at 12 years of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at 3 years.~~ B*oth 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 (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 74 patients aged 6 to 48 months following administration of 0.15 mg/kg i.v. ondansetron every 4 hours for three doses for the treatment of chemotherapy induced nausea and vomiting and 41 surgery patients aged 1 to 24 months following administration of a single 0.1 mg/kg or 0.2 mg/kg i.v. dose of ondansetron. Based on the population pharmacokinetic parameters for subjects aged 1 month to 48 months, administration of a 0.15 mg/kg i.v. dose of ondansetron every 4 hours for three doses would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery subjects aged 5 to 24 months and previous paediatric studies in cancer (aged 4 to 18 years) and surgical (aged 3 to 12 years) subjects, at similar doses.

3 FIRST ROUND OF ASSESSMENT

3.1 PHARMACOKINETICS

3.1.1 Introduction

Pharmacokinetic data are available from one PONV trial (study no. S3A40319, hereafter referred to as 319), from one CINV trial (study no. S3A40320, hereafter referred to as 320) and from a population PK analysis.

Table 3: Overview of pharmacokinetic trials

Study number	Design	Indication	Age range	No of patients providing PK samples
S3A40**319**	Randomised double-blind placebo-controlled	PONV (prophylaxis)	1-24 months	n = 41
S3A40**320**	Open-label	CINV	6-48 months	n = 74

Supporting pharmacokinetic data were submitted in form of summary reports of trials S3AP48, S3AP47, S3GK02.

Assessor's comment

Pharmacokinetic data provided as full reports are limited to patients aged up to 4 years. The summary reports for trials S3AP48 and S3AP47 do not provide any pharmacokinetic data.

Trial S3GK02 investigated PK parameters in children aged 3-7 years and 8-12 years undergoing strabismus surgery (number of patients per group not specified). The summary report gives the following information '*Following both 2 and 4mg ondansetron i.v., the children experienced greater maximum serum concentrations and overall exposure (indicated by AUC∞) than adults receiving ondansetron 4mg i.v. …Assuming pharmacokinetic linearity and by reference to standard growth tables a weight-based dosing of 0.05mg/kg i.v. should result in paediatric patients aged between 2 and 12 years receiving comparable exposure to ondansetron as adults receiving 4mg i.v. ….The dose recommended for an efficacy study in paediatric patients is 0.1mg/kg for children under 40kg in order to adjust for the higher emetic rate seen in children, the therapeutic concerns about underdosing and the favourable safety profile of ondansetron'.*

3.1.2 Study 319: Pharmacokinetics in PONV

Trial 319 included 51 children aged 1 to 24 months weighing ≥ 3 kg scheduled to undergo procedures requiring general anaesthesia with ASA physical status of 1, 2 or 3. Groups were stratified for age (1 to ≤ 4 months and >4 to 24 months).

Following induction of anaesthesia, a first group of children received a single dose of ondansetron hydrochloride 0.1 mg/kg by slow intravenous injection (n=24) in study arm 1. A second group of children then received 0.2mg/kg in study arm 2 (n=27). The dose for study arm 2 was extrapolated to result in an AUC in the range of 200 to 400ng.h/ml based on the efficacious range seen in other studies.

Blood samples were collected at 1, 2, 4, 6 (0.1mg group only), 8 hours and 18-24 hours (0.2mg group only) after injection. Serum ondansetron concentrations were determined using an HPLC/MS/MS method with a lower limit of quantification of 0.5 ng/mL.

The PK analysis included 254 samples from 41 subjects. 10 subjects were excluded as they did not provide an adequate number of samples. Results are outlined in Table 4 below.

Table 4: Study 319 PK results by treatment and age group (geometric mean and 95% CI)

Dose	**0.1 mg/kg**		**0.2 mg/kg**	
Age	**1-4 month old**	**>4 – 24 month old**	**1-4 month old**	**>4 – 24 month old**
	N=9	N = 12	N =10	N = 10
C_{max} (ng/mL)	74 (46, 118)	90 (52, 153)	160 (109, 234)	196 (125, 307)
AUC_{inf} (ng-h/mL)	220 (144, 337)	201 (158, 255)	559 (424, 736)	287 (222, 371)
$t_{1/2}$ (h)	5.9 (4.5, 7.8)	3.1 (2.8, 3.6)	6.2 (4.0, 9.7)	2.4 (2.2, 2.8)
Cl (mL/min)	45.08 (25.5, 79.7)	76.32 (62.5, 93.2)	29.34 (22.4, 38.5)	107.73 (78.4, 148.1)
Cl (L/h) ✶	2.70	4.58	1.76	6.46
Vd_{ss} (L)	23.1 (13.0, 41.1)	20.7 (17.9, 23.9)	15.7 (12.0, 20.6)	22.7 (17.8, 29.0)
Wt-norm Cl (mL/min/kg)	7.58 (4.95, 11.60)	8.34 (6.54, 10.55)	5.96 (4.53, 7.85)	11.62 (8.98, 15.04)
Wt-norm Cl (L/h/kg) ✶	0.45	0.50	0.35	0.69
Wt-norm Vdss (L/kg)	3.90 (2.37, 6.40)	2.23 (1.85, 2.69)	3.17 (2.35, 4.29)	2.44 (1.96, 3.04)

✶Conversion performed by assessor

AUC_{inf} and C_{max} increased with the doubling of the dose from 0.1 mg/kg to 0.2 mg/kg in both age groups (1-4 months and > 4 to 24 months).

Clearance and volume of distribution were dependent on body weight and age. Clearance was slower, volume of distribution was higher and half-life was greater in the 1-4 month age group as compared to the older age group.

The MAH concludes that no dose adjustment is necessary in this younger age group, as only a single dose of ondansetron is recommended for the treatment of postoperative vomiting.

No PK-PD evaluation was performed.

Assessor's comment

Study 319 included only 19 patients in the age range 1 – 4 months. The applicant should clarify how many patients were 1 month old – an age at which the development of CYPs relevant to the metabolism of ondansetron (2D6, 3A4 and 1A2) is still in progress. Overall, the data confirm the expected with respect to change in clearance (per kg) with age – an increase to toddler then a decrease to adult; the former reflecting maturation of enzyme systems, the latter reflecting the greater liver size per body weight of young children.

The recommendation of 0.1mg/kg up to 4mg as a single dose does not reflect clinical reality where ondansetron is usually prescribed at 0.1mg/kg two or three times a day as needed. In addition, because of the cost of ondansetron, it is usually reserved for at risk patients or patients undergoing procedures where PONV is more common. Accordingly, it would be useful to have more information on the PK and efficacy of multiple rather than single doses in risk patients as needed. The recommendation of a 'slow' IV infusion seems vague and could result in markedly different exposure profiles in different patients.

3.1.3 Study 320: Pharmacokinetics in CINV

In trial 320, pharmacokinetics of ondansetron were investigated as secondary outcome in patients aged 6 to 48 months. Three doses of ondansetron 0.15 mg/kg were administered at 4 hourly intervals. Samples were drawn immediately prior to administration of the second dose and at 2-5 minutes, 0.5-1.5 hours and 2-3 hours after administration of the second dose, immediately prior to the administration of the 3rd dose and 2 to 5 minutes and 12-24 hours after the third dose.
Fewer than 20 patients aged 6 to 12 months participated in the trial; hence the pharmacokinetic results were only reported as part of the Population PK analysis (see below).

3.1.4 Population Pharmacokinetic Analysis

The primary objective of this analysis was to develop a basic PK model that would characterise the population pharmacokinetics of ondansetron in paediatric oncology and surgery patients aged 1 to 48 months.

Sampling data from trials 319 and 320 were included (115 subjects, 727 PK samples). Table 5 summarises the distribution of patients regarding age ranges and diagnosis.

Table 5 - Distribution of patients providing PK data

AGE RANGE	NUMBER OF SUBJECTS	NUMBER (%) CANCER PATIENTS	NUMBER (%) SURGERY PATIENTS
1 month to 6 months-old	20	0	20 (100%)
>6months to 12 months-old	21	9 (43%)	12 (57%)
>12 months to 24 months-old	31	22 (71%)	9 (29%)
>24 months to 48 months old	43	43 (100%)	0
1 month to 48 months	115	74 (64%)	41 (36%)

Assessor's comment

The patient population showed an unequal distribution for diagnosis and age. Cancer patients predominate and there are higher numbers of patients in the older age groups. The majority of surgery patients are in the very young age group.

Data were analysed using NONMEM version 5.0. Data were fitted to a two-compartment model with a constant rate (zero-order) infusion and first order elimination. The model was described by the following parameters: total clearance CL, volume of central compartment V1, volume of peripheral compartment V2, inter-compartmental clearance CLd.

The following covariates were tested by forwards inclusion and backwards elimination: age, gender, body weight, height, body surface area, race, pre-dose liver function tests and co-existing disease.

In the final model, clearance is a function of weight and age, and volume of distribution is a function of weight. When compared to weight, body surface area was not a better predictor of ondansetron pharmacokinetics. Increasing age had a negative effect on clearance, and for any given patient weight, as age increased, the model predicted clearance decreased. However, given that weight increases with age within this sub-population, and that the positive effect of weight on clearance is greater than the negative effect of age on clearance ($\theta 2 > \theta 3$), clearance was still predicted to increase with age when weight is considered.

Ondansetron clearance in children still remains greater than ondansetron clearance in adults until the child is 12 to 15 yrs old. The relationship between age and clearance was further examined using two linear relationships between age and CL; one before and one after 12mos of age. The data may have been too variable or too sparse to describe such a relationship, and this algorithm would not perform the covariance step due to negative prediction errors.

Table 6 compares the parameter estimates and variability of the base model to the final model.

Table 6: Comparison of the Pharmacokinetic Parameter Estimates of the Base Model and Final Model

Parameter	Base Model Population Parameter	Std Error of Parameter Estimate	Inter Subject Variability, CV%	Final Model Population Parameter	Std Error of Parameter Estimate	Inter Subject Variability, CV%
CL (L/h) = θ_1	5.29	0.526	82%	5.67	0.333	78%
V1 (L) = θ_4	3.26	0.523	221%	5.65	0.749	167%
CLd (L/h) = θ_5	93.6	10.4	-	78.1	8.77	-
V2 (L) = θ_7	27.8	2.07	63%	31.2	1.66	48%
θ_2 (WT on CL)	-	-	-	0.759	0.107	-
θ_3 (AGE on CL)	-	-	-	- 0.352	0.097	-
θ_5 (WT on V1)	-	-	-	0.641	0.088	-
θ_8 (WT on V2)	-	-	-	0.29	0.068	-
	Residual Variance	Std Error	Residual CV%	Residual Variance	Std Error	Residual CV%
σ^2 proportional	0.11	0.071	33%	0.127	0.055	36%
σ^2 additive	13.1	13.8	-	-	-	-

Source: Attachment 14.5 Output for Model 12 and Model 48

The final model was validated by estimating the confidence interval of parameters using bootstrapping. Following bootstrapping, parameter estimates for CL normalised to body weight, volume of distribution and half-life were calculated.

Table 7 shows the predicted PK parameters (95% CI) for an average subject aged 1 month to 48 months.

Table 7: Predicted PK Parameters for the Typical Patient Aged 20.5 Months and Weighing 10.78 kg

PK Parameter	Predicted Median (95%CI)
CL (L/h)	5.67 (5.01, 6.60)
CL (L/h/kg)	0.582 (0.509, 0.671).
Vdss (L/kg) Where V1 + V2 =Vdss	3.7 (3.3, 4.1)
T1/2 (h)	4.9 (4.2, 5.8)

Assessor's comment

Simulation data are only presented only for this 'typical patient'. Typical PK parameters for patients at the extremes of age (1 month, 48 months) are not provided.

The model predicted median ondansetron clearance for paediatric cancer and surgery patients, aged 1 month to 48 months, was 5.67 L/h (5.01, 6.60). Weight normalized clearance in these patients was comparable to that observed in paediatric surgery patients aged 5 - 24 months (Study 0319). The MAH states that this exposure would also be consistent with the exposure achieved in previous paediatric studies in cancer patients (aged 4 to 18 years) and surgical patients (aged 3 to 12 years) at similar doses.

Tables 8 shows the predicted PK parameters for cancer patients and compares them to pharmacokinetic results from previous trials in older children (4-18 years) or adults.

Table 8: Ondansetron Pharmacokinetic Parameters in Cancer Patients

Subjects (study)	N (age range)	CL (L/h/kg)	Vdss (L/kg)	AUC_∞ (ng-h/mL)	Cmax (ng/mL)	T1/2 (h)
Adult Cancer (S3A-282)	N=12 (19-69)	0.318 (0.226, 0.449)	1.41 (1.07, 1.86)	1413.7** (1000.9, 1996.7)	124.6 (99.9, 155.4)	4.1 (2.5 – 5.7)
Ped. Cancer (S3A-150)	N=21 (4-18)	0.599 (0.472, 0.759)	1.90 (1.59, 2.27)	247.3 (194.8, 314.1)	165.0 (129.1, 210.8)	2.6 (1.8 – 5.1)
POP PK Population***	N=115 (1–48mos)	0.582 (0.509, 0.671)	3.65 (3.32, 4.12)	257.4 (231.7, 309.9)	—	4.9 (4.2 – 5.8)

* All values are expressed as Geometric means (95%CI) except for T1/2 which is shown as median (range).

** S3A-282 PK collected after 3rd dose of 0.15mg/kg q2hr compared to after 3rd dose of 0.15mg/kg q4h in S3A-150.

** *Population of 65% Cancer patients and 35% Surgery patients

Assessor's comment

The PK estimates determined in the population PK analysis for cancer patients are not directly comparable with the actual PK results from previous trials in older children (4-18 years) or adults. Doses and dosing intervals differed across trials and the population PK analysis was performed on 36% surgery patients.

Comparisons are made for a 'typical patient aged 20.5 months weighing 10.78kg'. Comparisons based on predictions for patients at the extremes of age (1 month, 48 months) are not provided.

Tables 9 shows the calculated (not predicted) mean PK parameters for surgery patients aged 1 – 4 months and 5-24 months and compares to them to pharmacokinetic results from a previous trial in older children (3-12 years).

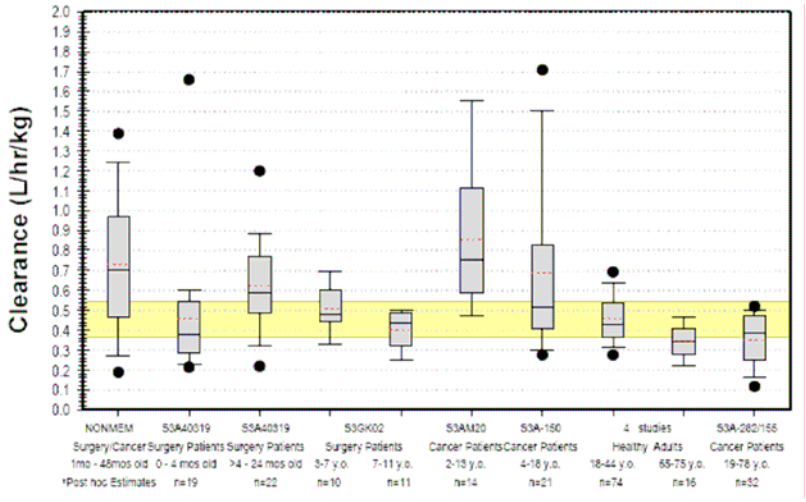
Table 9: Ondansetron Pharmacokinetic Parameters in Surgery Patients

Subjects (study)	N (age range)	CL (L/h/kg)	Vdss (L/kg)	AUC_∞ (ng-h/mL)	Cmax (ng/mL)	T1/2 (h)
Ped Surgical (S3GK02)	N=21 (3-12)	0.439 (0.386, 0.499)	1.65 (1.46, 1.86)	239.6 (208.0, 276.0)	115.7 (99.0, 135.2)	2.8 (1.8 – 5.42)
Ped Surgical (S3A40319)	N= 22 (5 - 24mos)	0.581 (0.486, 0.693)	2.3 (2.1, 2.7)	200.6 (164.7, 244.2)	127.8 (88.1, 185.5)	2.7 (1.9 – 4.2)
Ped Surgical (S3A40319)	N=19 (1-4mos)	0.401 (0.319, 0.504)	3.5 (2.7, 4.5)	359.3 (261.1, 494.6)	110.6 (79.6, 153.7)	6.9 (1.5 – 14.8)

* All values are expressed as Geometric means (95%CI) except for T1.2 which is shown as median (range).

Figure 1 shows actual weight-normalized ondansetron clearance data across studies in paediatric and adult, cancer and surgery patients across different age ranges.

Figure 1: Weight Normalized Ondansetron Clearance by Type of Patient and Age.



The MAH concludes that despite the age-related changes in mean ondansetron pharmacokinetic parameters, the wide inter-subject variability observed for clearance and half-life results in considerable overlap between the values of subjects in each age group. Therefore, dosage need not be adjusted based on age alone without any clinical evidence of inadequate efficacy or limiting toxicity.

