CLINICAL REVIEW

Application Type	NDA
Submission Number	20-007
Submission Code	S-035
Letter Date	September 28, 2004
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Reviewer Name	Lolita A. Lopez, M.D.
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Established Name	Ondansetron Hydrochloride
(Proposed) Trade Name	Zofran
Therapeutic Class	$5HT_3$ -Antagonist
Applicant	GlaxoSmithKline (GSK)
Priority Designation	Priority
Formulation	Intravenous (IV)
Dosing Regimen	Single dose of 0.1 mg/kg and Three doses of 0.15 mg/kg/dose
Indication	Prevention of PONV Prevention of CINV
Intended Population	Pediatric patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The approval of intravenous ondansetron hydrochloride (IV Zofran®) is recommended by this Medical Officer for the following indications:

- Prevention of chemotherapy induced nausea and vomiting (CINV) in pediatric cancer patients 6 months to 48 months old who are receiving moderately to highly emetogenic chemotherapy
- Prevention of postoperative induced nausea and vomiting (PONV) in pediatric patients 1 month to 24 months old undergoing routine surgery under general anesthesia.

For the indication of prevention of CINV, three doses of 0.15 mg/kg/dose of IV Zofran is recommended. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, and subsequent doses should be administered 4 hours and 8 hours after the first dose. The drug should be infused over 15 minutes.

For the prevention of PONV, a single dose of 0.1-mg/kg for patients weighing ≤ 40 kg, with a maximum single dose of 4-mg for patients > 40 kg is recommended. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review (see Appendix) and the sNDA Team's labeling recommendations.

1.2 Recommendation on Postmarketing Actions

No postmarketing commitments are recommended for this sNDA.

1.2.1 Risk Management Activity

No risk management steps are recommended.

1.2.2 Required Phase 4 Commitments

There are no Phase 4 commitments recommended.

1.2.3 Other Phase 4 Requests

There are no Phase 4 requests for this sNDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zofran® (ondansetron hydrochloride), a selective 5-HT_3 antagonist, is an oral and parenteral antiemetic agent. It is the first selective serotonin blocking agent to be marketed. The injection form was originally approved for the treatment of chemotherapy-induced nausea/vomiting by the FDA on January 4, 1991; oral dosage forms were approved for the treatment of post-operative nausea/vomiting in April 1995 and an orally disintegrating tablet, Zofran ODT® was approved in February 1999.

Zofran IV (intravenous) is currently approved for the prevention of chemotherapy-induced nausea and vomiting (CINV) in adults and children 4 to 18 years old (three doses of 0.15 mg/kg), and for the prevention of post-operative nausea and vomiting (PONV) in adults and children 2 to 12 years old (single 0.1 mg/kg dose). Although there is little information available on the use of Zofran in pediatric patients younger than 2 years of age, it is being used off-label substantially in pediatric population younger than it is indicated for.

The Agency has identified Zofran® as a drug for which additional pediatric clinical trial data (on the IV formulation) would be useful to clinicians and their patients. The sponsor, GlaxoSmithKline, submitted a Proposed Pediatric Study Request (PPSR) on September 28, 1999; and on June 29, 2001, a Written Request was issued by the Agency. Pediatric studies were asked to be conducted to evaluate efficacy, safety, and pharmacokinetics of Zofran in pediatric cancer patients aged 6 months to 48 months and surgical patients 1 month to 24 months old. The studies submitted in this NDA efficacy supplement are in response to the Written Request issued to the sponsor which was amended on March 1, 2002; March 11, 2004; and September 7, 2004. The sponsor conducted three clinical studies: a pharmacokinetic study (*S3A40319)*, and two efficacy and safety studies *(S3A40320* and *S3A40323).* A total of 816 patients were enrolled.

Study S3A40319 is a phase IV, multi-center, pharmacokinetic study of Zofran IV that enrolled 51 pediatric patients 1 month to 24 months of old who had routine surgery under general anesthesia. The doses utilized were 0.1 mg/kg and 0.2 mg/kg. The results of this study were submitted and reviewed by the Agency prior to selecting doses and initiating subsequent efficacy studies, S3A40320 and S3A40323.

To support the indication of prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric cancer patients 6 months to 48 months old, the sponsor conducted Study S3A40320. This is an open-label, safety and efficacy study of three doses of Zofran IV (0.15 mg/kg/dose) in 76 cancer patients 6 months to 48 months old receiving moderately to highly emetogenic chemotherapy. The dose selected for this study was based on the results of the PK evaluation performed in Study S3A40319, a review of the worldwide literature on the use of Zofran in children, a survey of the use of Zofran by oncologists in the Children's Oncology Group (COG), and the current prescribing information for prevention of CINV and vomiting in older (> 4years) pediatric patients.

To support the indication of prevention of post-operative nausea and vomiting (PONV) in surgical patients 1 month to 24 months old, Study S3A40323 was conducted. This is a randomized, double-blind, placebo-controlled study assessing the efficacy of a single dose of Zofran IV (0.1 mg/kg) for the prevention of PONV in pediatric surgical patients 1 to 24 months old who are undergoing general anesthesia. A total of 689 patients were enrolled, 335 received Zofran.

1.3.2 Efficacy

Zofran IV is already indicated for the prevention of CINV in adults and children 4 to 18 years old, and prevention of PONV in adults and children 2 to 12 years old. Two other $5HT_3$-antagonists, granisetron and dolasetron, are indicated for CINV are in patients 2 to 12 years old. In addition, dolasetron is indicated for the prevention of PONV in patients 2 to 12 years old.

The sponsor evaluated pediatric surgical patients 1 to 24 months to claim for the indication of prevention of PONV as well as cancer patients 6 to 48 months to claim for the indication of prevention of CINV. These studies were conducted in fulfillment of the Written Request; the study endpoints were appropriate and the study design and population were adequate for the indication proposed.

In order to determine the appropriate dose to be used in the efficacy trial, a pharmacokinetic study S3A40319 was conducted. This was a phase IV, multi-center, two-arm, single dose PK study of Zofran IV that enrolled 51 pediatric surgical patients 1 month to 24 months old who underwent general anesthesia. (See Biopharm Review for detailed comments). The doses utilized were 0.1 mg/kg and 0.2 mg/kg. The results of this study were reviewed by the Agency prior to selecting doses and initiating subsequent efficacy studies, S3A40320 and S3A40323.

<u>Prevention of Post-operative Induced Nausea and Vomiting (PONV)</u>

The indication of prevention of PONV was supported by Study S3A40323, a randomized, double-blind, placebo-controlled multicenter study assessing the efficacy of Zofran IV (0.1 mg/kg) for the prevention of PONV in pediatric surgical patients 1 to 24 months old who are undergoing routine surgery under general anesthesia. A total of 689 patients were enrolled, 336 received Zofran. The dose selected for this study was based on the results from the PK study (S3A40319), the current prescribing information in pediatric patients, and a literature review.

The primary efficacy endpoint in this study was the proportion of patients who experienced at least one episode of emesis during the 24-Hour Assessment Phase. The results of the study show that there were more patients who experienced one or more emetic episodes in the placebo group, 93/335 (28%) compared to the Zofran group, 38/335 (11%).The common odds ratio was

0.33 (95% CI, 0.22 to 0.5; p<0.0001), which suggests that the odds of vomiting after receiving Zofran was roughly a third compared to placebo. The results were similar in the intent-to-treat (ITT) and per-protocol (PP) population.