Assessor's comment

The analysis was done on data from a rather small number of patients (115) with an inverse age-contribution from CINV and PONV. It appears that CINV vs. PONV was not included as a covariate in the analysis? Does anaesthesia and surgery alter the kinetics of ondansetron as it does with many other drugs? Also, rather than simply compare tabulated mean PK parameters in this group of patients (1-48 mo) with those for children 4-18 y and adults, the full data across age could have been combined in a more rigorous Population PK analysis. This would have to assume dose and time linearity of the PK. I agree that it would be useful to compare simulated exposure profiles at different ages and, particularly to see the predicted profile in a 1 month baby. Although there is overlap in age-related changes in PK parameters (Fig 1), concern is for the outliers. Therefore, this overlap, in itself, does not mitigate concern for patients at the extreme of risk – and these are likely to be at the lower age limit. Since the concentrations of plasma proteins that bind drugs increase with age from birth this might be another confounding issue in the interpretation of the PK data. Ideally, comparisons of exposure should be made on the basis of unbound plasma drug concentrations rather than total plasma drug concentrations. However, since ondansetron seems only to be bound to the extent of 60-70% this may not be a big factor in this case?

The MAH should comment on above questions.

3.2 CLINICAL EFFICACY

3.2.1 Introduction

Pivotal efficacy data are available from one randomised, double-blind, placebo-controlled trial in PONV and one open-label non-comparative trial in CINV.

Results from the PONV trial were published by Khalil SN et al (Anesth Analg. 2005 Aug;101(2):356-61).

Table 10: Overview of submitted trials

Study number	Design	Indication	Age range	Duration	No of patients
S3A40**320**	Randomised double-blind placebo-controlled	PONV (prophylaxis)	1-24 months	24 hours	689
S3A40**323**	Open-label uncontrolled	CINV (prophylaxis)	6-48 months	24 hours	76

Summary reports of PONV trials S3A-380, S3A-381, S3GT11, S3GT09, and CINV trials S3AM20, GLZOF008, S3A-239, S3AB3006 and S3AB4003 were submitted as supporting data.

Assessor's comment

These summary reports do not add relevant data. For PONV, only trial S3GT11 included children under the age of 2 years, but age distribution is not stated.

For CINV, S3AM20 included one patient aged 11 months (apparently a protocol violation). Trials GLZOF008, S3AB3006 and S3AB4003 included patients from ages 7 months and 1 year, but again age distribution is not stated in any of the reports.

3.2.2 PONV Trial 323

The trial was performed at 28 centres in the US and Canada between December 2002 and July 2003.

Design and methods

This was randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of a single 0.1 mg/kg dose of intravenous ondansetron for the prevention of postoperative emesis in 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 either as inpatients or outpatients provided they had an ASA status of I, II or III. Exclusion criteria included gastroesophageal reflux disease, cardiac or neurosurgical procedures, anaesthesia using halothane or propofol, emesis (retching and/or vomiting) in the 24 hours prior to surgery, use of phenothiazines, metoclopramide or systemic corticosteroids within 48 hours of study drug administration except when used as rescue medication, and evidence of clinically significant neurologic, renal, hepatic, cardiovascular, metabolic, endocrine disorders.

Subjects were randomized in a 1:1 ratio to receive within five minutes following induction of anaesthesia either a single dose of 0.1 mg/kg of ondansetron or an equivalent volume of saline. Randomisation was stratified for anticipated use of opiods. Study medication was injected intravenously in no less than 30 seconds (or as slowly as possible, given the small volume). Any emetic rescue medication, including ondansetron, could be given if necessary.

The primary endpoint was the proportion of subjects who experienced an emetic episode during the 24-hour Assessment Phase. An emetic episode was defined as a single vomit or retch or any number of continuous vomits and/or retches. Emetic episodes were separated by the absence of both vomiting and retching for ≥3 minutes.

Secondary endpoints included time to first emetic episode, time to rescue medication, categorization of emetic episodes (complete response/partial response/therapeutic failure), proportion of subjects who received rescue medication, and the proportion of subjects who experienced emetic episodes after receiving rescue medication.

Subjects who were prematurely withdrawn and did not experience an emetic episode and those who received rescue medication in the absence of emesis were considered to have had an emetic episode.

Assessor's comment

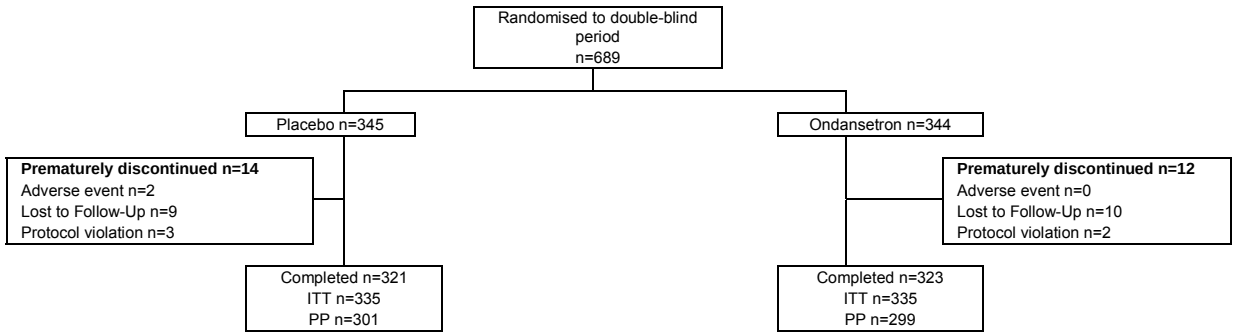
The trial only evaluated postoperative vomiting but not nausea; this is considered acceptable in this age group as the included patients were too young to adequately express any nausea.

Results

Disposition of subjects/Baseline characteristics:

Figure 2 shows the participant flow. Baseline characteristics are outlined in Table 11. Details of surgical procedures are outlined in Table 12.

Figure 2 Participant Flow



Assessor's comment

The study report does not include information on numbers of patients screened.

Table 11: Demographic details ITT population

	Placebo (n=335)		Ondansetron (n=335)	
	n	(%)	n	(%)
Sex				
Female	84	(25)	80	(24)
Male	251	(75)	255	(76)
Age (months)				
Mean ± SD	12.2 ± 6.0		12.7 ± 6.3	
Min – Max1	1 – 24		1 – 42	
Height (cm)2				
Mean ± SD	73.9 ± 8.6		74.1 ± 10.3	
Min – Max	48 - 96		27 - 97	
Weight (kg)				
Mean ± SD	9.8 ± 2.3		10.0 ± 2.4	
Min/Max	4 - 19		4 - 20	
ASA Classification				
Class 1	240 (72)		249 (74)	
Class 2	90 (27)		83 (25)	
Class 3	5 (1)		3 (<1)	
Surgical Status				
Inpatient	47 (14)		49 (15)	
Outpatient	288 (86)		285 (85)	
Concurrent opioid use				
Yes	194		196	
No	141		139	

Table 12: Surgical procedures ITT population

Surgical Procedure	n	(%)	n	(%)
Other	189	(56)	186	(56)
Hernia repair	39	(12)	44	(13)
Orchidopexy	40	(12)	40	(12)
Plastic surgery	38	(11)	42	(13)
Myringotomy	37	(11)	36	(11)
Adenoidectomy	19	(6)	24	(7)
Orthopaedic	15	(4)	10	(3)
Strabismus surgery	11	(3)	12	(4)
Hydrocelectomy	4	(1)	6	(2)
Dental procedure	3	(<1)	6	(2)
Tonsillectomy	4	(1)	4	(1)

The groups were similar with respect to the type of surgery performed, duration of anaesthesia, history of PONV or motion sickness.

Major protocol violations were identified for approximately 10% of patients in each group (placebo n=34, ondansetron n=36). The most common violations were use of systemic corticosteroids (3% placebo, 4% ondansetron) and lack of diary data collection (3% both groups).

Assessor's comment

Only a minority of patients had surgical procedures reported to be associated with a high risk of PONV.

The protocol violations could have impacted on the interpretation of efficacy. It is reassuring to note that the results of the PP analysis of the primary parameter were consistent with that of the ITT analysis.

The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo (28%) than those receiving ondansetron (11%). The difference between treatment groups was statistically significance ($p < 0.0001$).

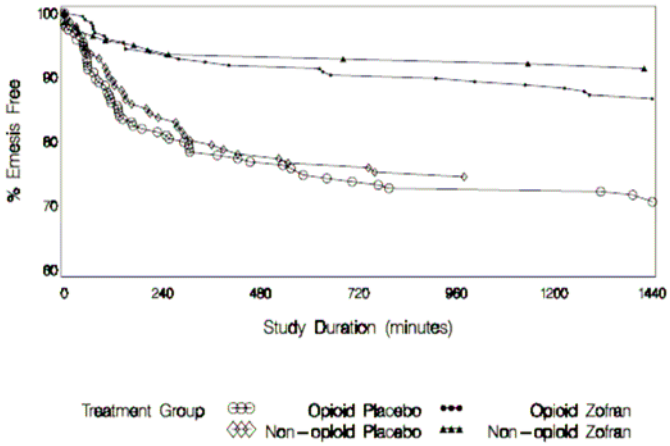
The results in the opioid and non-opioid strata were similar. The PP results were consistent with ITT results.

Secondary efficacy outcomes are summarised in Table 13 and Figure 3 overleaf.

Table 13: Secondary efficacy outcomes

	Placebo (n=335)		Ondansetron (n=335)	
	n	(%)	n	(%)
Complete Response	242	(72)	297	(89)
Partial Response (1 to 2 emetic episodes)	57	(17)	19	(6)
Therapeutic Failure (>2 emetic episodes or requiring rescue or withdrawal)	26	(8)	9	(3)
Incomplete/Missing Data	10	(3)	10	(3)

Figure 3: Time to first emetic episode



The median time to first emetic episode (ITT) was 207 minutes for ondansetron and 135 minutes for placebo ($p < 0.0001$).

Median time to first rescue/withdrawal (ITT) was 91 minutes for placebo and 85 minutes for ondansetron.

21 (6%) placebo patients and 6 (2%) ondansetron patients received rescue medication as originally defined by the protocol during the 24 hours following discontinuation of anaesthesia. Overall, 32 (10%) of placebo and 18 (5%) of ondansetron subjects received rescue antiemetic medication(s) or withdrew from the study prematurely. 7/21 (33%) placebo patients and 0/6 (0%) ondansetron patients reported emetic episodes following administration of rescue medication.

	Placebo	Ondansetron	Odds/Hazard Ratio	95% CI	p-Value
Subjects with emetic events: (Primary endpoint)	28%	11%	0.33 (odds ratio)	(0.22, 0.5)	<0.0001
Median Time to 1st Emetic Event (mins)	135	207	0.36 (hazard ratio)	(0.24, 0.52)	<0.0001
Median Time to 1st Rescue Med (mins)	91	85	0.52 (hazard ratio)	(0.29, 0.93)	0.025

Assessor's comment

This trial demonstrated efficacy in the prevention, but not in the treatment, of postoperative vomiting (POV). Efficacy in the treatment of POV can reasonably be extrapolated from older children, but the lack of data in under 2-year olds should be reflected in the SmPC.

The trial only evaluated postoperative vomiting but not nausea; this is considered acceptable in this patient population as the included patients were too young to adequately express any nausea.

The effect of ondansetron was statistically significant. The absolute difference in complete response rate for ondansetron vs. placebo was 17%. This is comparable to results in older children (difference between 13% and 29%, see Table 14 below).

Assessor's comment, cont'd.

In the supporting trials including older children (S3A-380, S3A-381, S3GT11, S3GT09) the complete response rates for placebo ranged between 34 - 47%and for ondansetron 53 - 68%. The high rate of 'placebo-response' in this trial (72%) may reflect the fact that PONV is rarer in children aged <2 years as compared to older children (1). Additionally, the inclusion criteria were not restricted to procedures associated with moderate/high risk of PONV and only a minority of patients had surgical procedures reported to be associated with a high risk of PONV.

No evidence has been provided with respect to the minimal effective or optimum dose. It cannot be excluded that a lower dose might have resulted in similar efficacy in this patient group. The proposed recommended dose reflects the dose used in the trial.

The trial results should be reflected in SmPC section 5.1. Section 4.2 should clarify that only a single dose is recommended.

3.2.3 PONV supporting trials

Summary reports were submitted for PONV trials S3A-380, S3A-381, S3GT11, S3GT09.

Table 14: Complete response rates for emesis 0-24h in supportive PONV trials

	Age range	Design	Indication	% Complete response rates 0-24h	
				Placebo	Ondansetron
S3A380	2 - 12 yrs (n=433)	DB, PC	Prevention	39	68
S3A381	2 - 12 years (n=375)	DB, PC	Treatment	34	53
S3GT11	2 - 12 years[1] (n=427)	DB, PC	Prevention	47	60
S3GT09	2 - 12 years[2]	DB, PC	Prevention	35	58

[1] One protocol violator aged 1 year
[2] One protocol violator aged 16 year

3.2.4 CINV Trial 320

Design and methods

The trial was performed at 22 centres in the US, Canada, Australia, Austria, Spain and Israel between March 2003 and March 2004.

It was an open-label, non-comparative, single-arm study to obtain qualitative efficacy data for the prevention of CINV, to evaluate safety and tolerability, and to determine pharmacokinetics of ondansetron in children aged 6 to 48 months.

Screening was performed on the day that study medication was administered or within the previous 7 days. The assessment phase began with the start of intravenous ondansetron and continued for 24 hours after the initiation of the first dose of moderately or highly emetogenic chemotherapy.

Included subjects had a Lansky Performance Status Scale score ≥60 and were scheduled to receive ≥1 cycle of moderately/highly emetogenic cancer chemotherapy on an in-patient basis for which they were expected to receive a prophylactic 5-HT_3-receptor antagonist.

Assessor's comment

Emetogenic potential of cancer chemotherapy was determined by the investigator. It would appear that the protocol did not define this parameter.

Exclusion criteria included pre-existing aetiologies for emesis, retching and/or vomiting in the 24 hours prior to surgery, use of phenothiazines, metoclopramide or systemic corticosteroids within 48 hours of study drug administration, abdominal or pelvic irradiation within 48 hours prior to administration of study drug or during the 24-hour assessment phase, severe concurrent illness or evidence of clinically significant neurological, renal, hepatic, cardiovascular, metabolic, endocrine disorders, active, or a recent (in the opinion of the investigator) history of hepatic disease including known liver metastases.

All children received three 0.15 mg/kg doses of intravenous ondansetron, administered at 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Ondansetron was to be diluted in 5% dextrose or 0.9% sodium chloride and administered over 15 minutes.

Assessor's comment

The dose used in the trial reflects the proposed 'alternative' dosing regimen of three intravenous doses of ondansetron 0.15mg/kg at 4-hourly intervals.

The method of administration used in the trial (dilution of ondansetron in 5% dextrose or 0.9% sodium chloride and administration over 15 minutes) is not reflected in the proposed SmPC.

Antiemetic rescue medication (except for phenothiazines ondansetron and other 5-HT3 receptor antagonists) could be given when three emetic episodes occurred within a 15 minute period, at physician discretion, or at any time upon subject/parent/guardian request.

There were four co-primary endpoints:

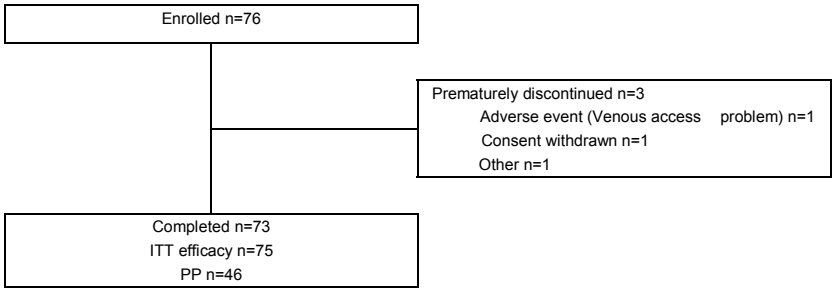
1. Incidence of emetic episodes during the 24-hour assessment phase;
2. Proportion of subjects receiving rescue antiemetic medication during the 24-hour assessment phase;
3. Time to first rescue antiemetic medication;
4. Parent/guardian's overall satisfaction with ondansetron in preventing chemotherapy induced vomiting.

The definition of emetic episodes was identical to the one used in trial 323 (see above). In addition, a post-hoc analysis of time to first emetic episode was performed.

Results

Figure 4 shows the participant flow. The study report does not include information on numbers of patients screened.

Figure 4 Participant Flow



74% of patients had had prior emesis following prior chemotherapy. 24% of patients received highly emetogenic chemotherapy.

A large number of major protocol violations were identified (n=29, 39%). The most common violations were study duration <22 hours and use of ondansetron as rescue medication.

Assessor's comment

These protocol violations could have affected the interpretation of efficacy.