The secondary efficacy endpoints include: time to first emetic episode, time to first rescue medication, incidence of emetic episodes, proportion of patients receiving rescue medication, and proportion of patients with emetic episodes after the receipt of rescue medication(s).

The overall median time to first emetic episode (ITT population) was 135 minutes (2.2 hours) for the patients in the placebo group and 207 minutes (3.5 hours) for patients in the Zofran group. A total of 32 (10%) of placebo and 18 (5%) of Zofran patients received rescue antiemetic medication(s) or withdrew from the study prematurely. The overall median time to first rescue/withdrawal was 91 minutes and 85 minutes after placebo and Zofran, respectively.

The Zofran group had more patients who had a complete response (no emetic episode) compared to the placebo group (89% vs. 72%) and fewer therapeutic failures (3% vs. 8%). Therapeutic failure was defined as 3 or more emetic episodes, use of rescue medication, or withdrawal from the study. It is this reviewer's opinion that the most practical and clinically meaningful endpoint is the percentage of patients with a complete response (no emetic episode) within the 24-hr Assessment Phase. This will be the most useful information that clinicians could use when using this medication.

Of the patients who received rescue medication in the placebo group, 7 (33%) of the patients experienced between 1 and >5 emetic episodes following administration of rescue medication. None of the patients in the Zofran group experienced emesis following administration of the rescue medication. It appears that further emetic episodes are prevented when rescue medication is administered in patients who received prophylactic Zofran, compared to patients who had placebo alone.

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

The indication of CINV was supported by S3A40320, an open-label study of three doses of Zofran IV (0.15 mg/kg) in 76 cancer patients 6 to 48 months old receiving moderately to highly emetogenic chemotherapy. The dose selected for this study was based on the results from the PK study (S3A40319), a survey of the use of Zofran by oncologists in the Children's Oncology Group (COG) and the current prescribing information.

There were four co-primary efficacy endpoints in this study: incidence of emesis, proportion of patients who received supplemental antiemetic medications during the 24-hour assessment period, time to first rescue antiemetic medication, and parent/guardian overall satisfaction. The ITT population included all patients who received at least one dose of study medication and chemotherapy. The PP population was defined as those patients who received the study medication, chemotherapy, and who met all important protocol requirements, i.e., did not have any major protocol deviations.

The study has shown that for the prevention of CINV, more than half of the patients (56%, ITT; 61%, PP) had a complete response (no emetic episode) to Zofran. This is comparable to the percentage of complete response in cancer patients older than 48 months of age (complete response=58%). In addition, S3A40320 has shown that a greater proportion of patients did not require rescue medications (69%, ITT; 83% PP) and majority (80%) of the patients parents/guardian are very satisfied with its use. Below is a tabulated summary of the principal efficacy endpoints results.

Table 1: Primary Efficacy Endpoints Results (S3A40320)

		ITT N = 75	PP N=46
		n (%)	n (%)
Incidence of emetic episodes	Complete Response (0 emetic episode)	42 (56)	28 (61)
	Partial Response (1-2 emetic episodes)	8 (11)	8 (17)
	Failure (3 emetic episodes, use of rescue meds, or withdrawal)	25 (33)	10 (22)
Summary of patients who received rescue medication	NO	52 (69)	38 (83)
	YES	23 (31)	8 (17)
Median time to first rescue antiemetic medication		955 mins (~16 hrs) (n = 23)	791mins (~13hrs) n=8
Median time to first emetic episode		625 mins (~10 hrs) (n = 21)	
Parent/guardian satisfaction	Very Satisfied	60 (80)	35 (76)

Sponsor's table

1.3.3 Safety

Safety was evaluated in the three pediatric studies submitted in this NDA. Study S3A40319 is an open-label PK study in surgical patients, S3A40320 is an open-label study in chemotherapy patients and S3A40323 is a randomized, placebo-control trial in surgical patients.

A total of 797 patients received the study medication; 334 patients received placebo and 463 patients received Zofran IV. Among the patients who received Zofran IV, 51 surgical patients were randomized to receive a single dose of either 0.1 or 0.2 mg/kg of Zofran IV (S3A40319), 76 chemotherapy patients received three doses of 0.15 mg/kg of Zofran IV (S3A40320) and 336 surgical patients received a single dose of 0.1 mg/kg of Zofran IV (S3A40323).

Adverse events were reported in 35% (18/51) of patients in S3A40319, 28% (21/76) of patients in S3A40320 and 18% of patients in both placebo and Zofran groups (59/334 placebo, 62/336 Zofran) in S3A40323. The most commonly (≥ 2%) reported adverse events in the three studies were decreased oxygen saturation, vomiting, agitation, nausea, irritability, stomach discomfort, pyrexia, bronchospasm, post-procedural pain and diarrhea.

Serious adverse events were reported in five patients (1%) who received Zofran and three (1%) patients in patients who received placebo. The serious adverse events reported in patients who received Zofran were: convulsions, dehydration, respiratory depression, staphylococcal infection; one patient reported nodal arrhythmia, hypocapnia and hypoxia. In patients who received placebo, tachycardia, bronchospasm and exacerbated pain were reported. All of these serious adverse events are regarded by the investigator as not related to the study medication except for tachycardia (placebo group), which could possibly be related to the study medication. No deaths are reported during the course of these studies. The studies submitted in this NDA did not identify any new safety concerns in the use of Zofran IV in pediatric patients 1 month to 48 months.

1.3.4 Dosing Regimen and Administration

The sponsor is proposing the following dosing regimen for the indication of CINV and PONV:

Prevention of Chemotherapy-Induced Nausea and Vomiting (6 months to 48 months old):

Three doses of *0.15 mg/kg/dose IV*. The first dose to be administered 30 minutes before the start of emetogenic chemotherapy and subsequent doses to be administered 4 hours and 8 hours after the first dose. The drug should be infused over 15 minutes.

Prevention of Postoperative-Induced Nausea and Vomiting (1 month to 24 months old)

Weight ≤ 40 kg: Single dose of *0.1-mg/kg IV*.
Weight > 40 kg: Single dose of *4-mg IV*.
The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes immediately prior to or following anesthesia induction, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery.

The safety and efficacy of the above doses have been demonstrated in older children. The proposed dosing regimen is similar to the current recommendations in older children for the prevention of CINV (4 to 18 years old) and prevention of PONV (2 to 12 years of age), as stated in the label. The dosing regimen proposed by the sponsor is appropriate for the indication being sought.

In adults, the mean elimination half-life of Zofran is 5.7 hours; for those age 15 years and younger, half-life is about 2.4 hours. PK study S3A40319 submitted by the sponsor in this sNDA indicates that Zofran clearance and volume of distribution were dependent on body weight and age. Clearance of Zofran in surgical patients 1 to 4 months old is lower than patients who are

>4 to 24 months old, but comparable to weight-normalized clearance in patients aged 3 to 12 years. The half-life in surgical patients aged >4 to 24 months was similar to the half-life in surgical patients aged 3 to 12 years (mean=2.9 hr). For patients who are 1 to 4 months old, half-life was 6.7 hours (~ 2.5-fold longer than the >4 to 24 months patients). This is may be a reflection of age-related changes in metabolic systems. See Dr. Suliman Al-Fayoumi's Biopharmaceutics Review of this NDA for details. No dose adjustment is necessary for patients aged 1 to 4 months since only a single dose of IV Zofran is recommended for the prevention of PONV; however, clinicians should be made aware that clearance in this age group is lower, half-life is longer and therefore they should be monitored more closely. This should be reflected in the label of this drug.

As reflected in the label, in adult patients with impaired hepatic function (Child-Pugh score of $\geq$ 10), a single maximum dose of 8 mg infused over 15 minutes for PONV is recommended. No dosage adjustment is recommended in renally-impaired or geriatric patients.

There is no specific antidote for ondansetron overdose; management is supportive. In adults, individual doses as large as 150 mg and total daily dosages (three doses) as large as 252 mg (more than 10 times the recommended daily dose) have been administered intravenously without significant adverse events. Transient episodes of "sudden blindness" (amaurosis) and hypotension have been reported by patients in an overdose setting. A vasovagal episode with transient second-degree heart block was observed in a patient who had an infusion of 32 mg ondansetron over 4 minutes. This is reflected in the current label of Zofran.

1.3.5 Drug-Drug Interactions

The concomitant use of apomorphine with drugs of the $5HT_3$ antagonist class (including ondansetron, granisetron, dolasetron, palonosetron, and alosetron) is contraindicated.
This is based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

Ondansetron (Zofran®) is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.

1.3.6 Special Populations

The population evaluated in this NDA are pediatric surgical patients who are 1 month to 24 months old and post-chemotherapy patients who are 6 months to 48 months old.

Geriatric

No new data submitted by the sponsor regarding this population. No dosage adjustment is necessary for elderly patients.

Chronic Hepatic Disease

No new information is supplied regarding this population. It is reflected in the ondansetron label that in adult patients with mild-to-moderate hepatic impairment, clearance is reduced twofold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In adult patients with severe hepatic impairment (Child-Pugh score of 10 or greater), clearance is reduced twofold to threefold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. A total daily dose of 8 mg should not be exceeded in adult patients with severe hepatic impairment.

Chronic Renal Impairment

No new data were submitted regarding this population.

Race

No new significant data were submitted regarding this population.

Nursing Mothers

Ondansetron is excreted in the breast milk of rats but it is not known whether ondansetron is excreted in human milk. Therefore, caution should be exercised when this drug is administered to a nursing woman because many drugs are excreted in human milk.

Pregnancy Use

This efficacy supplement has no new information on pregnant women. Ondansetron is currently listed as Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. However, in pregnant women, there are no adequate and well-controlled studies; therefore, this drug should be used during pregnancy only if clearly needed.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zofran® (ondansetron hydrochloride) is a selective 5-HT_3 antagonist available as an oral and parenteral antiemetic agent. Ondansetron preferentially blocks the serotonin 5-HT_3 receptors found centrally in the chemoreceptor trigger zone and peripherally at vagal nerve terminals in the intestines. It is still unknown whether the action of this drug is mediated centrally, peripherally, or a combination of both. Emesis during chemotherapy and radiation therapy appears to be associated with the release of serotonin from enterochromaffin cells in the small intestine. Blocking these nerve endings in the intestines prevents signals to the central nervous system.

Ondansetron is also a weak antagonist of the 5-HT_4 receptor, and may bind to other serotonin receptors as well. It has also been demonstrated that it binds to the opioid μ receptor, the clinical implications of which is uncertain. It has no dopamine-receptor blocking activity; multiple oral doses slows colonic transit time.

2.2 Currently Available Treatment for Indications

There are other 5-HT_3 receptor antagonists approved for the prevention of nausea and vomiting in children who are two years and older. Dolasetron is approved for the prevention of both chemotherapy-induced nausea and vomiting (CINV) and postoperative-induced nausea and vomiting (PONV) in pediatric patients two years and older. Granisetron is approved only for CINV in this age group. Below is a table of approved anti-emetic medications in children.

Table 2: Approved Anti-emetic Medications in Children

	PONV	CINV
Ondansetron	≥ 2 yrs. old	≥4 yrs. old
Dolasetron	≥ 2 yrs. old	≥ 2 yrs. old
Granisetron	Adults	≥ 2 yrs. old

Reviewer's table

There is currently no approved treatment for the prevention nausea and vomiting in pediatric patients less than two years old.

2.3 Availability of Proposed Active Ingredient in the United States

Zofran is the first selective serotonin blocking agent to be marketed. The injection form was originally approved for the treatment of chemotherapy-induced nausea/vomiting by the FDA on January 4, 1991. Oral dosage forms were approved for the treatment of post-operative nausea/vomiting in April 1995; an orally disintegrating tablet, Zofran ODT® was approved in February 1999.

2.4 Important Issues With Pharmacologically Related Products

The concomitant use of drugs in the $5HT_3$ antagonist class (including ondansetron, granisetron, dolasetron, palonosetron, and alosetron) with apomorphine is contraindicated. Apomorphine is a non-ergoline dopamine agonist indicated for the acute, intermittent treatment of hypomobility, "off" episodes associated with advanced Parkinson's disease. This contraindication is based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

2.5 Presubmission Regulatory Activity

Zofran IV is currently approved for the prevention CINV in adults and children 4 to 18 years old and PONV in adults and children 2 to 12 years old. There is little information available on the use of Zofran in pediatric patients younger than 2 years of age. Zofran was identified by the Agency as a drug for which additional pediatric clinical trial data would be useful to clinicians and their patients. The sponsor, GlaxoSmithKline, submitted a Proposed Pediatric Study Request (PPSR) on September 28, 1999. On June 29, 2001, a Written Request was issued by the Agency to the sponsor. Pediatric studies were asked to be conducted to evaluate efficacy, safety, and pharmacokinetics of Zofran in pediatric cancer patients aged 6 months to 48 months, and pediatric surgical patients 1 month to 24 months old. The studies submitted in this NDA efficacy supplement are in response to the Written Request which was amended on March 1, 2002, March 11, 2004 and September 7, 2004. The following are dates and the corresponding amendments:

- March 1, 2002: The Agency modified the date of submission of study reports from June 26, 2004 to December 30, 2004 as requested by the sponsor.
- March 11, 2004: Due to the sponsor's difficulty in recruiting pediatric cancer patients 6 months to 12 months old (S3A40320) and refusal of parents to subject their children to a study because of their very young age, the Agency amended the Written Request to include data from surgical patients in the population PK analysis of pediatric cancer patients.
- September 3, 2004: The word "must" was replaced by "should" in stating specific information on ethnic and racial information in the Written Request.

2.6 Other Relevant Background Information

Zofran has been marketed worldwide since 1990 and has not known to be withdrawn from the market due to safety reasons.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

No new CMC or animal toxicology studies were submitted in this supplemental NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The data utilized in this review were based on the sponsor's electronic submission, and the Agency's amended Written Request was used as a reference. Included in the sponsor's electronic submission are three studies: a PK study (S3A40319) which was the basis of the dose used in the subsequent studies; S3A40320, an-open label safety and efficacy study in cancer patients 6 to 48 months old; and S3A40323, a randomized, double-blind, placebo-controlled safety and efficacy study in surgical patients 1 to 24 months old. A search and summary of the worldwide literature on the use of Zofran in the pediatric population was also submitted by the sponsor.