Results for principal efficacy endpoints for the ITT Population are outlined in Table 15 overleaf:

Table 15: Efficacy results trial 320

Co-primary efficacy endpoints		N (%)
Incidence of emetic episodes	Complete Response (0 emetic episodes)	42 (56)
	Partial Response (1-2 emetic episodes	8 (11)
	Failure (≥ 3 emetic episodes, use of rescue medication, or withdrawal)	25 (33)
Summary of subjects who received rescue medication		23 (31)
Median time to first rescue antiemetic medication		955 minutes (~16 hrs.) (n = 23)
Parent/guardian satisfaction	Very Satisfied	60 (80)
	Somewhat satisfied	10 (13)
	Neither satisfied nor dissatisfied	1 (1)
	Somewhat dissatisfied	3 (4)
	Very dissatisfied	1 (1)

Assessor's comment

Due to the open-label non-comparative design of the trial, efficacy results cannot be expected to provide robust data. Whilst it is accepted that a placebo-controlled trial would not have been justified in infants receiving chemotherapy regimens with high or moderate emetogenic potential, a randomised double-blind parallel-group trial design against a licensed active comparator could have been used.

Complete control of emesis was comparable to that reported for older children on the worst day of chemotherapy from other trials (see Table 16 below).

Data from a recent retrospective review of antiemetic surveys for children who received emetogenic chemotherapy indicated that complete protection from both acute and delayed nausea and emesis was more likely in children under the age of 3 years as compared to older children. (*Holdsworth MT et al, Acute and delayed nausea and emesis control in paediatric oncology patients, Cancer 2006,106:931-40*). Although the antiemetic regimen was different to the one proposed by the MAH, and the retrospective design hampers robust conclusions, the findings of this review together with the results of the open-label trial may be taken to support an extrapolation of the ondansetron efficacy data from older children and adults to children aged 6 months and above.

The trial has not been designed to define the optimal dose and schedule for ondansetron. It cannot be excluded that a single dose of ondansetron might have resulted in similar efficacy.

3.2.5 CINV supporting trials

Supporting data are available from previously conducted trials. Only summary reports were submitted.

Table 16: Complete response rates for emesis on the worst day of chemotherapy in supportive CINV trials

	Age range (no. of patients enrolled)	Design	Dose	Complete control of emesis on worst day of chemotherapy
S3AB3006	1 – 18 yrs. (n=415)	DB, R	Days of chemotherapy: Ondansetron 5 mg/m^2 i.v. + after 8-12 hrs ondansetron 4 mg p.o. OR: Ondansetron 0.45 mg/kg i.v. + after 8-12 hrs placebo p.o. Post-chemotherapy for 3 days both groups: 4 mg ondansetron syrup b.d.	49% (5 mg/m^2 i.v. + ondansetron 4 mg p.o.), 41% (0.45 mg/kg i.v. + placebo p.o.)
S3AB4003	1-17 yrs (n=438))	DB, PC	Days of chemotherapy: Ondansetron 5 mg/m^2 i.v. + 2-4 mg dexamethasone p.o. + Placebo syrup + after 6-8 hrs ondansetron 4 mg p.o. OR: Ondansetron 8mg syrup + 2-4 mg dexamethasone p.o. + Placebo i.v. + after 6-8 hrs ondansetron 4 mg p.o. Post-chemotherapy for 2 days both groups: 4 mg ondansetron syrup b.d.	73% (i.v.), 71% (syrup)
S3A-239	4 - 11 years (n=28)	OL, non-comparative	0.15 mg/kg ondansetron i.v. + at 4 and 8 hrs ondansetron p.o. (4 mg < 12 yrs, 8 mg ≥ 12 yrs).	42%
S3AM20	2-17 yrs (n=109)	OL, non-comparative	Days of chemotherapy at 8-hourly intervals: SA <0.6 m2: 5 mg/m^2 i.v. SA 0.6-1.2 m^2: 5 mg/m^2 i.v. SA >1.2 m^2: 8 mg i.v. Post-chemotherapy for 3-5 days: ondansetron p.o. at 8-hourly intervals: SA <0.6 m2: 2 mg SA 0.6-1.2 m^2: 4 mg p.o. SA >1.2 m^2: 8 mg	Only interim summary report available
GLZOF008	7 months – 14 yrs. (n=61)	OL, R Ondansetron vs. customary treatment in non-cisplatin chemotherapy	Days of chemotherapy at 12-hourly intervals: 3 mg/m^2 to 8 mg according to BSA, either i.v. or p.o. Post-chemotherapy for 3 days: Ondansetron p.o. 12-hourly	No conclusions regarding comparisons with control group due to poor recruitment, protocol violations etc.

Assessor's comment

The oral dose for ondansetron in the two pivotal trials was 4 mg b.d. for all children up to the age of 17 or 18 years. This is reflected in the current prescribing information.

The MAH should justify the proposal to increase the recommended dose for oral administration for children with a BSA >1.2 m^2 to 8 mg b.d.

3.2.6 Assessor's conclusions on efficacy

Efficacy has been demonstrated for the prevention of postoperative nausea in children aged 1 to 24 months at the proposed recommended dose of 0.1mg/kg (single dose only). The SmPC should be amended to provide clear information that only a single dose is recommended.

3.3 SAFETY

Assessor's comment

Section 4.8 currently does not include any information on paediatric adverse events.

3.3.1 Clinical trial data

Clinical trial safety data for children aged 1- 48 months are available from trials 319, 320 and 323. These data were not summarised. All trials used the intravenous formulation of ondansetron. 335 surgical patients received a single dose of 0.1mg/kg, 51 surgical patients received a single dose of either 0.1 or 0.2mg/kg and 76 chemotherapy patients received three doses of 0.15mg at 4hourly intervals.

ECG monitoring was not performed in any of these trials.

Serious adverse events and deaths

No deaths were reported in trials 319, 320 and 323.

Serious adverse events were reported for 5 patients receiving ondansetron; these are summarised in Table 17 below (source: trial reports).

Table 17: Serious adverse events reported from trials 319, 320 and 323

Trial ID	Serious adverse event
319	Seizures (n=1)
	Respiratory Depression (n=1)
	Dehydration (n=1)
320	No SAE
323	Hypocapnia, Hypoxia, Nodal arrhythmia (n=1)
	Staphylococcal infection (n=1)

Discontinuation due to adverse events

No subjects were prematurely discontinued from ondansetron in trials 319 and 323. One patient was prematurely discontinued from trial 320 because of vascular access complication.

Adverse events

Adverse events were reported in 28% (21/76) of CINV patients (Trial 320). The most common adverse events in this patient population were nausea, irritability and stomach discomfort.

Adverse events were reported in 35% (18/51) of PONV patients in trial 319. Increasing the dose of ondansetron did not result in a commensurate increase in the numbers of subjects with AEs reported; more subjects in the 0.1 mg/kg group experienced at least one AE compared to the 0.2 mg/kg group. The most common adverse events in this patient population were decreased oxygen saturation (10%), vomiting (10%), and agitation (6%).

In trial 323 conducted in PONV patients, adverse events were reported for 18% of patients in both groups (62/336 ondansetron; 59/334 placebo). There was no clinically important difference in the frequency or type of events reported for each treatment group. The most common adverse events were pyrexia, bronchospasm, post-procedural pain and diarrhoea.

3.3.2 Postmarketing reports

The MAH performed a review of their worldwide safety database to identify post-marketing reports for ondansetron in patients aged ≤18 years as compared to older patients. The data lock point was 28 February 2005. Clinical trials reports were excluded.

362 reports in patients aged ≤18 years containing 1163 adverse events were retrieved. Line listings for these reports were provided. By comparison, there were 3448 reports from the population aged ≥18 years, containing a total of 8774 events.

The majority of paediatric reports were from subjects who received ondansetron for CINV. PONV was the second most reported treatment indication. In addition there were a small number of spontaneous reports relating to subjects whose mother received ondansetron for hyper-emesis gravida.

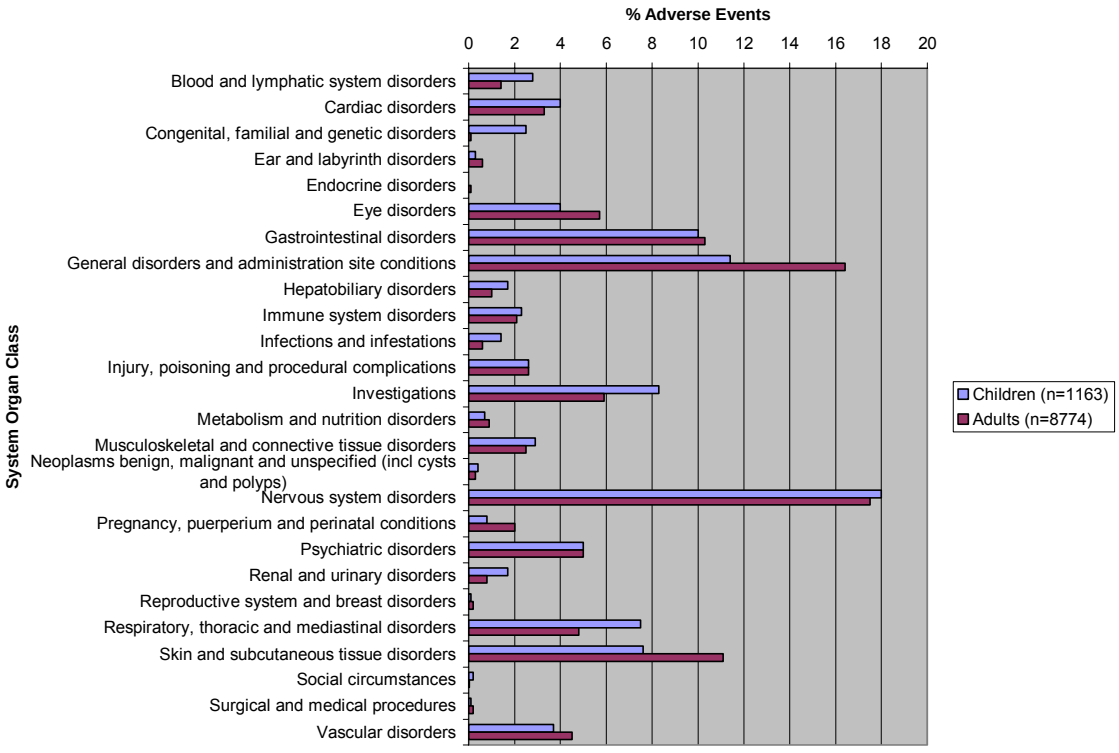
Individual case reports were categorised under the MedDRA SOC for the primary adverse event (the most medically important event term) on the case.

The three most frequent MedDRA SOCs under which paediatric adverse events were classified were Nervous System Disorders (18%), General Disorders and Administration Site Conditions (11.4%) and Gastrointestinal Disorders (10%).

A comparison of the distribution of adverse events by System Organ Class (SOC) in paediatric versus adult patients is presented in Figure 5 overleaf.

Assessor's comment
No comparison has been performed to compare incidence of adverse events across the different paediatric age groups (children ≤2 years and ≥2 years, adolescents).

Figure 5 Comparison of SOC distribution for paediatric versus adult AE reports



Distribution of adverse events between the adult and paediatric populations was evaluated using Chi-Square test. This test indicated that there were statistically significant differences in reporting for two SOCs: *General disorders and administration site conditions* and *Skin and subcutaneous tissue disorders*. Details are only reported for events unique to the ≤18 years-group in the 2 SOCs mentioned above. These events are outlined in the Table 18 below.

Table 18: Events unique to the ≤18 years-group in 2 SOCs

SOC	Additional General Disorders Events Reported Only in the Paediatric Group	Additional Skin Disorders Events Reported Only in the Paediatric Group
Events	Application site irritation n=1 Application site pain n=1 Application site reaction n=1 Developmental delay n=2 Growth retardation n=1 Mobility decreased n=2 Sluggishness n=1	Hirsuitism n=2 Skin hypertrophy n=1

2 cases of developmental delay were reported, in one case associated with growth retardation. For case A0091795A no details are available. In the other case (B0064401A) the event was reported for a 7 month old girl with facial dysmorphism, deafness, cerebral ventricle dilatation, ill-defined disorder.

The unique Skin Disorders paediatric events were infrequent (n =3).

The MAH concluded that the reporting differences in the paediatric adverse events were not meaningful and that the safety of ondansetron in the paediatric population is comparable to that in the adult population.

Assessor's comment

The calculation of statistical significance for differences in frequencies is not considered of value as these are *spontaneous* reports from a population of unknown size.

Reports in the cardiac disorders SOC are discussed below.

A review of the line listings for SOCs with a greater percentage of cases reported for the ≤18 years- raises the following questions:

General disorders: 8 deaths are reported in under-18s, but no details are available. The MAH should provide case narratives.

Hepatobiliary disorders: The SmPC lists 'asymptomatic increases in liver function tests'. In children and adolescents 5 cases of hepatic failure were reported. 3 of these cases were in children ≤ 2 years, and were classified as 'possibly related'. In adults, there were 10 reports of hepatic failure. In addition cases of hepatitis and other liver disorders were reported in both the paediatric and adult patient population. In the latest PSUR the MAH states that hepatobiliary disorders were reviewed and it was decided not to amend the product information. The MAH should submit a review of hepatobiliary disorders with a view to amending the product information.

Respiratory disorders: Reactions in this SOC were more commonly reported for under 18's. Bronchospasm was commonly reported as an adverse event in the clinical trials and there were several reports of dyspnoea, apnoea, and bronchospasm in postmarketing reports for both children and adults. In the latest PSUR the MAH states that respiratory disorders were reviewed and it was decided not to amend the product information. The MAH should submit a review of respiratory disorders and discuss the requirements for amendment of the product information.

3.3.3 Adverse events of special interest

5-HT_3 antagonists interact with human cardiac sodium and potassium ion channels and have been associated with changes in ECG parameters. Because of a serious concern regarding the cardiovascular safety of dolasetron in children and adolescents, this particular 5-HT3 antagonist was recently contraindicated for use in children and adolescents in the EU. Consequently, the MAH was asked for a review of cardiac disorders in children.

The MAH performed a detailed search of their Safety Database using the following criteria:

> Data lock point(s): end date 31 August 2006
>
> Report types: All spontaneous reports, post-marketing surveillance reports, and unblinded serious clinical trial reports (attributable and non-attributable)
>
> Ondansetron was reported as a suspect drug

MedDRA preferred term(s): All events coded to the 'cardiac disorders system organ class which occurred in paediatric patients (≤18 years), plus the terms proposed by the MHRA (dizziness, hypotension, loss of consciousness, convulsions, and ECG changes), plus additional relevant preferred terms which were selected by reviewing a cumulative summary of adverse events for ondansetron (pulse absent, syncope and circulatory collapse).

90 paediatric reports were identified. The MAH states that for 2 reports a causal association to ondansetron could not be excluded. The remaining 88 reports were confounded by concomitant medications such as chemotherapeutic agents, concurrent illnesses, electrolyte abnormalities, past medical history of cardiac diseases, prolonged or unknown time to event onset, insufficient information, and in some cases the events occurred in the context of seriously ill patients. Details of these 88 reports have not been provided.

Report G0005846A: A 17 year old male with Hodgkin's disease experienced thoracic pain, palpitation and tachycardia 5 minutes after ondansetron infusion, which spontaneously resolved within 4 hours. A pre-ondansetron ECG was normal, post- ondansetron ECG showed S-T depression. Although a causal association to ondansetron could not be ruled out, the patient developed chest pain with S-T depression. The adverse reactions section of the ondansetron Global Data sheet (GDS) includes "*chest pain with or without S-T depression*".

Report B0425818A: An 11 year old male received IV ondansetron for 2 days (1 injection per day) for PONV. He experienced cardiac arrest, loss of consciousness, ocular revulsion, convulsion, and pallor during the second infusion which was interrupted. The patient was successfully resuscitated. Concomitant medications included morphine. An ECG performed 8 days later showed a prolonged QT interval. Although a causal association between this event and ondansetron could not be excluded, this report is confounded by the concomitant use of morphine. Additionally QT interval prolongation was identified 8 days later, and ondansetron has a short half-life (three hours).

Assessor's comment
It would appear that no ECG was obtained at the time of the ADR. The preoperative ECG findings have not been discussed by the MAH. It cannot be excluded that in this patient may have had a congenital long QT syndrome and additional lengthening of the QT interval caused by ondansetron may have caused arrhythmia and cardiac arrest.

Based on the above review of paediatric cardiac events, the MAH concludes that a causal association to ondansetron cannot be excluded, however considering the large overall patient exposure (877,271 patient treatment years), and evidence from >15 years of post marketing experience, there is very little evidence to suggest that QT prolongation is a significant safety concern in either adults or the paediatric patients who receive ondansetron. Furthermore the present SmPC contains a warning statement as given below:

"*Very rarely and predominantly with intravenous Zofran, transient ECG changes including QT interval prolongation have been reported. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances. In patients treated with anti-arrhythmic agents or beta adrenergic blocking agents and in patients with significant electrolyte disturbances*."