4.2 Tables of Clinical Studies

Table 3: Clinical Trials in Support of 20-007, S-035

Type of Trial	*Trial Name*	*Objective*	*Design*	*Dosage and Administration*	*Patients*	*Duration of Treatment*
Primary						
Efficacy and Safety	**S3A40320**	**To obtain safety and efficacy data on Zofran administered as 0.15 mg/kg IV x 3 doses**	**Open-label, single-arm, multicenter with a 24-hour assessment period.**	**Three doses of 0.15mg/kg IV doses of Zofran administered prophylactically for CINV**	**76 pediatric cancer patients 6 to 48 months old receiving moderately to highly emetogenic chemotherapy**	**24 hours**
Efficacy and Safety	**S3A40323**	**To evaluate the safety and efficacy of a single dose of 0.1 mg/kg of Zofran IV**	**Randomized, double-blind placebo-controlled, multi-center single-dose with a 24-hour assessment period.**	**Single-dose of 0.1 mg/kg IV Zofran administered prophylactically for PONV Matching Placebo**	**670 pediatric surgical patients 1 to 24 months old**	**24 hours**
Supportive						
PK	**S3A40319**	**To evaluate safety, tolerability and PK of two doses of IV Zofran**	**Phase IV, non-randomized, multi-center, two-arm, single-dose**	**Single-dose of 0.1 or 0.2 mg/kg of IV Zofran administered prophylactically for PONV**	**51 pediatric surgical patients 1 to 24 months old**	**24 hours**

Reviewer's table

4.3 Review Strategy

Three trials were reviewed in this efficacy supplement, two pivotal trials (S3A40319 and S3A40323) and one PK trial (S3A40319). The two pivotal trials were primarily emphasized in the efficacy review (the PK trial was supportive) while all three trials were included in the safety review. A literature review was also conducted to support safety and efficacy.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted for this NDA. Results of their investigation is still pending at the time this review was written.

4.5 Compliance with Good Clinical Practices

The sponsor states that this research was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including the 1996 version of the Declaration of Helsinki. Written informed consent was obtained from each patient's parent(s) or legal guardian(s) prior to the performance of any study-specific procedures. The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board.

4.6 Financial Disclosures

An FDA form 3454 was submitted certifying that the sponsor have not entered into any financial arrangement with the listed clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study and stated that their clinical investigators had no financial interest to disclose.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Ondansetron is known to undergo extensive metabolism, mainly by hydroxylation, followed by glucuronide or sulfate conjugation. In adults, the mean elimination half-life is 5.7 hours; for those age 15 years and younger, half-life is about 2.4 hours.

PK study S3A40319 submitted by the sponsor in this sNDA shows that Zofran clearance and volume of distribution were found to be dependent on body weight and age. Since body weight and age are highly correlated, dosing based on weight (mg/kg) is recommended. The half-life in surgical patients aged >4 to 24 months was similar to the half-life in surgical patients aged 3 to 12 years (mean=2.9 hr). For patients aged 1 to 4 months, half-life was 6.7 hours (~ 2.5-fold

longer than the >4 to 24 months patients). The change in clearance from neonates to adult may be a reflection of age-related changes in metabolic systems. No dose adjustment is necessary for patients aged 1 to 4 months since only a single dose of IV Zofran is recommended for the prevention of PONV. See Dr. Suliman Al-Fayoumi's Biopharmaceutics Review for details.

In vitro metabolism studies have shown that ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2). Therefore, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, no dosage adjustment is recommended for patients on these drugs due to limited available data.

In adult patients with mild-to-moderate hepatic impairment, clearance is reduced twofold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normal patients. In patients with severe hepatic impairment (Child-Pugh score 2 of 10 or greater), the maximum total daily dose should not exceed 8 mg (in adults) because clearance is reduced 2 to 3 fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours.

The concomitant use of apomorphine (a non-ergoline dopamine agonist) with drugs of the $5HT_3$ antagonist class (including ondansetron) is contraindicated. This is based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron. The route of metabolism of apomorphine in humans is not known. The potential routes of metabolism in humans include sulfation, N-demethylation, glucuronidation and oxidation.

5.2 Pharmacodynamics

Ondansetron is a selective 5-HT_3 receptor antagonist. It is not certain whether its antiemetic action in chemotherapy-induced emesis is mediated centrally in the chemoreceptor trigger zone of the area postrema or peripherally on the vagal nerve terminals or both.

As reflected in the label, in normal volunteers, single I.V. doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another study in six normal male volunteers, a 16-mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers.

5.3 Exposure-Response Relationships

As mentioned in the pharmacokinetics section (5.1) above, Zofran clearance and volume of distribution were found to be dependent on body weight and age. An $AUC_{0-\infty}$ of greater than

250 ng per h/mL achieved with a dose of 0.1 mg/kg/dose would be expected to safely prevent emesis in at least 60% of the postoperative pediatric patients ages 1 month to 24 months, based on the 60% to 68% complete response rate (no emetic episodes) achieved in three previous Phase III studies. It was agreed upon by the sponsor and the Agency that this percentage is acceptable.

In addition, three doses of 0.15 mg/kg of Zofran in cancer patients 6 months to 48 months old would result in systemic exposure levels similar to those achieved in cancer patients 4 years and older (complete response= 58%) and would be expected to provide adequate protection against CINV.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This sNDA is submitted to expand the population for which IV Zofran is indicated and to include additional efficacy information in surgical pediatric patients younger than 24 months and cancer patients younger than 48 months old. New information will be added in the following sections of the label: Clinical Pharmacology, Clinical Trials, Precautions, Adverse Reactions and Dosage and Administration. The proposed indications in this submission are:

- Prevention of chemotherapy-induced nausea and vomiting (CINV)in pediatric patients 6 months to 48 months
- Prevention of post-operative induced nausea and vomiting (PONV) in pediatric patients 1 month to 24 months

6.1.1 Methods

In order to determine the appropriate dose to be used in the efficacy trial, a pharmacokinetic study (S3A40319) was conducted. This was a phase IV, multi-center, two-arm, single dose PK study of Zofran IV that enrolled 51 pediatric surgical patients 1 month to 24 months of old who had general anesthesia. The doses utilized were 0.1 mg/kg and 0.2 mg/kg. The results of this study were reviewed by the Agency prior to selecting doses and initiating subsequent efficacy studies, S3A40320 and S3A40323.

To support the indication of prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric cancer patients 6 months to 48 months old, the sponsor conducted Study S3A40320. This is an open-label, safety and efficacy study of three doses Zofran IV (0.15 mg/kg) in 76 cancer patients on moderately to highly emetogenic chemotherapy. The dose selected for this study was based on the results of the PK evaluation of Study S3A40319, a review of the worldwide literature on the use of Zofran in pediatric patients, a survey of the use of Zofran by oncologists in the Children's Oncology Group (COG), and the current prescribing information for prevention of chemotherapy-induced nausea and vomiting in older (>4 years) pediatric patients.

To support the indication of prevention post-operative nausea and vomiting (PONV) in surgical patients 1 month to 24 months old, Study S3A40323 was conducted. This is a randomized, double-blind, placebo-controlled multicenter study assessing the efficacy of single dose of Zofran IV (0.1 mg/kg) for the prevention of PONV in pediatric surgical patients 1 to 24 months old who are undergoing routine surgery under general anesthesia.

6.1.2 General Discussion of Endpoints

The study endpoints utilized in this sNDA were appropriate in evaluating the efficacy of Zofran. These were: adverse events, number of emetic episodes during the treatment period, time to rescue and incidence of adverse events.

Prevention of Post-operative Induced Nausea and Vomiting (PONV)

> The primary efficacy endpoint in this study was the proportion of patients who experienced at least one episode of emesis during the 24-Hour Assessment Phase.
>
> The secondary efficacy endpoints include: time to first emetic episode, time to first rescue medication, incidence of emetic episodes, proportion of patients receiving rescue medication, and proportion of patients with emetic episodes after the receipt of rescue medication(s).
>
> The median time to first emetic event was calculated in those patients who had an emetic event, or who were assumed to have had an event due to premature withdrawal or receipt of rescue antiemetic medication.

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

> There were four co-primary efficacy endpoints in this study: incidence of emesis, proportion of patients who received supplemental antiemetic medications during the 24-hour assessment period, time to first rescue antiemetic medication, and parent/guardian overall satisfaction.

The efficacy parameters used in assessing the efficacy of Zofran in this NDA were appropriate. In my opinion, the most practical and clinically meaningful endpoint is the percentage of patients with a complete response (no emetic episode) within the 24-hr Assessment Phase. This will be the most useful information that clinicians could use when using this medication.

6.1.3 Study Design

The indication of prevention of PONV was supported by Study S3A40323, a randomized, double-blind, placebo-controlled multicenter study assessing the efficacy of single dose Zofran

IV (0.1 mg/kg) in pediatric patients 1 to 24 months old who are undergoing routine surgery under general anesthesia. A total of 689 patients were enrolled, 336 received Zofran.

In S3A40323, the study design and the size of population were both adequate for the study. The methods used in the study to minimize bias were appropriate. A double-blind methodology was maintained throughout the trial unless there is an emergency which involves the patient's welfare. The sponsor employed a randomization scheme that resulted in a comparable treatment arms with regards to demographic and baseline characteristics (ASA[1] Classification, surgical status and type of surgery). Patients were also stratified according to opioid use since it is well known that opioid use increases the incidence of emesis.

The indication of CINV was supported by S3A40320, an open-label, multi-center study of three doses of Zofran IV (0.15 mg/kg) in 76 cancer patients 6 to 48 months old receiving moderately to highly emetogenic chemotherapy. The dose selected for these studies was based on the results of the PK study (S3A40319), a literature search on the use of Zofran and the current prescribing information.

In S3A40320, the study was open-label and not placebo controlled, this is likely due to ethical reasons. Randomizing a cancer patient receiving moderately to highly emetogenic chemotherapy to receive placebo is concomitant to depriving him/her of receiving optimal care which could have potential detrimental effects. However, it would have been possible to conduct an active-control trial in patients 24 to 48 months old comparing Zofran to other approved antiemetic medications for this age such as dolasetron or granisetron. However, for patients younger than 24 months, the design would still have to be open-label since there is no approved anti-emetic medication for this age. It is this reviewer's opinion that the study design used by the sponsor provides a reasonable assessment of benefit in the use of Zofran IV in this population. This study design and patient population replicates the studies that have been conducted in the past with pediatric cancer patients older than 4 years old.

6.1.4 Efficacy Findings

In order to determine the appropriate dose to be used in the efficacy trial, a PK study (S3A40319) was conducted and reviewed by the Agency prior to selecting doses and initiating subsequent efficacy studies, S3A40320 and S3A40323. S3A40319 was a phase IV, multi-center, two-arm, single dose (0.1 mg/kg and 0.2 mg/kg dose) that enrolled 51 pediatric surgical patients 1 month to 24 months of old who had general anesthesia.

Prevention of Post-operative Induced Nausea and Vomiting (PONV)

The indication of prevention of PONV was supported by S3A40323, a randomized, double-blind, placebo-controlled, multicenter (22 in US and 6 in Canada) study assessing the efficacy of

1 American Society of Anesthesiologists

single dose Zofran IV (0.1 mg/kg) in 1 month to 24 months old patients who are undergoing routine surgery under general anesthesia. A total of 689 patients were enrolled, 336 received Zofran.

The primary efficacy endpoint in this study was the proportion of patients who experienced at least one episode of emesis during the 24-Hour Assessment Phase. The results of the study show that there were more patients who experienced one or more emetic episodes in the placebo group, 93/335 (28%) than in the Zofran group, 38/335 (11%).The common odds ratio was 0.33 (95% CI, 0.22 to 0.5; p<0.0001), which suggests that the odds of vomiting after taking Zofran was approximately a third compared to placebo. The results were similar in the intent-to-treat (ITT) and per-protocol (PP) population.

Emetic episodes were stratified according to opioid and non-opioid use; the percentage (58%) of patients in each stratum was well-balanced. It is believed that patients receiving opioids were likely to experience emesis than those not receiving opioids; this is evident in this study as well. The stratum-specific odds ratios were 0.37 (95% CI, 0.22-0.62; p=0.0001) for opioid and 0.28 (CI, 0.14-0.56; p=0.0002) for non-opioid. Overall, patients on Zofran had less episodes of emesis compared to placebo regardless of opioid use.

The secondary efficacy endpoints include: time to first emetic episode, time to first rescue medication, incidence of emetic episodes, proportion of patients receiving rescue medication, and proportion of patients with emetic episodes after the receipt of rescue medication(s).

- The overall median time to first emetic episode (ITT population) was 135 minutes (2.25 hrs) for the placebo group and 207 minutes (~3.5 hrs) for the Zofran group. This shows that the median time to first emetic episode was longer for patients in the Zofran group regardless of opioid use.
- A total of 32 (10%) of placebo and 18 (5%) of Zofran patients received rescue antiemetic medication(s) or withdrew from the study prematurely. The overall median time to first rescue/withdrawal was 91 minutes in the placebo group and 85 minutes in the Zofran group. There is a tendency for the patients in the Zofran group to receive rescue earlier than the placebo group.
- There were more patients in the Zofran group had more complete response compared to the placebo group (89% vs. 72%) and fewer therapeutic failures (3% vs. 8%). See table 4 below.

Table 4: Incidence of Emetic Episodes – ITT Population (S3A40323)

	Treatment Group			
	Placebo		Zofran	
	N=335		N=335	
	n	(%)	n	(%)
Complete Response (0 emetic episode)	242	(72)	297	(89)
Partial Response 1-2 emetic episodes	57	(17)	19	(6)
Therapeutic Failure>2 emetic episodes, use of rescue medications or withdrawal from the study	26	(8)	9	(3)
Incomplete/Missing Data	10	(3)	10	(3)

Sponsor's electronic submission S3A40323 p. 54

- Rescue medication was administered to 6% (21/336) of patients in the placebo group and 2% (6/335) of the of patients in the Zofran group.[2]
- None of the patients in the Zofran group had emesis after administration of rescue medication compared to 7 (33%) in the placebo group who experienced more than one emetic episode.