Assessor's comment

The MAH should propose a warning statement regarding interactions relating to QT-interval prolongation for SmPC section 4.5 *Interactions*. The proposed text should take into consideration that 5HT3-antagonists are likely to be administered together with chemotherapeutic regimens for childhood cancer that may themselves cause QT interval prolongation (e.g. arsenic trioxide) or are cardiotoxic and may thus increase the risk of arrhythmias (e.g. anthracyclines).

3.3.4 Assessor's conclusions on safety

The safety profile of ondansetron in infants and toddlers seems to reflect that in older children and adults, but further data are needed with respect to reported deaths, hepatobiliary and respiratory disorders before a final conclusions regarding safety can be reached.

3.4 PRODUCT INFORMATION

Section 4.2, CINV:

The proposed dose recommendations (see section 2.4 above) are confusing. The present dose recommendation for oral administration is 4 mg at 12-hourly intervals. The proposed dose recommendations for oral administration are confusing as they are varyingly given as 4mg 2x/day for *all children 6 months to 17 years* or 2-8 mg *depending on BSA*.

As an explanation, the MAH states the following:

'We are not seeking to increase the maximum recommended dose for CINV from 4mg to 8mg twice daily. The proposed dose of 8mg twice daily is in line with the current maximum adult dose and the MAH considers this to apply for children over the age of 12 or BSA 1.2m^2.'

The assessor notes that the currently licensed oral dose for all children (i.e. under the age of 18) is not 8mg but 4mg twice daily. This reflects the dose used in pivotal trials S3AB3006 and S3AB 4003 (see section 5.5 below). A doubling of the dose for adolescents and halving the dose for children with a BSA <0.6m^2 (up to app. 3 yrs. of age) would need to be adequately justified.

'The age at which a child can receive an adult dose may be calculated by using an average conversion factor based on the BSA and weight of an "average" 12 year old child. According to Dr. Steven Halls' BSA Calculator, an average 12 year old child 12 year-old weighing 50kg and 155cm tall would have a BSA of 1.47m^2. In this instance, dosing by BSA (5 mg/m^2 x 1.47m^2) would give a conversion equivalent to approximately 0.15 mg/kg (7.35mg / 50kg).'

The mean weight and height for 12 year olds in the UK are lower than in the US, being 39kg and 148cm, BSA 1.25 (UK1990 standard centile chart).

The following differences in dosage for CINV are evident for two patients at the extremes of the recommended paediatric age range (a typical 6 month old baby weighing 7.7 kg with BSA 0.4m^2 and a typical UK 12 year old weighing 39 kg with BSA 1.25 m^2):

Age	Dose Regimen 1		Dose Regimen 2	
	IV	Oral	IV	Oral
6 months	2mg	2mg BD	1.2mg	4mg BD
12 years	8mg	8mg BD	5.85mg	4 mg BD

No justification is provided for the differences between the two regimens. Nor is the breakdown of dosage by BSA related to the pharmacokinetic data.

3.5 OVERALL DISCUSSION AND CONCLUSIONS

Two pivotal efficacy trials have been submitted in support of this application. The results of the PONV trial indicate that the efficacy of a single dose of ondansetron in the *prevention* of postoperative vomiting in children aged 1 month to 2 years is of similar magnitude as that observed in older children in previous trials.

The recommendation of 0.1mg/kg up to 4mg as a single dose does not reflect clinical reality where ondansetron is usually prescribed at 0.1mg/kg two or three times a day as needed. In addition, because of the cost of ondansetron, it is usually reserved for at risk patients or patients undergoing procedures where PONV is more common. Accordingly, it would be useful to have more information on the PK and efficacy of multiple rather than single doses in risk patients as needed. In the absence of such data, the product information should clearly state that only one single dose of ondansetron should be administered. Possible risks arising from the potential use of repeat doses for PONV in children under the age of 24 months, with a particular view to those aged 1-4 months, and in patients with an ASA physical status ≥ 3 will need to be addressed by adequate risk minimisation measures.

Efficacy in the *treatment* of PONV has not been demonstrated for children aged <2 years, but results in older children can reasonably be extrapolated to infants and toddlers.

For CINV ondansetron is currently licensed without a lower age limit. One open-label non-comparative trial in 78 children aged 6 to 48 months demonstrated response rates in line with those demonstrated for children aged 1 -18 years. As half-life is prolonged in children aged < 4 months, and repeat dosing is required, the definition of a lower age limit is considered appropriate.

The proposed dose recommendations for CINV for children and adolescents aged 6 months to 17 years are not considered acceptable as they are confusing, have not been adequately justified or related to pharmacokinetic data. The different dose regimens, based on either BSA or weight, would result in markedly different doses for the same patient. The proposed doses for children with a BSA > $1.2m^2$ are considerably higher than those used in the pivotal trials S3AB3006 and S3AB 4003.

The safety profile of ondansetron in infants and toddlers seems to reflect that in older children and adults, but further data are required before a conclusion can be reached.

3.6 RECOMMENDATIONS

On the basis of the available evidence it is considered that the extension of age range for PONV and definition of a lower age limit for CINV is potentially approvable, provided the MAH satisfactorily addresses the following questions:

Pharmacokinetics:

CINV:

The MAH should provide simulations of the systemic exposure predicted by the different dosage regimens for a typical 6 month baby, a toddler and a typical UK 12 year old. These profiles should be discussed in relation to comparable profiles in adults, and to what is known about the relationship between the PK and PD of ondansetron.

PONV:

The MAH should clarify how many children in trial 319 were aged 1 month and how many had an ASA status of 3.

The recommendation of 0.1mg/kg up to 4mg as a single dose does not reflect clinical reality where ondansetron is usually prescribed at 0.1mg/kg two or three times a day as needed. In addition, because of the cost of ondansetron, it is usually reserved for at risk patients or patients undergoing procedures where PONV is more common. Accordingly, it would be useful to have more information on the PK and efficacy of multiple rather than single doses in risk patients as needed. The MAH should provide these data or justify the lack of them.

Population PK:

The MAH should justify why CINV versus PONV was not included as a covariate in the analysis and discuss the possible impact of the lack of inclusion of this covariate and clarify if anaesthesia and surgery alter the kinetics of ondansetron.

Assuming dose and time linearity of the PK the full data across age should have been combined in a more rigorous Population PK analysis rather than simply compare tabulated mean PK parameters in this group of 1-48 month patients with those for children 4-18 y and adults. The MAH should comment.

Simulated exposure profiles at different ages should be provided, particularly to see the predicted profile in a 1 month baby.

Although there is overlap in age-related changes in PK parameters, concern is for the outliers. Therefore, this overlap, in itself, does not mitigate concern for patients at the extreme of risk – and these are likely to be at the lower age limit. The MAH should comment.

Since the concentrations of plasma proteins that bind drugs increase with age from birth this might be another confounding issue in the interpretation of the PK data. Ideally, comparisons of exposure should be made on the basis of unbound plasma drug concentrations rather than total plasma drug concentrations. However, since ondansetron seems only to be bound to the extent of 60-70% this may not be a big factor. The MAH should comment.

Safety

- The MAH should provide additional safety data as follows:
    - Case narratives for postmarketing reports of deaths in children and adolescents.
    - A review of hepatobiliary disorders and a recommendation for the product information.
    - A review of respiratory disorders and a recommendation for the product information.
- The MAH should propose a warning statement regarding interactions relating to QT-interval prolongation for SmPC section 4.5 *Interactions*. The proposed text should take into consideration that 5HT3-antagonists are likely to be administered together with chemotherapeutic regimens for childhood cancer that may themselves cause QT interval prolongation (e.g. arsenic trioxide) or are cardiotoxic and may thus increase the risk of arrhythmias (e.g. anthracyclines).
- The MAH should address possible risks arising from the potential use of repeat doses for PONV in children under the age of 24 months, with a particular view to those aged 1-4 months, and in patients with an ASA physical status ≥ 3 and propose risk minimisation measures.

Product Information

- Dosage for CINV: No justification is provided for the differences between the two regimens for CINV. Nor is the breakdown of dosage by BSA related to the pharmacokinetic data. The MAH should provide simulations of the systemic exposure predicted by the different dosage regimens for a typical 6 month baby, a toddler and a typical 12 UK 12 year old. These profiles should be discussed in relation to comparable profiles in adults, and to what is known about the relationship between the PK and PD of ondansetron.
- The oral dose for ondansetron in the two pivotal trials including children up to the age of 18 years (S3AB3006 and S3AB 4003) was 4 mg bid, the intravenous dose was 5mg/m^2. This is reflected in the current prescribing information. The proposed doses for children with a BSA > 1.2m^2 are considerably higher than those used in the pivotal trials. The MAH should discuss.
- Dosage for PONV: The recommendation of 0.1mg/kg up to 4mg as a single dose does not reflect clinical reality where ondansetron is usually prescribed at 0.1mg/kg two or three times a day as needed. In addition, because of the cost of ondansetron, it is usually reserved for at risk patients or patients undergoing procedures where PONV is more common. Accordingly, it would be useful to have more information on the PK and efficacy of multiple rather than single doses in risk patients as needed. In the absence of such data, the product information should clearly state that only one single dose of ondansetron should be administered. The MAH should comment.

- Method of administration for CINV: The method of administration used in the supporting trial (dilution of ondansetron in 5% dextrose or 0.9% sodium chloride and administration over 15 minutes) is not reflected in the proposed SmPC. The product information should be amended to contain relevant specific advice.
- Method of administration for PONV: The recommendation of a 'slow' i.v. infusion is vague. No justification is provided for the recommendation to administer ondansetron *after* surgery for the *prevention* of PONV. (Proposed text: '*For prevention and treatment of PONV in paediatric patients …. ondansetron may be administered ….either prior to, at or after induction of anaesthesia, or after surgery'*.) The product information should be amended to contain specific and unambiguous advice.
- The product information should be amended to give clear recommendations regarding dose, method and timing of administration for CINV and PONV. These should not contain any conflicting advice and be supported by data. Cross-reference should be made to section 5.1.
- The results of the PONV trial should be reflected in section 5.1 of the SmPC (primary endpoint only). The SmPC should state that no data are available for the treatment of postoperative vomiting or for the prevention of delayed or prolonged CINV in children under 2 years of age.

4 SECOND ROUND OF ASSESSMENT

4.1 Pharmacokinetics CINV

Question

The MAH should provide simulations of the systemic exposure predicted by the different dosage regimens for a typical 6 month baby, a toddler and a typical UK 12 year old. These profiles should be discussed in relation to comparable profiles in adults, and to what is known about the relationship between the PK and PD of ondansetron.

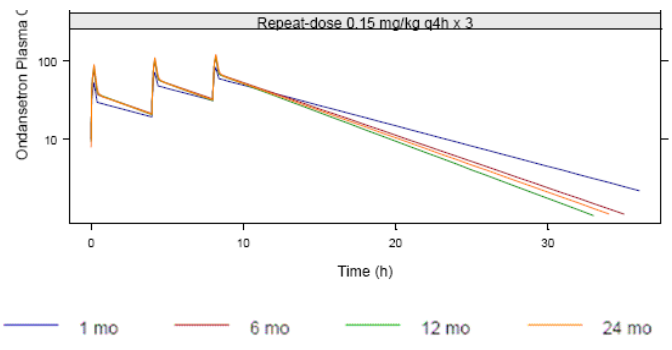
Summary of MAH's responses

Assessor's comment
The response includes data on PONV and several tables that were previously included in the Rapporteur's and the CoRapporteur's assessment reports. These data and tables are not included in the below summary as they are not considered relevant to CINV.

Repeat dosing was simulated only for CINV patients up to 24 months of age. As the primary objective of the population Pharmacokinetic (PK) analysis was to develop a basic PK model to characterise the population pharmacokinetics of ondansetron in paediatric oncology and surgery patients aged between 1 to 48 months, it was not used to simulate PK profiles for 12 year-old paediatric subjects.

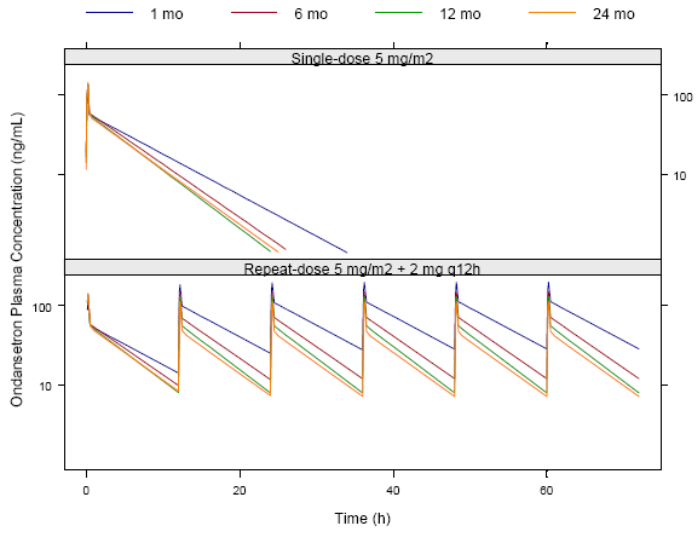
The following data are provided:

Figure 1 Population mean ondansetron plasma concentration (ng/mL) - time profile after repeat-doses (0.15 mg/kg every 4h over 15 minutes x 3 doses) of IV Zofran for CINV in typical 1, 6, 12, and 24 month-old paediatric subjects



Assessor's comment
The simulation does not include any oral doses for Day 2.

Figure 2 Population mean ondansetron plasma concentration-time profile after single (5 mg/m2 over 15 minutes) and repeat-doses (5 mg/m2 + 2 mg every 12h over 15 minutes x 5 doses) of IV Zofran in typical 1, 6, 12, and 24 month-old CINV paediatric subjects



Assessor's comment

The above figure indicates increases in peak and trough concentrations with repeat doses in 1-month old children.

Table 1 Ondansetron pharmacokinetic parameters for CINV after repeat-doses (0.15 mg/kg every 4h over 15 min x 3 doses), single dose (5 mg/m2 over 15 min) and repeat-doses (5 mg/m2 + 2 mg every 12h over 15 min x 5 doses) of IV Zofran in typical 1, 6, 12, and 24 month-old paediatric subjects

Dosage Regimen	Age (mo)	Weight[a] (kg)	Height[b] (cm)	BSA[b] (m^2)	Dose (mg)	Dose (mg/m^2)	AUC[c] (ng.h/mL)	Half-life (h)	Cmax[d] (ng/mL)	Tmax[d] (h)
0.1 mg/kg SD	1	4.5	54.5	0.261	0.45	1.72	174	5.81	197	EOI SD (30 sec)
	6	8.0	67.7	0.388	0.80	2.06	172	4.48	207	EOI SD (30 sec)
	12	10.2	76	0.464	1.02	2.20	164	4.11	186	EOI SD (30 sec)
	24	12.5	87	0.550	1.25	2.27	170	4.33	158	EOI SD (30 sec)
0.15 mg/kg every 4h x 3	1	4.5	54.5	0.261	0.68	2.59	260	5.81	88	EOI Dose 3 (15 min)
	6	8.0	67.7	0.388	1.20	3.09	258	4.48	114	EOI Dose 3 (15 min)
	12	10.2	76	0.464	1.53	3.30	245	4.11	122	EOI Dose 3 (15 min)
	24	12.5	87	0.550	1.88	3.41	255	4.33	128	EOI Dose 3 (15 min)
5 mg/m^2 SD	1	4.5	54.5	0.261	1.31	0.29	503	5.81	112	EOI SD (15 min)
	6	8.0	67.7	0.388	1.94	0.24	418	4.48	134	EOI SD (15 min)
	12	10.2	76	0.464	2.32	0.23	372	4.11	141	EOI SD (15 min)
	24	12.5	87	0.550	2.75	0.22	373	4.33	144	EOI SD (15 min)
2 mg every 12h RD[e]	1	4.5	54.5	0.261	2.00	0.44	771	5.81	199	EOI Dose 5 (15 min)
	6	8	67.7	0.388	2.00	0.25	431	4.48	150	EOI Dose 5 (15 min)
	12	10.2	76	0.464	2.00	0.20	321	4.11	129	EOI Dose 5 (15 min)
	24	12.5	87	0.550	2.00	0.16	272	4.33	112	EOI Dose 5 (15 min)

EOI = End of infusion, SD = Single-dose, RD = Repeat-dose
a. Weight and height for age were determined using the median value from UK1990 growth charts for boys
b. BSA calculated by Mosteller formula, BSA (m^2) = [height(cm)*weight(kg)/3600]$^{1/2}$
c. AUC represents AUC(0-∞) after a single dose, equal to AUC(0-τ) at steady-state.
d. Represents the PK profile (and time relative to last dose) where Cmax was calculated.
e. RD regimen initiated after initial dose of 5 mg/m^2 (5 additional doses, representing steady state, as BSA values were <0.6 m^2, a 2 mg every 12 hours RD regimen was used)

Assessor's comment:

With respect to Table 1 overleaf, please note that 6 months is the proposed lower age limit for CINV.

Taking into consideration the PK/PD relationship (see below), it would appear that the predicted PK parameters for oral dosing support the dose recommendation of 2mg twice daily repeat dose in those with a BSA < 0.6 m^2 but do not justify **4mg** twice daily for patients weighing ≤10kg.

The PK model was developed using intravenous dosing and did not include an absorption component. For this reason the simulations of repeat dose were performed assuming intravenous doses (i.e., 100% maximum oral bioavailability instead of actual tablet bioavailability of ~55%) and likely overestimate the exposures following repeat dosing. In Table 1, the AUC values shown after the repeat dosing of 2mg orally every 12 hours after an initial 5mg/m^2 dose are approximately 2-fold greater than what would actually be expected from oral repeat dosing.

The median C_{max} after the third dose of ondansetron 0.15 mg/kg in patients aged 1 to 24 months was predicted to be range from 88 to 128ng/mL (see Table 1 above). These values were lower than those observed in paediatric cancer patients aged 4 to 18 years in trial S3A-150.

Assessor's comment

S3A-150 was a PK study of three doses ondansetron 0.15mg/kg every 4 hours. The first dose was administered 30 minutes before chemotherapy, not immediately before chemotherapy as proposed now. It included two patients aged 4-6 years, eight patients aged 7-12 years and five patients aged 13-18 years. In addition, six leukaemia patients aged 7-18 years. The report does not include median values for C_{max}. The mean C_{max} (SD) was 189.9 ng/mL (109.5) for all included patients.

The median Cmax in the PK part of trial S3AM20 (BSA-based dosing, n=14, ages 2-13 yrs.) was 110 ng/ml (range 48.8 – 165.9). A full study report with respect to efficacy data has not been submitted for trial S3AM20.

Based on the Population PK analysis including patients aged up to 48 months, cancer patients aged 6 to 48 months who received an intravenous ondansetron dose of 0.15 mg/kg every 4 hours for 3 doses would be expected to achieve a systemic exposure (AUC) consistent with the exposure achieved in previous paediatric studies in cancer patients (aged 4 to 18 years) at similar doses. The prevention of emesis (efficacy measure) in 76 cancer patients aged 6 to 48 months in trial S3A40320 was essentially the same as for patients aged 4 to 18 years in Study S3A-150.

Assessor's note

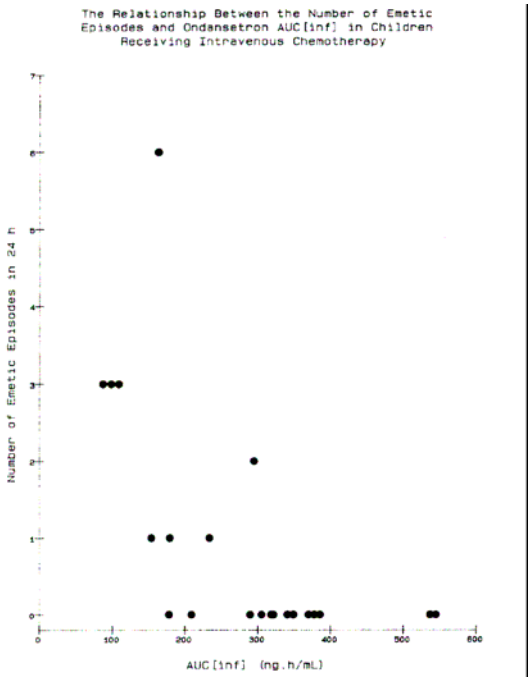
Complete control of emesis using the weight-based dosing regimen was achieved in 42/76 (55%) patients in trial S3A40320, and 10/21(47%) patients in S3A-150.

Complete control of emesis using the BSA-based regimen was achieved in 49% of patients in S3AB3006 (n=415, age 1 – 18 years). For trial S3AM20A, which also used BSA-based dosing, a full study report containing efficacy data has not been submitted.

The MAH notes that in paediatric cancer subjects aged 2 to 18 years old (n=35), it was determined, using an Emax model, that the AUC_{50} (AUC required to achieve a 50% response) was 170 ng-h/mL [Haberer, 1995][1], and that paediatric cancer subjects showed a 50% to 90% response rate with AUC_{inf} values ranging from 170 to 250 ng.h/mL (source not provided).

[1] Haberer LJ and Palmer JL. Evaluation of the Exposure-Response Relationship for Ondansetron in Pediatric Cancer Patients. Clin Pharm and Ther, 1995; 57(2): 156. **Only abstract provided**. These data are derived from trials S3AM20 (BSA-based dosing, n=14, ages 2-13 yrs.) and S3A-150 (weight-based dosing, n=21, ages 4-18 years).

PK/PD related data from trial S3A-150 are supplied in an Appendix to the response document and shown below:



The MAH notes that in general, surgical and cancer paediatric patients younger than 18 years tend to have a higher ondansetron clearance compared to adults leading to a shorter half-life in most paediatric patients.

In patients aged 1 month to 4 months, a longer half-life was observed due to the higher volume of distribution in this age group. After clearance is normalized by body weight, the clearance for the 1 to 4 month old age group was on average slower than for the > 4 to 24 months old group but consistent with weight-normalized clearance in paediatric subjects, 3 to 12 years old, studied in S3GK02. The change in clearance from neonates to adult may be a reflection of age related changes in metabolic systems.

Assessor's note:

S3GK02 was a PK study conducted in *non-cancer patients* aged 3 to 12 years. A comparison of PK parameters to older cancer patients would seem more appropriate. However, patients under the age of 6 months are to be excluded from the repeat dose regimen under the proposed SmPC.

See also assessor's comment in section 3.1 below.

Assessment of response

The MAH has not provided a discussion of the differences in pharmacokinetic profiles resulting from the different dose regimens, i.e. weight-based versus BSA-based. Nor have simulations been provided for children aged >24 months.

Therefore, the responses are difficult to interpret. Also, comparisons are made on the basis of supporting study reports that do not contain all relevant data.

Pharmacodynamic effects are correlated to an AUC_{50} of 170 ng-h/mL reported by Haberer. The predicted AUC for both dose regimens (weight-based or BSA-based) exceeds this value, indicating that sufficient exposure should be attained by either dose regimen.

The data do not allow for a comparison of the two different dose regimens with respect to efficacy as patient numbers are too small and the provided study reports do not contain adequate detail.

Assessor's conclusion

The MAH's response is noted.

The predicted PK parameters for oral dosing do not justify **4mg** twice daily for patients weighing ≤10kg.

In order to conclude this procedure, this issue may lapse provided the MAH amends the product information as outlined in Annex 1. The MAH is advised that the UK will require further analysis of PK data before a variation application can be granted.

4.2 Pharmacokinetics PONV

Question

The MAH should clarify how many children in trial 319 were aged 1 month and how many had an ASA status of 3.

The recommendation of 0.1mg/kg up to 4mg as a single dose does not reflect clinical reality where ondansetron is usually prescribed at 0.1mg/kg two or three times a day as needed. In addition, because of the cost of ondansetron, it is usually reserved for at risk patients or patients undergoing procedures where PONV is more common. Accordingly, it would be useful to have more information on the PK and efficacy of multiple rather than single doses in risk patients as needed. The MAH should provide these data or justify the lack of them.

Summary of MAH's responses

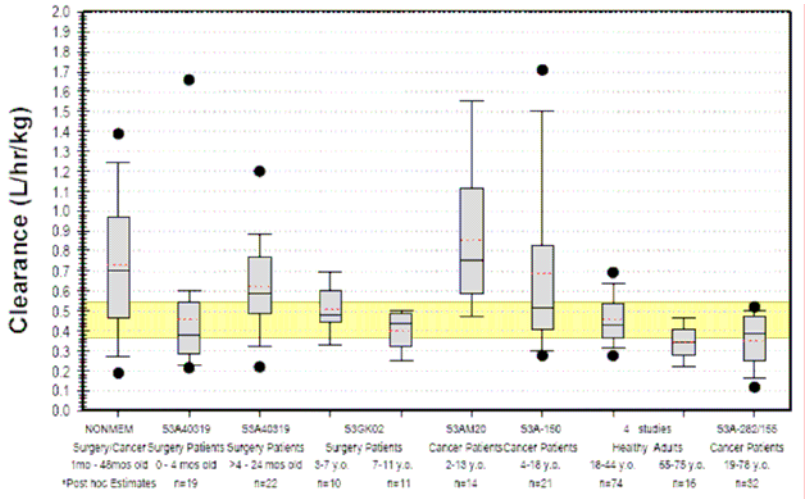
Six children were aged 1 month. The ASA classification was not required to be recorded.

The MAH has revised the dosage schedule to state that a single dose is given for prevention and treatment of PONV and notes that paediatric data for multiple doses of Zofran exist when administered for the prevention of CINV.

Assessment of response and conclusion

The number of one-month old children – an age at which the development of CYPs relevant to the metabolism of ondansetron is still in progress - is small. The data concerning ASA status have not been sampled; nothing that can be done about that in retrospect. However the accuracy of data sampling may be questioned.

The AUC is similar in 1 month old children to 2 year old children although the relationship of CL/kg versus age in surgical patients is parabolic – see figure below. Clearance/kg tends to be higher in cancer patients compared to surgical patients, and this issue was confounded in the NONMEM analysis by combining data for the two indications over a limited age range.



Given that the proposed SmPC now clearly indicates that only one single dose should be administered (see section 5.2 below), this issue is considered **resolved**. The MAH is advised that the UK will require further analysis of PK data before a variation application can be granted.

4.3 Population PK

Question CINV versus PONV

The MAH should justify why CINV versus PONV was not included as a covariate in the analysis and discuss the possible impact of the lack of inclusion of this covariate and clarify if anaesthesia and surgery alter the kinetics of ondansetron.

Summary of MAH's responses

CINV versus PONV were included as covariates in the analysis but were not found to correlate with PK parameters and were therefore not included in the final model.

Assessment of response

The data regarding a potential correlation of indication with PK parameters in the PK population analysis including children aged 1 – 48 months are contradicted by reports from older PK studies performed in children ≥ 2 years:

The report for trial S3AM20 (PK study in paediatric cancer patients aged 2 to 13 years and submitted as an appendix to the response document) states the following:

The clearance of ondansetron in the paediatric cancer patients in this and an earlier study were generally greater than any other group studied to date including healthy paediatric subjects. Although clearance was lower in the 10 to 13 year old patients than the remaining, younger, patients, the values did not approach adult values as had been observed in non-cancer paediatric patients of a similar age. ***Ondansetron clearance can therefore be ranked in the order: paediatric cancer patients > non-cancer paediatric patients > adults (healthy and cancer patients).*** *Additionally, it would appear that the convergence of paediatric and adult clearance values occurs at a later age in cancer patients than other groups. ..... The increase in clearance is proportionally greater than the increase in volume and therefore, in comparison to adults, elimination half-life is decreased in the paediatric population. .....Efficacy data was collected .... Of the 14 patients who had evaluable plasma concentration data only three reported any emetic episodes on the first day of treatment. All three of these patients had an AUC less than 300ng.h/ml which is consistent with the findings in study S3A-150.*

Question More rigorous Population PK analysis

Assuming dose and time linearity of the PK the full data across age should have been combined in a more rigorous Population PK analysis rather than simply compare tabulated mean PK parameters in this group of 1-48 month patients with those for children 4-18 y and adults. The MAH should provide such data.

Summary of MAH's responses

Although ondansetron PK is dose and time linear, age and weight were significant covariates in the paediatric population. In addition the physiological processes governing drug disposition mature significantly over the first year of life. These physiological maturational changes (i.e., changes in drug metabolizing enzymes and volume of distribution) are not necessarily linear with time. In order to characterize the PK in very young paediatric patients and not dilute out significant aspects in paediatric patients the Population PK analysis was performed on the age group of 1 to 48 months. Furthermore, the median weight-normalized clearance predicted from the Final Model, was extrapolated to a 70 kg subject using allometry scaling and was 0.527 L/h/kg. This value is consistent with those observed in adults (0.4-0.5 L/h/kg) and surgical patients aged 3-12 years (0.39-0.5 L/h/kg) (Assessor's comment: references unidentifiable).

Assessment of response:

The full PK data across the full age range (infant to adult) should have been combined in a more rigorous Population PK analysis. However, this has not been done and such data are therefore not available.

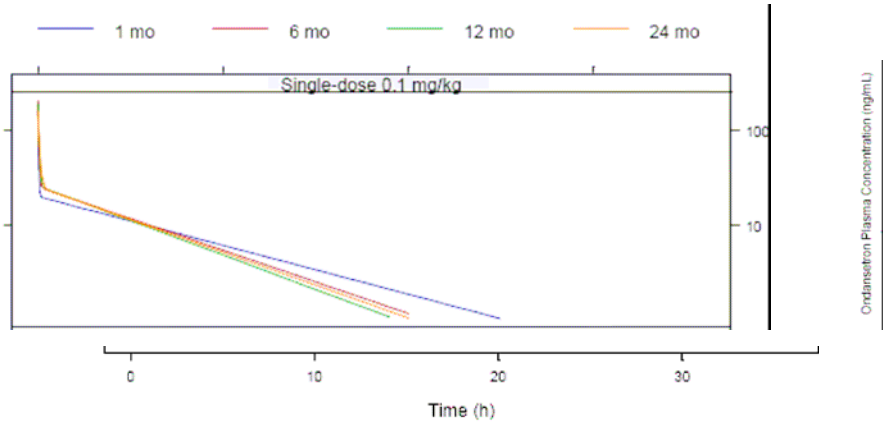
Question Simulated exposure profiles at different ages

Simulated exposure profiles at different ages should be provided, particularly to see the predicted profile in a 1 month baby.

Summary of MAH's responses

Simulated exposure profiles for CINV for a 1, 6 and 12 and a 24 month old child are provided in the response to question 1 (see pages 4 and 5).

The simulated exposure profile for PONV a 1, 6 and 12 and a 24 month old child is shown below.



Assessment of response:

The MAH's response is noted.

Question Concern for patients at the extreme of risk

Although there is overlap in age-related changes in PK parameters, concern is for the outliers. Therefore, this overlap, in itself, does not mitigate concern for patients at the extreme of risk – and these are likely to be at the lower age limit. The MAH should comment.

Summary of MAH's responses

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300mL/min at 12 years of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at 3 years. Use of weight based dosing (0.1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

Assessment of response:

The question of variability has not been addressed.

Question Plasma protein binding

Since the concentrations of plasma proteins that bind drugs increase with age from birth this might be another confounding issue in the interpretation of the PK data. Ideally, comparisons of exposure should be made on the basis of unbound plasma drug concentrations rather than total plasma drug concentrations. However, since ondansetron seems only to be bound to the extent of 60-70% this may not be a big factor. The MAH should comment.

Summary of MAH's responses

Plasma protein binding of ondansetron as measured in vitro is not significant (70% to 76%) over the pharmacologic concentration range (10 to 500 ng/mL) so comparisons of exposure based on unbound plasma drug concentrations would not likely differ significantly from comparisons based on total drug concentrations.

Assessment of response:

The MAH's response is accepted. Issue resolved.

Assessment of Population PK responses

The data regarding a potential correlation of indication with PK parameters in the PK population analysis including children aged 1 – 48 months contradict the findings from older PK studies (children ≥ 2 years).

The Population PK model mixes data from both PONV and CINV indications. Clearance is higher in CINV than PONV but this has not been detected as a covariate.

The full PK data across the full age range (infant to adult) should have been combined in a more rigorous Population PK analysis. The slower clearance in 1- 4 month old infants is taken into consideration by the proposed product information, so that only one single dose (for PONV) may be administered to those under the age of 6 months and section 5.2 clearly reflects the slower clearance in this age group.

Repeat doses (for CINV) are only proposed for those over the age of 6 months. Simulated AUC_{inf} values for CINV patients of 6, 12 and 24 months of age are above the antiemetic AUC_{50} quoted to be 170 ng.h/mL; however the source for the quoted AUC_{50} has not provided.

The assessor notes that a comparison across trials indicates that complete control of emesis demonstrated in the trial submitted in support of the label change (S3A40320, weight-based dosing, children aged 1-48 months, n=75) is comparable to that demonstrated in the pivotal trial (S3AB3006, BSA-based dosing, children aged 1-18 years, n=415).

Population PK - Conclusion

The MAH's responses are noted.

The lack of a more rigorous PK analysis is disappointing. The findings of the population PK analysis performed for infants (lack of correlation between indication and PK parameters) contradict findings in older children (correlation between indication and clearance).

The MAH is advised that the UK will require further analysis of PK data before a variation application can be granted. All the data (1 month to 18-44 year old patients) should be analysed to disclose variability in exposure with age over a wider age range than was done before. Clearance should be assessed in relation to body weight to the power 0.75, a maturation function should be included in the model, and PONV vs CINV should be assessed as a covariate over the wider age range.

For the purposes of the present procedure, the issue can be allowed to lapse.