The parent/guardian's satisfaction with study medication was also evaluated using a five-point scale, and the following were reported: Very satisfied = 92%, Somewhat satisfied = 6%, Neither satisfied nor dissatisfied = 2%, Somewhat dissatisfied < 1%, Very dissatisfied = 0. A great proportion of parents/guardians were very satisfied with the use of Zofran IV.

This reviewer agrees with the sponsor's findings that ondansetron is better than placebo for the primary endpoint (proportion of patients who experienced at least one episode of emesis) as well as for the secondary endpoints regardless of opioid use. In my opinion, the most clinically meaningful endpoint result is the percentage of patients with a complete response (no emetic episode) within the 24-hr Assessment Phase. The percentage of patients (89%) with a complete response in this study is quite impressive and it provides very useful information that clinicians could use when using this medication.

Dr. Milton Fan's Biometrics Review also confirms that results statistically significant in favor of ondansetron on "complete response" and were consisted among countries, race, gender, age, ASA and most surgery types. See Dr. Milton Fan's Statistical Review of this NDA.

2 Rescue medications that were administered included dexamethasone, dimenhydrinate, dimeticone, dolasetron, metoclopramide, and ondansetron. It should be noted that none of these medications is approved for the prevention of nausea and vomiting for children less than 2 years old.

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

The indication of prevention of CINV was supported by S3A40320, an open-label, multi-center study of three doses of Zofran IV (0.15 mg/kg) in 76 cancer patients 6 to 48 months old receiving moderately to highly emetogenic chemotherapy. This study was conducted in 22 centers: US, 16; Spain, 2; and 1 each in Australia, Austria, Canada, and Israel. The dose selected for this study was based on the results from the PK study (S3A40319), a survey of the use of Zofran by oncologists in the Children's Oncology Group (COG) and the current prescribing information.

There were four co-primary efficacy endpoints in this study: incidence of emesis, proportion of patients who received supplemental antiemetic medications during the 24-hour assessment period, time to first rescue antiemetic medication, and parent/guardian overall satisfaction.

A total of 42/75 (56%) patients in the ITT and 28/46 (61%) patients in the PP population had a complete response to Zofran; 69% in the ITT and 83% in the PP population did not receive rescue medication. Majority (~80%) of the patients' parents/guardian are very satisfied with its use. The proportion of patients who were considered as treatment failure was consistent to the proportion of patients who received rescue medications (33% and 31% respectively); the median time to first rescue medication is ~16 hrs. Below is a tabulated summary of the principal efficacy endpoints results.

Table 5: Primary Efficacy Endpoints Results (S3A40320)

		ITT N = 75	**PP N=46**
		n (%)	**n (%)**
Incidence of emetic episodes	*Complete Response* (0 emetic episode)	42 (56)	28 (61)
	Partial Response (1-2 emetic episodes)	8 (11)	8 (17)
	Failure (3 emetic episodes, use of rescue meds, or withdrawal)	25 (33)	10 (22)
Summary of patients who received rescue medication	NO	52 (69)	38 (83)
	YES	23 (31)*	8 (17)
Median time to first rescue antiemetic medication		**955 mins (~16 hrs)** (n = 23)	**791mins (~13hrs)** n=8
Median time to first emetic episode		**625 mins (~10 hrs)** (n = 21)	
Parent/guardian atisfaction	Very Satisfied	60 (80)	35 (76)

Adapted from sponsor's electronic submission S3A40320 p.4

*It should be noted that this percentage increases to 43% if the patients who received prophylactic dexamethasone are included. Dexamethasone is considered as a standard of antiemetic care in some patients, its prophylactic use was not prohibited during the study but was taken into consideration in the efficacy analyses.

It should be noted that in practice and in this trial, prophylactic dexamethasone was given as part of a chemotherapy (not as a rescue medication) in some cancer patients, its use in this study was taken into consideration in the efficacy analyses due to its anti-emetogenic effect. In a study by Alvarez, et.al., a randomized, double-blind study that evaluated 33 patients on highly emetogenic chemotherapy, results showed that combination of ondansetron and dexamethasone is superior to ondansetron alone in controlling emetic episodes in children.[3] The population studied was small, but this will be an interesting population to evaluate in the future. Results in this study (S3A40320) with regard to dexamethasone use is difficult to interpret because of the lack of control.

The results in this study has shown that prevention of emesis (complete response=56%) in pediatric patients 6 months to 48 months was similar to patients older than 48 months old (complete response= 58%). The success rate of this study is comparable to the efficacy rate of Zofran in preventing CINV in cancer patients 4 years and older.

6.1.5 Clinical Microbiology

This section is not applicable to this submission.

6.1.6 Efficacy Conclusions

For the indication of prevention of PONV, results of Study S3A40320 has shown that overall, ondansetron is better than placebo for the primary endpoint (11% vs. 28%) (95% CI, 0.22 to 0.5; $p<0.0001$), proportion of patients who experienced at least one episode of emesis as well as for the secondary endpoints regardless of opioid use. The secondary efficacy endpoints include: time to first emetic episode, time to first rescue medication, incidence of emetic episodes, proportion of patients receiving rescue medication, and proportion of patients with emetic episodes after the receipt of rescue medication(s). There were more patients in the Zofran group had more complete response compared to the placebo group (89% vs. 72%) and fewer therapeutic failures (3% vs. 8%). In addition, results were statistically significant in favor of ondansetron on "complete response" and were consistent among countries, race, gender, age, ASA and most surgery types.

For the indication of prevention of CINV, results of study S3A40323 have shown that 56% of patients had complete response (i.e., no emetic episode), which is comparable to the response (58%) in patients older than 48 months old. Thirty-three percent (33%) were considered as treatment failure and 31% received antiemetic medication. The median time first rescue antiemetic medication was ~16 hours and 80% of parent/guardian were very satisfied with the

3 Alvarez O, Freeman A, et.al. Randomized Double-Blind Crossover Ondansetron-Dexamethasone vs. Ondansetron-Placebo Study for the Treatment of CINV in Pediatric Patients with Malignancies. J. Ped Hematology/Oncology1995;145-1550.

medication. This study shows that Zofran has a clear benefit in patients receiving moderately to highly emetogenic chemotherapy when given as a prophylaxis and the results replicate the efficacy of Zofran in patients older than 48 months old.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety was evaluated in the three pediatric studies submitted in this NDA. The studies were reviewed individually and includes: S3A40319, an open-label PK study in surgical patients; S3A40320, an open-label study in chemotherapy patients; and S3A40323, a randomized, placebo-control trial in surgical patients. The sponsor assessed safety by monitoring adverse events (AEs) and serious adverse events (SAEs), and by performing physical examinations on patients. The only laboratory evaluations performed in these studies were baseline liver function tests (LFTs: ALT (SGPT), AST (SGOT), total bilirubin, and alkaline phosphatase); investigators were to repeat these laboratory measurements if clinically indicated.

In study S3A40319, a total of 32 adverse events (including 3 serious adverse events: convulsions, dehydration and respiratory depression) were reported by 18/51 (35%) patients during the study. None of these AEs were classified as severe except for the 3 mentioned serious adverse events; these serious adverse events resolved without sequelae except for the patient who developed convulsion. More patients in the 0.1 mg/kg group experienced at least one AE compared to the 0.2 mg/kg group; however, the number of patients in each arm is too small to draw a meaningful conclusion. The most commonly (>5%) reported adverse events in this study were decreased oxygen saturation, vomiting, and agitation.