4.4 Dose and method of administration CINV

Questions

- *The oral dose for ondansetron in the two pivotal trials including children up to the age of 18 years (S3AB3006 and S3AB 4003) was 4 mg bid, the intravenous dose was 5mg/m^2. This is reflected in the current prescribing information. The proposed doses for children with a BSA > 1.2m^2 are considerably higher than those used in the pivotal trials. The MAH should discuss.*
- *No justification is provided for the differences between the two regimens for CINV. Nor is the breakdown of dosage by BSA related to the pharmacokinetic data. The MAH should provide simulations of the systemic exposure predicted by the different dosage regimens for a typical 6 month baby, a toddler and a typical 12 UK 12 year old. These profiles should be discussed in relation to comparable profiles in adults, and to what is known about the relationship between the PK and PD of ondansetron.*
- *Method of administration for CINV: The method of administration used in the supporting trial (dilution of ondansetron in 5% dextrose or 0.9% sodium chloride and administration over 15 minutes) is not reflected in the proposed SmPC. The product information should be amended to contain relevant specific advice.*

- *The SmPC (section 4.2) should state that no data are available for the prevention of delayed or prolonged CINV in children under 2 years of age. The product information should be amended to give clear recommendations regarding dose, method and timing of administration for CINV. These should not contain any conflicting advice and be supported by data. Cross-reference should be made to section 5.1.*

Summary of MAH's responses

The MAH states that the approved 5mg/m^2 dosing regimen was based on data from studies such as S3AM20 where doses were calculated according to the body surface area (BSA) of the child. The results from S3AM20 demonstrate that 8 mg orally twice daily can be safely administered to those subjects with BSA >1.2.

Assessor's comment
Note that the pivotal trials S3AB3006 and S3AB 4003 used an oral dose of 4mg ondansetron twice daily, not 8 mg and that no final study report has been made available for S3AM20.

The MAH states that it is generally accepted that BSA may not be accurately calculated if body weight is < 10 kg or height < 33 cm. However, a dose of approximately 0.15 mg/kg is not expected to be detrimental to the patient and has been used in clinical trials. Therefore, the MAH recommends a revised recommended dosing for children weighing <10 kg, with dosing by body weight only in this patient group.

The MAH proposes to add the following statement to the SmPC: 'Zofran injection may be diluted in 5% dextrose or 0.9% sodium chloride (see section 6.6) and administered over not less than15 minutes.'

The MAH proposes to amend the SmPC as follows:

4.2 Posology and Method of Administration

Chemotherapy and Radiotherapy

Children and Adolescents (aged 6 months to 17 years)

Oral Formulations and Injection:

The initial intravenous dose of ondansetron should be administered immediately before chemotherapy, based on bodyweight or BSA (see section 5.1). For patients less than 10 kg dosing by bodyweight is recommended (see Table A below). For patients over 10 kg dosing by Body Surface Area may be used (Table B).

Table A: Dosing by bodyweight

Body Weight	Day 1[b]	Day 2[b]	Duration of repeat dosing
	Initial Intravenous Dose[a]	Repeat Oral Dose	
< 40 kg	3 doses of 0.15 mg/kg every 4 hours	4 mg syrup or tablet every 12 hours	Up to 5 days
> 40 kg	3 doses of 0.15 mg/kg every 4 hours	8 mg syrup or tablet every 12 hours	Up to 5 days

a. Single intravenous dose must not exceed 8 mg.
b. Total daily dose must not exceed adult dose of 32 mg.

Table B: Dosing by Body Surface Area:

BSA	Day 1[b]	Day 2[b]	Duration of repeat dosing
	Initial Intravenous and Oral Dose[a]	Repeat Oral Dose	
< 0.6 m^2	5 mg/m^2 i.v. plus 2 doses of 2 mg syrup or tablet every 12 hours	2 mg syrup every 12 hours	Up to 5 days
0.6 to 1.2 m^2	5 mg/m^2 i.v. plus 2 doses of 4 mg syrup or tablet every 12 hours	4 mg syrup or tablet every 12 hours	Up to 5 days
> 1.2 m^2	8 mg i.v. plus 2 doses of 8 mg syrup or tablet every 12 hours	8 mg syrup or tablet every 12 hours	Up to 5 days

a. Single intravenous dose must not exceed 8 mg.
b. Total daily dose must not exceed adult dose of 32 mg.

Zofran injection may be diluted in 5% dextrose or 0.9% sodium chloride (see section 6.6) and administered over not less than 15 minutes.

There are limited data on the use of Zofran in the prevention of delayed or prolonged nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy in children below 2 years of age.

A calculation of actual doses resulting from the different proposed dosing regimens (BSA or weight-based) has been provided as follows overleaf:

Table 2: Calculation of actual doses for typical patients resulting from the proposed dosing regimens: ***Dose Regimen 1: weight based, Dose Regimen 2: BSA-based***

Age	Weight (kg)	BSA (m^2)	Dose Regimen 1		Dose Regimen 2	
			Day 1 Total Daily Dose	Day 2 Total Daily Dose	Day 1 Total Daily Dose	Day 2 Total Daily Dose
			IV	Oral	IV/Oral	Oral
6 months	8	0.39	3.6mg	4.4mg	3.0mg	2.2mg
3 years	14.5	0.62	6.3mg	4.4mg	4.2mg	4.4mg
12 years	39	1.27	17.6mg	8.8mg	10.8mg	8.8mg

1. In calculating the total daily dose a tablet bioavailability of 55% was assumed such that a 4mg tablet dose = 2.2mg and a 4mg i.v. dose = 4mg.

Assessor's comment

Note that the new 'alternative' weight-based dose recommendations (Dose Regimen 1) result is higher total daily doses that the currently licensed BSA-based regimen of 5mg/m^2 for all patients. Also, newly proposed oral dose recommendations for 12-year olds are double the currently licensed dose for children in either of the dose regimens (both weight- and BSA-based).

Simulations of the systemic exposure predicted by the different dosage regimens have only been provided for infants and toddlers (see Table 1, page 5). Systemic exposure predicted by the different dosage regimens for a typical UK 12 year old has not been modelled.

In addition, it is not clear to the assessor how the MAH derived at the doses stated in the table above.

Dose Regimen 2:

The currently licensed posology is as follows:

Children: Zofran may be administered as a single intravenous dose of 5mg/m2 immediately before chemotherapy, followed by 4mg orally twelve hours later. 4mg orally twice daily should be continued for up to 5 days after a course of treatment.

Assuming a single intravenous dose of 5mg/m^2 and the BSA given in the table above, the i.v. doses for 6 months, 3 years and 12 years would be 1.95mg, 3.1mg and 6.35mg.

Assuming one further single oral dose of 2mg (BSA < 0.6m^2) and 4mg (BSA > 0.6m^2) after 12 hours and a bioavailability of 55% of the oral dose, this would result in total daily doses of 3.05 mg, 5.3mg and 8.55 mg on Day 1.

Assessment of response

The proposed amendments regarding method of administration are acceptable.

The proposed limitation of the lower age range to 6 months is also considered acceptable, as there are no data from efficacy or PK data from trials in paediatric CINV patients aged <6 months and simulations predict accumulation with repeat dosing in young infants (see Figures 1 and 2, pages 4 and 5).

The proposed dose recommendations are not considered acceptable:

The present dose recommendation for the management of CINV is a single dose of 5mg/m^2 immediately before chemotherapy, followed by 4mg orally 12 hours later. No justification has been provided for the proposed increase to **2 doses** of 4mg (or 8mg see below).

The present dose recommendation for oral dosing of the entire paediatric population, including infants, children and adolescents, is 4mg twice daily. The MAH supports the proposed twofold increase of the recommended dose to 8mg twice daily with the statement '*the age at which a child can receive an adult dose is around 12 years old*'. The assessor considers this an inadequate justification: assuming an acceptable safety profile such a dose increase would have to be supported by data demonstrating superiority of 8mg over 4mg twice daily in terms of efficacy. No such data are available. **The dose recommendation of 8mg twice daily is therefore not considered acceptable.**

Furthermore, the proposed dose recommendations still result in different total daily doses for the same patient depending on whether doses are calculated by weight or BSA. For example, the oral dose for a child who weighs >10kg (and < 40kg) and has a BSA < 0.6m^2, the oral dose may be either 2mg twice daily or 4 mg twice daily p.o.

For a 12-year old (assuming a weight of 39kg and BSA 1.27m^2) the proposed dosing regimens for Day 1 would result in total daily dose may be as follows:

- Based on body weight: (0.15mg i.v. x 3) x 39kg **= 17.55 mg**
- Based on BSA: (5mg x 1.27m^2 = 6.35mg i.v.) + (2 x 4mg mg p.o. - assuming 55% bioavailability = 4.4mg) = **10.75mg**

The currently licensed dose for this 12-year old is 6.35mg (5mg x 1.27m^2) plus *one* dose of 4mg p.o. after 12 hours. Assuming that chemotherapy is administered in the morning, the oral dose would be administered in the evening, resulting in a total daily dose of 10.35mg, as opposed to the proposed 14.35mg resulting from 2 oral doses in addition to the i.v. dose on Day 1.

The newly proposed recommendation for 2 oral daily doses on Day 1 has not been justified by the MAH.

In the absence of robust data in support of the weight-based dosing regimen with resultant higher doses and in the absence of data supporting the proposed increase of oral doses on Day 1, **the proposed dosing by body weight is considered inadequately justified**.

However, it is recognised that the alternative weight-based dosing regimen has been licensed in the US for years. It has also recently been licensed in some European countries and is used in hospitals. The safety review has not identified any safety concerns particular to this dosing regimen (but note that the safety review did not specifically address BSA versus weight-based dosing).

Taking into consideration clinical practice in Europe and the safety profile of ondansetron, the provision of advice regarding weight-based dosing recommendations is considered acceptable, provided the prescriber is warned that this will result in higher total daily doses and exposure (both sections 4.2 and 4.4). The MAH should commit to providing a breakdown of paediatric adverse events (including reports from post-marketing) with the next PSUR.

The recommendation to administer 2 oral doses on Day 1 is not considered acceptable.

Taking into consideration the data presented in Table 1 (see page 5), the proposed reduction of the oral dose from 4mg to 2mg for those with a BSA <0.6 m^2 is considered acceptable.

The MAH has not provided any robust clinical trial data that would allow for an assessment of either efficacy or safety or ondansetron in the prevention of delayed or prolonged nausea and vomiting in CINV. The statement that there are '*limited* data' in this indication should therefore be amended to read '*There are* ***no data*** *from controlled clinical trials on the use of Zofran in the prevention of delayed or prolonged nausea and vomiting…. in children'*.

Assessor's conclusions

The issue may be considered **resolved provided the SmPC is amended as follows**:

Paediatric Population:

Chemotherapy -induced nausea and vomiting: Children aged ≥6 months and adolescents

The dose for chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based doing results in comparable efficacy but higher total daily doses – see sections 4.4.and 5.1.

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

Dosing by BSA:

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5mg/m^2. The intravenous dose must not exceed 8mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 1 below.

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	*Day1[a,b]*	*Days 2-6[b]*
< 0.6m^2	*5 mg/m^2 i.v.* *2 mg syrup or tablet after 12 hours*	*2 mg syrup or tablet every 12 hours*
> 0.6m^2	*5 mg/m^2 i.v.* *4 mg syrup or tablet after 12 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.*

Dosing by bodyweight:

Weight-based doing results in comparable efficacy but higher total daily doses – see sections 4.4. and 5.1.

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

Two further doses 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 twelve hours later and may be continued for up to 5 days. See Table 2 below.

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

Weight	*Day1[a,b]*	*Days 2-6[b]*
≤10kg	*Up to 3 doses of 0.15mg/kg at 4-hourly intervals.*	*2 mg syrup or tablet every 12 hours*
> 10kg	*Up to 3 doses of 0.15mg/kg at 4-hourly intervals.*	*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.*

Proposed text for section 5.1

Paediatric population:

Emesis and nausea induced by cancer 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. On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 i.v. + after 8-12 hrs ondansetron 4 mg p.o. or ondansetron 0.45 mg/kg i.v. + after 8-12 hrs placebo p.o. 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/m2 i.v. + ondansetron 4 mg p.o.) and 41% (0.45 mg/kg i.v. + placebo p.o.). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days.

A double-blind randomised placebo-controlled trial 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 i.v. together with 2-4 mg dexamethasone p.o. and in 71% of patients when ondansetron was administered as syrup at a dose of 8mg + 2- 4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in open-label, non-comparative, single-arm study. All children received three 0.15 mg/kg doses of intravenous 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 patients.

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

Prevention of post-operative 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). 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).

The MAH is invited to propose concise text to reflect the results of the pivotal PONV trials (prevention and treatment, S3A380, S3A381, S3GT11, S3GT09) in children aged 2-12 years.

4.5 Dose and method of administration PONV

Questions

- *Dosage for PONV: The recommendation of 0.1mg/kg up to 4mg as a single dose does not reflect clinical reality where ondansetron is usually prescribed at 0.1mg/kg two or three times a day as needed. In addition, because of the cost of ondansetron, it is usually reserved for at risk patients or patients undergoing procedures where PONV is more common. Accordingly, it would be useful to have more information on the PK and efficacy of multiple rather than single doses in risk patients as needed. In the absence of such data, the product information should clearly state that only one single dose of ondansetron should be administered.*
- *Method of administration for PONV: The recommendation of a 'slow' i.v. infusion is vague. No justification is provided for the recommendation to administer ondansetron after surgery for the prevention of PONV. (Proposed text: 'For prevention and treatment of PONV in paediatric patients …. ondansetron may be administered ….either prior to, at or after induction of anaesthesia, or after surgery'.) The product information should be amended to contain specific and unambiguous advice.*
- *The SmPC (section 4.2) should state that no data are available for the treatment of postoperative vomiting in children under 2 years of age. The product information should be amended to give clear recommendations regarding dose, method and timing of administration for PONV. These should not contain any conflicting advice and be supported by data. Cross-reference should be made to section 5.1.*
- *The results of the PONV trial should be reflected in section 5.1 of the SmPC (primary endpoint only).*

Summary of MAH's responses

There are no paediatric data on multiple doses for PONV. The company has revised the dosage schedule to advise that a single dose should be given for prevention and treatment of PONV.

The MAH proposes the following changes to the SmPC:

Section 4.2 Method of administration should be amended to recommend that the injection is given over not less than 30 seconds.

Regarding method of administration reference will be made in section 4.2 to section 6.6 which specifies recommended infusion solutions.

The proposed new text now reads as follows:

Post-Operative Nausea and Vomiting

Children and Adolescents (aged 1 month to 17 years):

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; slow i.v. injection is recommended for this purpose.

Injection:

For prevention ~~and treatment~~ of PONV 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 either prior to, at or after induction of anaesthesia~~, or after surgery~~.

For the treatment of PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of Zofran 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 limited data on the use of Zofran in the treatment of PONV in children below 2 years of age.

Assessment of response and conclusion

The proposed amendments are considered acceptable, with exception of the following statement:

There are limited data on the use of Zofran in the treatment of PONV in children below 2 years of age.

Only one of the submitted trials evaluated treatment of PONV in children (S3A381) and this trial did not include children under the age of 2 years.

In conclusion, this question can be considered **resolved provided 'limited data' is replaced by 'no data'.**

4.6 Additional safety data

Question Case narratives for postmarketing reports of deaths

The MAH should provide additional safety data as follows:

Case narratives for postmarketing reports of deaths in children and adolescents.

A review of respiratory disorders and a recommendation for the product information.

MAH's response (verbatim)

The case narratives for post marketing reports of deaths in children and adolescents are provided in Appendix 1. The GSK worldwide safety database was searched on 19 October 2007 with a data lock of 30 September 2007 for post-marketing reports of death in children and adolescents. A total of 24 reports of death were identified. Eleven reports involved males, ten reports involved females and three involved foetal deaths where the gender of the patient was not identified. Ten (42%) of the patients received ondansetron for chemotherapy induced nausea and vomiting (CINV), 3 (13%) for post-operative nausea and vomiting (PONV), 5 (21%) of the patients received ondansetron for unspecified nausea and vomiting. Six (25%) patients received ondansetron via in utero exposure. The age distribution of these patients can be seen below:

Age	Number of Patients
Foetal reports	4
Less than 1 year	3
1 to 4 years	5
5 to 12 years	6
13 to 17 years	6

Seventeen of the reports were confounded due to underlying disease, concomitant drugs, time to onset, concurrent conditions, past medical history, or insufficient information. The four foetal deaths included two voluntary terminations due to foetal abnormalities (A0129923A and B0302860A) one foetal death secondary to the mother's suicide 20 weeks after her last dose of ondansetron (A0375122B) and an intrauterine death reported in a patient diagnosed with synovial sarcoma who was receiving ondansetron for CINV (B0432255B). The causal relation cannot be excluded in three reports; however, all of these events occurred in the context of other significant complicating factors such as concomitant medications including anaesthetic agents, analgesic drugs, or concurrent conditions.

B0002672A. This 14-year-old underwent surgery for correction of severe thoracic scoliosis and a history of asthma. The patient received ondansetron for post-operative nausea the following day. The patient had received cyclizine for PONV and morphine for analgesia (20mg IV post-op, then 43.8 SC) postsurgery. A morphine PCA pump was set up. A possible morphine overdose was suspected and morphine infusion was stopped. The post-mortem diagnosis was hypoxic brain damage and respiratory depression. The reporting physician did not think the events were drug related.

A0043280A. This 11-year-old received ondansetron for post-operative nausea and vomiting prior to a tonsillectomy. Post procedure vital signs were good and there was no nausea or vomiting. The patient was discharged. Eight to 10 hours later the patient complained of abdominal cramping without emesis or diarrhoea. Twelve hours later the patient was pronounced dead on arrival at the local hospital. Post-mortem showed no clots in the oropharynx and no evidence of vascular surgical injury but there was blood in the gastric lumen. Reporting physician stated that the event was possibly related to ondansetron as a contributing factor in that it prevented vomiting which might have revealed the true extent of the post-operative bleeding.

A0587087A. This is a report of a 17-day-old who was exposed to ondansetron and paroxetine in utero who died from sudden infant death syndrome. Prenatal testing revealed no evidence of birth defects. Upon delivery the patient was 20 inches in length and weighed 7 pounds, 3 ounces, head circumference was 13.5 inches. APGAR score was 8/9. Post-mortem findings were normal and did not show any signed of ventricular septal defects.

There was no overall pattern to these events although the subjects underlying cancer and concurrent conditions were contributing factors. After review of all identified cases it was concluded that even though ondansetron could not be ruled out as a contributing factor in these deaths, there is no mechanism to explain the role of ondansetron in these deaths.

Question Review of hepatobiliary disorders

The MAH should provide additional safety data as follows: A review of hepatobiliary disorders and a recommendation for the product information.

Summary of MAH's responses

The MAH has submitted a review of their postmarketing safety database up to 30 September 2007. (Appendix 3 of the response document)

Assessor's comment
Note that this review specifically *excluded* adverse events reported from clinical trials.

There were 212 serious and non-serious reports of hepatobiliary disorders of which 181 were adult cases and 31 paediatric cases.

Of the 31 paediatric cases, 24 were spontaneous reports. The MAH states that 19 of the reports were confounded by concomitant medications, identifiable causes of the hepatobiliary dysfunction other than ondansetron, negative rechallenge or recovery of hepatic function while still on ondansetron. Details of the remaining 5 cases are provided.

A0008296A - is a report of a 10 year old girl who received oral ondansetron for cyclic vomiting associated with delayed emptying syndrome over the course of six months. Two to three days into her third course of therapy she became jaundiced. Concomitant medications included erythromycin, cisapride and ibuprofen. Her most recent course of therapy was reduced without symptoms.

A0044366A - is a report of a 10 year old girl who received i.v. ondansetron 1 mg/kg daily for weeks for treatment of nausea and vomiting of unspecified cause. She developed pancreatitis with elevated amylase and lipase, dilated common bile duct but no gallstones. Ondansetron was reduced and symptoms improved.

A0563895B - is a new born girl who showed mild jaundice and a total bilirubin of 9.9 mg/dL at 36 hours after taking ondansetron. Twelve hours later bilirubin had increased to 14.2 mg/dL. The neonate had been exposed to ondansetron in utero. Coombs test was positive and her bilirubin count was slowly climbing prior to discharge three days later. At last known follow-up approximately 18 months later the mother and baby were reported doing well.

B0416506A - is a report of an 18 year old male who received i.v. ondansetron for postoperative nausea. Concurrent medications included unspecified anaesthetics. Approximately one month post procedure the patient presented with fulminant hepatitis.

A0419341A - is an infant who received ondansetron in utero and via breast milk and subsequently developed liver failure. The infant's mother was taking ondansetron during and post pregnancy for nausea and vomiting and reported no adverse events. The case history of both the mother and infant is poorly documented. The infant was born with increased total bilirubin levels (unspecified) and was in liver failure at the time of reporting. The bilirubin levels had worsened and the event was unresolved.

The MAH has performed a Disproportionality Analysis using the MGPS (Multi-item Gamma Poisson Shrinker) method and concludes that this analysis has not identified hepatobiliary events as safety signal for any patient subpopulation.

Assessor's comment

The MGPS is considered appropriate when dealing with small numbers of reports. Signal scores EBGM05, defined as the lower 95% confidence interval limit of EBGM (Empirical Bayes Geometric Mean), are used to screen potential signals. A potential safety signal is usually defined as any drug-event combination that has signal score EBGM05 ≥ 2. The score for cytolytic hepatitis was 2.202 for AERS EB05 2007Q1 (Ondansetron – hepatobiliary system review, UM2007/00364/00, page 12). The MAH has not commented on this.

The MAH concludes '*While our experience with this patient population is limited, one can extrapolate the data to conclude that paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function*' but also states that '*there is no change required to the product information*'.

Assessor's comment

The latter two statements would appear to be contradictory. The warning statement proposed by the MAH should be included in section 4.4 of the SmPC.

Question Review of respiratory disorders

The MAH should provide additional safety data as follows: A review of respiratory disorders and a recommendation for the product information.

Summary of MAH's responses

The MAH has submitted a review of their postmarketing safety database up to 30 September 2007. (Appendix 2 of the response document).

The database contained 533 serious and non-serious reports in the Respiratory SOC. 69 (13%) were paediatric and 464 (87%) were adult patient reports. Of the paediatric respiratory reports, 68 (98.5%) were spontaneous reports:

Approximately 41% of the respiratory events were reported in association with an event of hypersensitivity or anaphylaxis. Hypersensitivity and anaphylactic/anaphylactoid reactions have been reported in association with the use of ondansetron. The ondansetron Global Datasheet defines the frequency of these events as rare (>0.01% and 0.1%).

Approximately 18% of the respiratory events were reported in association with significant concurrent clinical condition or adverse event (cardiac conditions, convulsions, congenital disorders). Seizures have been reported in association with the use of ondansetron. The ondansetron Global Datasheet defines the frequency of seizures as uncommon (>0.1% and 1.0%) and arrhythmias, chest pain with or without ST segment depression, bradycardia also as uncommon.

One event was a post-marketing study report of a 10-year-old boy who developed cough, fever and elevated C-reactive protein. A diagnosis of retinoic acid syndrome was made. The events resolved 12 days after onset and were considered related to tretinoin and not ondansetron by the investigator.

Details of 7 'key cases' are provided.

A0006792A - is an 18 month old male who was exposed to ondansetron in utero and experienced apnoea and bradycardia. No further information was provided with the report.

A0041021A - is a 10 year old male on his third day of his 6th cycle of at home chemotherapy for stage four rhabdomyosarcoma. He had received 0.15mg/kg of i.v. ondansetron and methyprednisolone 4mg/kg. At the completion of infusion the patient complained of dizziness and collapsed with no pulse and without breathing. Resuscitation attempts were unsuccessful. The patient had received ondansetron and chemotherapy (mesna, ifosfamide, etoposide) many times previously without incident. Reporting pharmacist indicated the event was unlikely due to ondansetron.

A0432090A - is an 11 year old girl who received i.v. ondansetron for an unspecified indication. Concurrent conditions included congenital heart disease. Concomitant medications included i.v. cefuroxim and p.o. clarithromycin. Approximately 1 hour after receiving ondansetron infusion the patient experienced respiratory failure and decreased oxygen saturation. Three hours later she died. The cause of death is unknown.

A0549211A - is a 1 year patient who received 2mg i.v. bolus ondansetron for acute vomiting and diarrhoea. Subsequently that same day the patient experienced respiratory depression and bradycardia. The patient received "reanimation by ambu" and the events resolved. Reporting physician considered the events related to ondansetron. No further information was provided with the report.

B0000725A - is a 20 month old girl who received ondansetron for treatment of chemotherapy induced nausea and vomiting. She had completed her seventh course of chemotherapy. The patient was doing well on day ten except for some recurrent vomiting, when she suddenly became very ill in the evening. Seven hours later her condition had further deteriorated and she died. The reporting physician commented that a possible relationship between ondansetron and the development of pulmonary symptoms which led to death must be investigated. At post mortem no clear cause of death was found although the examination revealed fleshy lungs due to either fulminant infection or previous damage resulting from fibrotic changes associated with bleomycin.

B0002672A - is a 14 year old female who underwent surgery and received 4mg i.v. ondansetron for postoperative nausea and vomiting. She was on morphine PCA concurrently. Within 60 minutes of receiving ondansetron her respiratory rate had slowed, she was agitated, arching her back, clenching her fists and she was not responding to commands. A morphine overdose was suspected. Rescue treatment was initiated although she remained unresponsive and brain death was confirmed. The cause of death post-mortem was hypoxic brain damage and respiratory depression. The reporting physician did not think the events were related to ondansetron.

G0007763A - is a 14 year old boy who experienced apnoea after receiving injectable ondansetron and metoclopramide. Apnoea occurred twice after receiving ondansetron and once after metoclopramide. Apnoea occurred 15-30 minutes after administration of each medication. The patient did not breathe for more than 20 seconds and oxygen saturation decreased to 70-80%. Symptoms resolved with stimulation.

In addition, the following adverse event reports from 3 'key' paediatric trials were provided:

One SAE report of respiratory depression in a one month old boy one day after receiving 0.2 mg/kg ondansetron. The episode occurred following fentanyl administration and resolved with manual ventilation and delivery of 0.4mg naloxone.

One SAE report of bronchospasm in a 10 month old boy on placebo.

One SAE report of nodal arrhythmia, hypoxia and hypocapnia in a 19 month old boy undergoing surgery. Approximately 36 minutes after receiving ondansetron the subject started to over-breath the ventilator and he converted to a junctional bradycardia. Treatment included intravenous atropine and all symptoms resolved within 5 minutes. Immediately prior to the event a small amount of air was observed in the IV line. The investigator considered the episode unrelated to ondansetron and possibly associated with intravenous air.

The MAH has performed a Disproportionality Analysis using the MGPS (Multi-item Gamma Poisson Shrinker) method. The MAH states that this analysis has not identified respiratory events as safety signal for any patient subpopulation.

Assessor's comment
EB05 scores ≥ 2 were reported for the following preferred terms: laryngeal oedema, respiratory arrest, respiratory depression, and stridor. An EB05 score of 1.99 was reported for apnoea. The MAH has not commented on these scores.

The MAH states that respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Assessor's comment
The warning statement proposed by the MAH should be included in section 4.4 of the SmPC.

Question Possible risks arising from the potential use of repeat doses for PONV in children under the age of 24 months

The MAH should address possible risks arising from the potential use of repeat doses for PONV in children under the age of 24 months, with a particular view to those aged 1-4 months, and in patients with an ASA physical status ≥ 3 and propose risk minimisation measures.

MAH's response (verbatim)

The Company recommends single doses for PONV. The dose schedule has been revised to include the words; a single dose is recommended for the prevention and/or treatment of PONV.

Question SmPC section 4.8

The safety information available for the paediatric population should be reflected in section 4.8.

Summary of MAH's responses

The MAH states that the reporting differences in the paediatric adverse events were not meaningful and that the safety of ondansetron in the paediatric population is comparable to that in the adult population. In fact the spectrum of events derived from the adult group was more extensive than that observed for the paediatric group.

The MAH proposes the following text for section 4.8: '*The adverse event profile in children and adolescents was comparable to that seen in adults.*'

Assessment of responses regarding safety and conclusion

It would appear that there are some safety signals in the respiratory SOC that will need to be addressed by the MAH. A review of the entire safety database for ondansetron would go beyond the scope of the current procedure, and the MAH is therefore requested to thoroughly address this issue in the next Periodic Safety Update Report. The same applies to hepatobiliary disorders.

The proposed statement for section 4.8 is accepted.

Issue resolved provided the MAH complies with the following:

The MAH must commit to thoroughly addressing the safety signals in the respiratory system and hepatobiliary disorders organ classes (SOCs) in the next Periodic Safety Update Report.

The paediatric information should be stated under the sub-heading '*Paediatric population*'.

Section 4.4. must be expanded to include a warning statement to reflect the following of the MAH's recommendations:

- Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.
- Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

4.7 Product Information

Questions

Section 4.2: see Questions 5.1.3 and 6.1.3 above

Section 5.1: see Question 6.1.4 above.

The MAH should propose a warning statement regarding interactions relating to QT-interval prolongation for SmPC section 4.5 Interactions. The proposed text should take into consideration that 5HT3-antagonists are likely to be administered together with chemotherapeutic regimens for childhood cancer that may themselves cause QT interval prolongation (e.g. arsenic trioxide) or are cardiotoxic and may thus increase the risk of arrhythmias (e.g. anthracyclines).

Section 5.2 should be amended to accurately and concisely reflect the PK data. The MAH's text proposal should take into account the data requested above.

MAH's responses section 4.5 (verbatim)

GSK does not believe that adding a statement regarding the potential QT-interval prolongation and increased risk of arrhythmias related to chemotherapeutic regimens that may be co-administered with 5HT3-antagonistes to section 4.5 (Interactions) of the Zofran SPC is appropriate and are not implementing this request.

The transient ECG changes, including QT-interval prolongation seen rarely with Zofran administration are already adequately addressed within section 4.4 (Special warnings and precautions for use) of the Zofran SPC. Current text below:

'Very rarely and predominantly with intravenous Zofran, transient ECG changes including QT interval prolongation have been reported'.

The statement being requested for inclusion regarding the adverse events associated with concomitant chemotherapeutic regimens would not, in the opinion of GSK, add any value to the SPC.

As standard practice a physician prescribing Zofran concomitantly with any chemotherapeutic regimen would review the full prescribing information for the co-administered medicinal product and as such will be fully aware of the respective adverse event profiles. The physician would therefore be alerted to any potential for the co-administered medicinal product to cause QT prolongation or cardiotoxic events and thus be fully aware of potential overlapping adverse event profiles.

It is considered that it is inappropriate to included statements in the Interactions section of an SPC relating to the potential for an additive effect on adverse events when medicinal products are given concomitantly. Rather, the interactions section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and in vivo pharmacokinetic studies.

Assessment of response and conclusion section 4.5

The MAH's response is not accepted.

Issue not resolved. The following text must be included via a variation application within three months of finalisation of this procedure (imposition):

'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)'

MAH's responses section 5.2 (verbatim)

In study S3A40319, a total of 51 patients were dosed and contributed safety data. Of these 41 patients provided sufficient PK data needed to calculate individual PK parameters (this was not a population PK study).

The arithmetic half-life values included in Table 12.4 of the CSR match the 3rd paragraph in Section 9.1 Pharmacokinetics under Discussion and Conclusions section of the CSR (p55):

The half-life in the >4 to 24 month old subjects (2.5 to 3.2 hours) was similar to the half-life in surgical patients 3 to 12 years old. Whereas, the half-life in the 1 to 4 month old group (6.2 to 7.2 hours) was about 2.5-fold longer than in the >4 to 24 month age group. No dose adjustment is necessary in the younger age group, as only a single dose of ZOFRAN is recommended for the treatment of postoperative vomiting.

Averaging the 2.5 hours (>4 to 24 month old age group) and 3.2 hours (1 to 4 month old age group) for the 0.2 mg/kg dose group produces an average of 2.85 or 2.9 hours. Similarly, averaging the 7.2 hours (>4 to 24 month old age group) and 6.2 hours (1 to 4 month old age group) for the 0.1 mg/kg dose group produces an average of 6.7 hours. It should be noted that the arithmetic mean values (Table 12.4 in CSR has both Arithmetic and Geometric Means) do not exactly match the geometric mean values provided in the in-text table of the CSR Section 7.3 Pharmacokinetic Results. Geometric mean data is quoted when summarizing S3A40319 data alone (in accordance with current Working Practice). However, when comparing to older studies, such as S3GK02, which did not calculate geometric mean values, then the standard arithmetic values should be compared.

The study report for clinical trial S3GK02 is provided in Appendix 4.

The Company has revised the text for Section 5.2 Pharmacokinetic Properties in response to the questions raised. The revised text is presented overleaf with new text in red italics and deleted text in blue strikethrough.

5.2. Pharmacokinetic Properties

Special Patient Populations

Children and Adolescents (aged 1 month to 17 years)

~~Oral formulations and Injection: In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg/kg ondansetron prior to undergoing surgery.~~ *In paediatric* ~~P~~patients aged 1 to 4 months *(n=19) undergoing surgery, weight normalised* ~~had a~~ clearance ~~when normalised to body weight that~~ was approximately 30% slower than in patients aged 5 to 24 months *(n=22)* but comparable to the patients aged 3 to 12 years. The half-life in the *patient population aged* 1 to 4 month ~~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. ~~No dose adjustment is necessary for patients aged 1 to 4 months as only a single i.v. dose of ondansetron is recommended for the treatment of postoperative nausea and vomiting.~~ 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 the 1 to 4 month patient population~~.