In study S3A40320, 76 pediatric cancer chemotherapy patients received three doses of 0.15 mg/kg/dose of Zofran IV. A total of 21 (28%) of patients had one or more adverse events; none were severe or serious. The most common ($\geq$ 2%) adverse events reported were nausea, irritability and stomach discomfort. None of the reported adverse events were related to the study drug except for rash, which could be possibly related to the Zofran use.

In study S3A40323, 670 surgical patients received a single dose of the study medication; Zofran, 336 and Placebo, 334. Eighteen percent (18%) of patients in each treatment group had one or more adverse events. In the Zofran group, the most common ($\geq$ 2%) adverse events reported were pyrexia and diarrhea; in the placebo group, pyrexia, bronchospasm and post-procedural pain. Most of these AEs were classified as mild. The following were classified as severe: pain, laryngospasm and irritability (placebo group) and hypercapnia, hypoxia and nodal arrhythmia (all 3 events reported by a single patient in the Zofran group). None of these severe AEs were considered related to the study drug. Three patients in the placebo and 2 patients in the Zofran group (1% each group) had non-fatal adverse events which were most likely not related to the study drug.

The studies submitted in this NDA did not identify any new safety concerns in the use of Zofran IV in pediatric patients 1 month to 48 months old and the safety profile is similar to Zofran use in patients older than 4 years old.

7.1.1 Deaths

There were no deaths reported in the studies included in this supplemental NDA.

7.1.2 Other Serious Adverse Events

Serious adverse events were reported in five patients (1%) who received Zofran and three (1%) patients in patients who received placebo. The serious adverse events reported in patients who received Zofran were: convulsions, dehydration, respiratory depression, staphylococcal infection; one patient reported all three events, nodal arrhythmia, hypocapnia and hypoxia. In patients who received placebo, tachycardia, bronchospasm and exacerbated pain were reported. As with the investigator's opinon, this reviewer agrees that none of these serious adverse events can be attributed to Zofran.

7.1.3 Dropouts and Other Significant Adverse Events

There were a total three patients who were withdrawn from the study due to reported adverse events. Patient 25116 (S3A40320) discontinued from the study per the mother's request due to a dislodged IV catheter after 9 minutes of initial Zofran IV infusion. This incident of accidental dislodging of IV cannot be possibly related to Zofran use. In study S3A40323, two patients who were on placebo were discontinued from the study due to bronchospasm (patient 24019) and tachycardia (patient 24352).

The Written Request identified drug-specific safety considerations which includes constipation, extrapyramidal reactions, redness/inflammation at the injection site, rash, hypersensitivity reactions, seizures and liver function abnormalities. Among these identified concerns, constipation (1), rash (2) and redness/inflammation at the injection site (1) were reported in patients who received Zofran.

In addition, only baseline liver function tests (SGPT, SGOT, bilirubin and alkaline phosphatase) were assessed and no follow-up assessment was done. The sponsor stated that (in S3A40323), it was anticipated that the vast majority of patients would be outpatients, making it logistically impractical to require that patients return to the clinic for follow-up laboratory assessments and in study S3A40320 a risk-benefit consideration was assessed and an effort was made to minimize the total amount of blood drawn from each patient and due to the lack of a randomized control group and polypharmacy, abnormalities would be difficult to interpret. In both studies, the sponsor's were to repeat these laboratory tests if clinically indicated. None of the patients required a repeat liver function test due to an adverse event.

7.1.5 Common Adverse Events

Adverse events were directly monitored during the Prestudy, Treatment, and Post-treatment. Due to the very young age and limited verbal communication skills of the patients in the study, monitoring of AEs was dependent on direct observation. The parents or guardians also provided their input on the children's condition. For those who were outpatients (surgical patients in S3A40323), parents or guardians documented adverse events on a diary card and provided the information to study personnel in a telephone call at the end of the 24-Hour Assessment Phase. The personnel inquired about adverse events by asking the following standard questions of the parent/guardian:
1. "Has your child had any other medical problems or seemed to act differently in any way since receiving study medication (S3A40320) / surgery (S3A40323) ?"
2. "Has your child needed to take any medicines, other than those provided in this study, since his/her last assessment?"

Verbatim adverse events were coded using the Medical Dictionary for Regulatory Activities (MEDRA). The tables below list the most common adverse events per study.

Table 6: Most Commonly Reported Adverse Events (>5% of patients)
Study S3A40319

	IV Zofran Dose				
	0.1 mg/kg		0.2 mg/kg		Total
Age Group	1 to 4 m n=12	> 4 to 24 m n=12	1 to 4 m n=15	> 4 to 24 m n=12	N=51
Decreased O_2 Saturation[1]	1 (8%)	3 (25%)	0 (0%)	1 (8%)	5 (10%)
Vomiting[2]	2 (17%)	1 (8%)	1 (7%)	1 (8%)	5 (10%)
Agitation	2 (17%)	1 (8%)	0 (0%)	0 (0%)	3 (6%)

Adapted from sponsor's electronic submission S3A40319 p. 52
1 Reported in table as Abnormal blood gas level
2 Reported in table as Nausea and vomiting

Table 7: Summary of Most Frequent Adverse Events (S3A40320)
(≥to 2% in either treatment group)

Adverse Event	Zofran (N = 76)	
	n	(%)
Any adverse event	21	(28)
Nausea	5	(7)
Irritability	3	(4)
Stomach Discomfort	2	(3)

Adapted from sponsor's electronic submission S3A40320 p.52

Table 8: Summary of Most Frequent Adverse Events (≥to 2% in either treatment group) Study S3A40323

	Treatment Group			
Adverse Event	**Placebo**		**Zofran**	
	(N = 334)*		**(N = 336)***	
	n	**(%)**	**n**	**(%)**
Any Event	59	(18)	62	(18)
Pyrexia	14	(4)	14	(4)
Bronchospasm	6	(2)	2	(<1)
Post-procedural pain	6	(2)	4	(1)
Diarrhea	3	(<1)	6	(2)

Adapted from sponsor's electronic submission S3A40323 p. 61

***Note that one patient, (Subject 35383.23460) was randomized to placebo but actually received ZOFRAN. Therefore, the number of subjects in the ITT and Safety populations differed by one.**

7.1.6 Less Common Adverse Events

The number of patients in this study is not adequate to detect or evaluate less common adverse events.

7.1.7 Laboratory Findings

The only laboratory studies performed were baseline liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and total bilirubin. No follow-up assessments were done; however, laboratory test were to be repeated if clinically indicated. No patients were reported to need a follow-up laboratory assessment. No other laboratory studies were performed in this sNDA.

7.1.8 Vital Signs

Blood pressure and heart rate were obtained on the day that chemotherapy was administered prior to administration of the first dose of Zofran (S3A40320) or prior to induction of anesthesia, within 5 minutes after administration of study medication (S3A40323), and again at the end of the 24-Hour Assessment Phase or at the time of discharge, whichever occurred first.

In the placebo-controlled study, S3A40323, there were no clinically significant differences detected in blood pressure or heart rate between the placebo and Zofran groups.

7.1.9 Electrocardiograms (ECG)

No ECG evaluation was done in this NDA.