In ~~a study of 21~~ paediatric patients aged ~~between~~ 3 ~~and~~*to* 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron ~~following a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old)~~ 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* ~~these~~ changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 74 *paediatric cancer* patients aged 6 to 48 months ~~following~~ *and 41 surgery patients aged 1 to 24 months following intravenous* administration of ~~0.15 mg/kg i.v.~~ ondansetron. *Based on the population pharmacokinetic parameters for patients aged 1 month to 48 months, administration of the adult weight based dose (0.15 mg/kg intravenously* every 4 hours for ~~three~~ 3 doses~~) for the treatment of chemotherapy induced nausea and vomiting and 41 surgery patients aged 1 to 24 months following administration of a single 0.1 mg/kg or 0.2 mg/kg i.v. dose of ondansetron. Based on the population pharmacokinetic parameters~~

~~for subjects aged 1 month to 48 months, administration of a 0.15 mg/kg i.v. dose of ondansetron every 4 hours for three doses~~ would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery ~~subjects~~ *patients* (aged 5 to 24 months) ~~and previous~~, paediatric ~~studies in~~ cancer *patients* (aged 4 to 18 years), and surgical *patients* (aged 3 to 12 years) ~~subjects~~, at similar doses, *as shown in Table C. This exposure (AUC) is consistent with the exposure-efficacy relationship described previously in paediatric cancer subjects, which showed a 50% to 90% response rate with AUC values ranging from 170 to 250 ng.h/mL.*

Table C. Pharmacokinetics in Paediatric Patients 1 Month to 18 Years of Age

Study	*Patient Population (Intravenous Dose)*	*Age*	*N*	*AUC (ng.h/mL)*	*CL (L/h/kg)*	*Vd_{ss} (L/kg)*	*$T_{½}$ (h)*
				Geometric Mean			*Mean*
S3A40319[1]	*Surgery (0.1 or 0.2mg/kg)*	*1 to 4 months*	*19*	*360*	*0.401*	*3.5*	*6.7*
S3A40319[1]	*Surgery (0.1 or 0.2mg/kg)*	*5 to 24 months*	*22*	*236*	*0.581*	*2.3*	*2.9*
S3A40320 & S3A40319 Pop PK[2,3]	*Cancer/Surgery (0.15mg/kg q4h/ 0.1 or 0.2mg/kg)*	*1 to 48 months*	*115*	*257*	*0.582*	*3.65*	*4.9*
S3KG02[4]	*Surgery (2 mg or 4 mg)*	*3 to 12 years*	*21*	*240*	*0.439*	*1.65*	*2.9*
S3A-150	*Cancer (0.15mg/kg q4h)*	*4 to 18 years*	*21*	*247*	*0.599*	*1.9*	*2.8*

1. Ondansetron single intravenous dose: 0.1 or 0.2 mg/kg
2. Population PK Patients: 64% cancer patients and 36% surgery patients.
3. Population estimates shown; AUC based on dose of 0.15 mg/kg.
4. Ondansetron single intravenous dose: 2 mg (3 to 7 years) or 4 mg (8 to 12 years)

<u>Assessment of response and conclusion section 5.2</u>

The limited data provided are reflected in the SmPC text proposed by the MAH. The data are difficult to interpret. In the absence of further data the proposed text is considered acceptable.

The MAH is advised that the UK will require further analysis of PK data before a variation application can be granted.

5 FINAL RECOMMENDATIONS

The extension of the licensed age range for PONV to one month and the definition of the lower age limit for CINV of 6 months may be considered acceptable for the purpose of this procedure.

For PONV, only a single dose prophylaxis is considered acceptable.

Taking into consideration clinical practice in Europe and the safety profile of ondansetron, the provision of advice regarding weight-based dosing recommendations for CINV may be considered acceptable for the purpose of this procedure on the following provisions:

- The prescriber must be warned that this will result in higher total daily doses and exposure.
- The prescriber must be informed that the comparative efficacy of these two different dosing regimens has not been investigated in clinical trials and that cross-trial comparison indicate similar efficacy for both regimens. Cross-reference must be made to sections 4.4 and 5.1.
- The present wording 'Oral dosing can commence twelve hours later' must be maintained. The proposed dose recommendation of two oral doses on Day 1 of chemotherapy is not considered acceptable.
- The oral dose for children with a BSA <0.6 m2 must be 2mg.
- The oral dose must be limited to 2mg for children weighing ≤10kg.
- The available paediatric information as well as the limitations of the paediatric database must be clearly reflected in the product information and amended as outlined in Annex 1 to this report.
- The following statement must be included in section 4.4: *Chemotherapy -induced nausea and vomiting: When calculating the dose on an mg/kg basis and administering three doses at 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 indicate similar efficacy for both regimens – see section 5.1.*

In addition, section 4.4. must be expanded to include the following warning statements reflecting the MAH's recommendations:

- *Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.*

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

- The available data must be clearly described in 5.1.
- The following text must be included in section 4.5: '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)'. The relevant variation application must be submitted within three months of finalisation of this procedure.
- The MAH must commit to thoroughly addressing the safety signals in the respiratory system and hepatobiliary disorders organ classes (SOCs) in the next Periodic Safety Update Report.
- The paediatric information throughout the SmPC should be stated under the sub-heading 'Paediatric population'.

The SmPC should be amended in line with the text given in Annex 1.

The MAH is advised that the UK will require further analysis of PK data before a variation application can be granted. All the data (1 month to 18-44 year old patients) should be analysed to disclose variability in exposure with age over a wider age range than was done before. Clearance should be assessed in relation to body weight to the power 0.75, a maturation function should be included in the model, and PONV vs CINV should be assessed as a covariate over the wider age range.

Annex 1

SPC comparison Present – Proposed by MAH – Final text

<table>
<tr><th>SmPC Section</th><th>Present text</th><th>Text proposed by MAH</th><th>Final text</th></tr>
<tr><td>4.1</td><td>Zofran is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV).</td><td>No changes proposed</td><td><u>Adults:</u>
Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, Prevention and treatment of post-operative nausea and vomiting (PONV)
<u>Paediatric Population:</u>
Management of chemotherapy -induced nausea and vomiting in children aged ≥6 months
Prevention and treatment of post-operative nausea and vomiting in children aged ≥1 month</td></tr>
<tr><td>4.2</td><td><u>Chemotherapy and radiotherapy</u>
<u>Children:</u> Zofran may be administered as a single intravenous dose of 5mg/m2 immediately before chemotherapy, followed by 4mg orally twelve hours later. 4mg orally twice daily should be continued for up to 5 days after a course of treatment.
<u>Post-operative nausea and vomiting (PONV):</u>
<u>Children (aged 2 years and over):</u> For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia.
For treatment of established PONV in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of 0.1mg/kg up to a</td><td>4.2 Posology and Method of Administration
Chemotherapy and Radiotherapy
Children and Adolescents (aged 6 months to 17 years)
Oral Formulations and Injection:
The initial intravenous dose of ondansetron should be administered immediately before chemotherapy, based on bodyweight or BSA (see section 5.1). For patients less than 10 kg dosing by bodyweight is recommended (see Table A below). For patients over 10 kg dosing by Body Surface Area may be used (Table B).
Table A: Dosing by bodyweight
<table><tr><th rowspan="2">Body Weight</th><th>Day 1[a]</th><th>Day 2[b]</th><th rowspan="2">Duration of repeat dosing</th></tr><tr><th>Initial Intravenous Dose[a]</th><th>Repeat Oral Dose</th></tr><tr><td>< 40 kg</td><td>3 doses of 0.15 mg/kg every 4 hours</td><td>4 mg syrup or tablet every 12 hours</td><td>Up to 5 days</td></tr><tr><td>> 40 kg</td><td>3 doses of 0.15 mg/kg every 4 hours</td><td>8 mg syrup or tablet every 12 hours</td><td>Up to 5 days</td></tr></table>a. Single intravenous dose must not exceed 8 mg.
b. Total daily dose must not exceed adult dose of 32 mg.

….continued overleaf</td><td><u>Paediatric Population:</u>
<u>Chemotherapy -induced nausea and vomiting in children aged ≥ 6 months and adolescents</u>
The dose for chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based doing results in higher total daily doses compared to BSA-based dosing – see sections 4.4.and 5.1.
There are no data from controlled clinical trials on the use of Zofran in the prevention of chemotherapy-induced delayed or prolonged nausea and vomiting. There are no data from controlled clinical trials on the use of Zofran for radiotherapy-induced nausea and vomiting in children.
<u>Dosing by BSA:</u>
Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5mg/m2. The intravenous dose must not exceed 8mg.
Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 1 below.
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
<table><tr><th>BSA</th><th>Day1[a,b]</th><th>Days 2-6[b]</th></tr><tr><td>< 0.6m^2</td><td>5 mg/m^2 i.v.
2 mg syrup or tablet after 12 hours</td><td>2 mg syrup or tablet every 12 hours</td></tr><tr><td>> 0.6m^2</td><td>5 mg/m^2 i.v.
4 mg syrup or tablet after 12 hours</td><td>4 mg syrup or tablet every 12 hours</td></tr></table>a The intravenous dose must not exceed 8mg. b The total daily dose must not exceed</td></tr>
</table>

<table>
<tr><th>SmPC Section</th><th>Present text</th><th>Text proposed by MAH</th><th>Final text</th></tr>
<tr>
<td></td>
<td>maximum of 4mg.

There is limited data on the use of Zofran in the prevention and treatment of PONV in children under 2 years of age.</td>
<td>
Table B: Dosing by Body Surface Area:
<table>
<tr><th rowspan="2">BSA</th><th>Day 1[b]</th><th>Day 2[b]</th><th rowspan="2">Duration of repeat dosing</th></tr>
<tr><th>Initial Intravenous and Oral Dose[a]</th><th>Repeat Oral Dose</th></tr>
<tr><td>< 0.6 m²</td><td>5 mg/m² i.v. plus 2 doses of 2 mg syrup or tablet every 12 hours</td><td>2 mg syrup every 12 hours</td><td>Up to 5 days</td></tr>
<tr><td>0.6 to 1.2 m²</td><td>5 mg/m² i.v. plus 2 doses of 4 mg syrup or tablet every 12 hours</td><td>4 mg syrup or tablet every 12 hours</td><td>Up to 5 days</td></tr>
<tr><td>> 1.2 m²</td><td>8 mg i.v. plus 2 doses of 8 mg syrup or tablet every 12 hours</td><td>8 mg syrup or tablet every 12 hours</td><td>Up to 5 days</td></tr>
</table>
a. Single intravenous dose must not exceed 8 mg.
b. Total daily dose must not exceed adult dose of 32 mg.

Zofran injection may be diluted in 5% dextrose or 0.9% sodium chloride (see section 6.6) and administered over not less than 15 minutes.

There are limited data on the use of Zofran in the prevention of delayed or prolonged nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy in children below 2 years of age.

Post-Operative Nausea and Vomiting

Children and Adolescents (aged 1 month to 17 years):

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; slow i.v. injection is recommended for this purpose.

Injection:

For prevention ~~and treatment~~ of PONV 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 either prior to, at or after induction of anaesthesia~~, or after surgery~~.

For the treatment of PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of Zofran 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 limited data on the use of Zofran in the treatment of PONV in children below 2 years of age.
</td>
<td>
adult dose of 32 mg.

<u>Dosing by bodyweight:</u>

Weight-based dosing results in higher total daily doses compared to BSA-based dosing – see sections 4.4. and 5.1.

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

Two further doses 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 twelve hours later and may be continued for up to 5 days. See Table 2 below.

Table 2: Weight-based dosing for Chemotherapy - Children aged ≥6 months and adolescents
<table>
<tr><td>Weight</td><td>Day1[a,b]</td><td>Days 2-6[b]</td></tr>
<tr><td>≤10kg</td><td>Up to 3 doses of 0.15mg/kg at 4-hourly intervals.</td><td>2 mg syrup or tablet every 12 hours</td></tr>
<tr><td>> 10kg</td><td>Up to 3 doses of 0.15mg/kg at 4-hourly intervals.</td><td>4 mg syrup or tablet every 12 hours</td></tr>
</table>
a The intravenous dose must not exceed 8mg. b The total daily dose must not exceed adult dose of 32 mg.

<u>Prevention of post-operative nausea and vomiting:</u>

The text proposed by the MAH is accepted provided the following changes are made

Heading to be amended to read:

'Paediatric population

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

'Limited data' to be replaced by 'no data': There are ~~limited~~ <u>no</u> data on the use of Zofran for the treatment of postoperative vomiting in children under 2 years of age.
</td>
</tr>
<tr>
<td>4.4</td>
<td></td>
<td>No changes proposed in submitted SmPC, but body text of response</td>
<td>The following statements should be added:</td>
</tr>
</table>

SmPC Section	Present text	Text proposed by MAH	Final text
		document recommends: Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions. Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.	Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions. Paediatric Population: Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function. Chemotherapy -induced nausea and vomiting: When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/m^2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicate similar efficacy for both regimens – see section 5.1.
4.5	No information on interaction with QT-prolonging drugs	No changes proposed	**The following statements must be added:** 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)' *Assessor's comment: section 4.4 reads: Very rarely and predominantly with intravenous Zofran, transient ECG changes including QT interval prolongation have been reported. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.*
4.8	No information regarding paediatric population	The adverse event profile in children and adolescents was comparable to that seen in adults.	The paediatric information should be stated under the sub-heading 'Paediatric population'. The proposed text is acceptable.
5.1	No information regarding paediatric population	No changes proposed	<u>Paediatric population:</u> <u>Chemotherapy -induced nausea and vomiting:</u> 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. On the days of chemotherapy, patients received either ondansetron 5 mg/m2 i.v. + after 8-12 hrs ondansetron 4 mg p.o. or ondansetron 0.45 mg/kg i.v. + after 8-12 hrs placebo p.o. 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/m2 i.v. + ondansetron 4 mg p.o.) and 41% (0.45 mg/kg i.v. + placebo p.o.). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. A double-blind randomised placebo-controlled trial 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 i.v. together with 2-4 mg dexamethasone p.o. and in 71% of patients when ondansetron was administered as syrup at a dose of 8mg + 2- 4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days.

SmPC Section	Present text	Text proposed by MAH	Final text
			The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in open-label, non-comparative, single-arm study. All children received three 0.15 mg/kg doses of intravenous 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 patients. Another open-label, non-comparative, single-arm study investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4mg for children aged < 12 yrs and 8 mg for children aged ≥ 12 yrs (total no. of children n= 28). Complete control of emesis was achieved in 42% of patients. Prevention of post-operative 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). 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). **The MAH is invited to propose concise text to reflect the results of the pivotal trials in the prevention and treatment of PONV in children aged 2-12 years. (**S3A380, S3A381, S3GT11, S3GT09)
5.2	In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300mL/min at 12 years of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at 3 years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum)	5.2. Pharmacokinetic Properties 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 month was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron. In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.	Paediatric population: In the absence of further data the proposed text is considered acceptable. **The MAH is advised that the UK will require further analysis of PK data before a variation application can be granted.**

SmPC Section	Present text	Text proposed by MAH	Final text
	compensates for these changes and is effective in normalising systemic exposure in paediatric patients.	Population pharmacokinetic analysis was performed on 74 paediatric cancer patients aged 6 to 48 months and 41 surgery patients aged 1 to 24 months following intravenous administration of ondansetron. Based on the population pharmacokinetic parameters for patients aged 1 month to 48 months, administration of the adult weight based dose (0.15 mg/kg intravenously every 4 hours for 3 doses) would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery patients (aged 5 to 24 months), paediatric cancer patients (aged 4 to 18 years), and surgical patients (aged 3 to 12 years), at similar doses, as shown in Table C. This exposure (AUC) is consistent with the exposure-efficacy relationship described previously in paediatric cancer subjects, which showed a 50% to 90% response rate with AUC values ranging from 170 to 250 ng.h/mL. Table C. Pharmacokinetics in Paediatric Patients 1 Month to 18 Years of Age	

Study	Patient Population (Intravenous Dose)	Age	N	AUC (ng.h/mL)	CL (L/h/kg)	Vd_{ss} (L/kg)	$T_{½}$ (h)
				Geometric Mean			Mean
S3A40319[1]	Surgery (0.1 or 0.2mg/kg)	1 to 4 months	19	360	0.401	3.5	6.7
S3A40319[1]	Surgery (0.1 or 0.2mg/kg)	5 to 24 months	22	236	0.581	2.3	2.9
S3A40320 & S3A40319 Pop PK[2,3]	Cancer/Surgery (0.15mg/kg q4h/ 0.1 or 0.2mg/kg)	1 to 48 months	115	257	0.582	3.65	4.9
S3KG02[4]	Surgery (2 mg or 4 mg)	3 to 12 years	21	240	0.439	1.65	2.9
S3A-150	Cancer (0.15mg/kg q4h)	4 to 18 years	21	247	0.599	1.9	2.8

1 Ondansetron single intravenous dose: 0.1 or 0.2 mg/kg

2 Population PK Patients: 64% cancer patients and 36% surgery patients.

3 Population estimates shown; AUC based on dose of 0.15 mg/kg.

4 Ondansetron single intravenous dose: 2 mg (3 to 7 years) or 4 mg (8 to 12 years)