7.1.10 Immunogenicity

No data was provided regarding immunogenicity.

7.1.11 Human Carcinogenicity

The label of Zofran states that carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day, respectively. It was not mutagenic in standard test for mutagenicity.

7.1.12 Special Safety Studies

There are no special safety studies done in this sNDA.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

7.1.14 Human Reproduction and Pregnancy Data

Zofran is listed as Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

7.1.15 Assessment of Effect on Growth

This NDA did not specifically assess the effect of Zofran on growth. With the 14 years of experience with the use of Zofran, it is unlikely that a previously undetected rare event will now be found to occur in this young population. Late effects can not be conclusively ruled out.

7.1.16 Overdose Experience

There is no specific antidote for ondansetron overdose; management is supportive. In adults, individual doses as large as 150 mg and total daily dosages (three doses) as large as 252 mg (more than 10 times the recommended daily dose) have been administered intravenously without significant adverse events. Transient episodes of “sudden blindness" (amaurosis) and hypotension (and faintness) have been reported by patients in an overdose setting. A vasovagal episode with transient second-degree heart block was observed in a patient who had an infusion of 32 mg ondansetron over 4 minutes. This is reflected in the current label of Zofran.

7.1.17 Postmarketing Experience

Zofran has been marketed worldwide since February 23, 1990 and in the United States since January 4, 1991. In the United States alone, more than 1.4 million prescriptions have been written since approval. There has been substantial experience with its successful use in the prevention of nausea and vomiting associated with highly emetogenic chemotherapy, as well as in the management of postoperative nausea and vomiting.

The safety profile for Zofran use in both adults and children (surgical patients ≥ 2 years old and cancer patients ≥ 4 years old) is well-characterized. Zofran has never been withdrawn from any market for any safety reason. No new safety update data was submitted by the sponsor with this sNDA.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 797 patients received the study medication in three studies; 334 patients received placebo and 463 patients received Zofran IV. Among the patients who received Zofran IV, 51 surgical patients were randomized to receive a single dose of either 0.1 or 0.2 mg/kg of Zofran IV (S3A40319, a PK study), 76 chemotherapy patients received three doses of 0.15 mg/kg of Zofran IV (S3A40320, an open-label efficacy and safety study) and 336 surgical patients received a single dose of 0.1 mg/kg of Zofran IV (S3A40323, placebo-controlled efficacy and safety study). See the tables below for disposition of patients in individual studies.

The sponsor performed the appropriate and adequate safety monitoring for patients in this study. Zofran has been previously approved for CINV and PONV in the United States since 1991 and is approved for use in children as young as two years old. Surgical patients are expected to only have a single exposure to Zofran and chemotherapy patients are expected to receive three doses. The regimen used in the indications proposed are already approved in older pediatric patients and is not expected to result in any new safety concerns in patients 1 to 24 months old. The below lists the disposition of study patients in PK Study S3A40319.

Table 9: Disposition of Study Patients (Study S3A40319)

	IV Zofran Dose		Total
	0.1 mg/kg	0.2 mg/kg	N=51
	N=24	N=27	
No. patients who Completed Study	23 (96%)	23 (85%)	46 (90%)
No. patients who Withdrew Prematurely	1 (4%)	4 (15%)	5 (10%)
Reasons for Premature Discontinuation			
Consent withdrawn	1 (100%)	3 (75%)	4 (80%)
Other (Surgeon request)	0 (0%)	1 (25%)	1 (20%)

Adapted from sponsor's electronic submission S3A40319 p.39

The table below shows the number and percentage of patients who completed or withdrew from the study for Study S3A40320, prevention of chemotherapy induced nausea and vomiting.

Table 10: Patients who Completed the Study or Withdrawn– ITT Population (Study S3A40320)

	Number	(%)
Number in ITT Population	**75**	**(100)**
Completed Study	**73**	**(97)**
Prematurely Withdrew	**2**	**(3)**
Reason for Premature Withdrawal		
Consent withdrawn	**1**	**(1)**
Other (Venous access problem)	**1**	**(1)**

Adapted from sponsor's electronic submission S3A40320 p. 38

This next table shows the number and percentage of patients who completed or withdrew from the study for study S3A40323 prevention of postoperative induced nausea and vomiting.

Table 11: Patients who Completed the Study or Withdrawn-ITT Population (Study S3A40323)

	Treatment Group					
	Placebo		Zofran		Total	
	(N=335)		(N=335)		(N=670)	
	n	(%)	n	(%)	n	(%)
Completed Study	321	(96)	323	(96)	644	(96)
Prematurely withdrawn[1]	14	(4)	12	(4)	26	(4)
Reason for Premature Withdrawal						
Adverse event	2	(<1)	0		2	(<1)
Lost to follow-up	9	(3)	10	(3)	19	(3)
Protocol violation	3	(<1)	2	(<1)	5	(<1)

Adapted from sponsor's electronic submission S3A40323 p. 39

1 One investigator (#35581) reported that three patients were withdrawn due to protocol violations; however, the time of withdrawal indicates that the patients completed the 24-Hour Assessment Phase; 2 patients, 1 patient was in the Zofran group.

7.2.1.1 Study Type and Design/Patient Enumeration

This table lists the studies submitted with this NDA and includes the design, drug dose and number pf patients who participated in the study.

Table 12: Study Types

Type of Trial	***Design***	***Dosage and Administration***	***Patients***
Efficacy and Safety ***S3A40320***	Open-label, single-arm, multicenter	Three doses of 0.15mg/kg IV doses of Zofran administered prophylactically for CINV	76 cancer patients 6 to 48 months old on moderately to highly emetogenic chemotherapy
Efficacy and Safety ***S3A40323***	Randomized, double-blind placebo-controlled, multi-center, single-dose	Single-dose 0.1 mg/kg IV Zofran administered prophylactically for PONV *(Matching Placebo)*	670 surgical patients 1 to 24 months old
PK ***S3A40319***	Phase IV, non-randomized, multi-center, two-arm, single-dose	Single-dose of 0.1 or 0.2 mg/kg of IV Zofran administered prophylactically for PONV	51 pediatric surgical patients 1 to 24 months old

Reviewer's Table

All studies had a 24-hour assessment phase after study drug administration.

7.2.1.2 Demographics

A total of 797 patients were evaluated in the three studies submitted in this sNDA. Majority (71%) of the patients were males, and 29 % were females. The patients were predominantly white (63%) followed by blacks (15%) and Hispanic white (14%). Two percent (2%) were Asian and 5% of patients of patients were classified as others (middle-eastern or multi-racial background). The age range for all three studies was 1 month to 48 months old. There are no data concerning any significant effect of race or gender on the safety and efficacy of Zofran use. In study S3A40320, 10/75 (13%) were 6 to 12 months old and 65/75 (87%) were 13 to 48 months old. In study S3A40323, 49% were 1 to 12 months old and 51% were 13 to 24 months old. In study S3A40319, 27 (53%) were 1 to 4 months old and 24 (47%) were >4 to 24 months old.

7.2.1.3 Extent of exposure (dose/duration)

See section 7.2.1.1 and table 11.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not Applicable

7.2.2.3 Literature

The sponsor provided a thorough search and review of the world literature on the use of ondansetron in particular pediatric populations. This is to investigate the efficacy, safety and dosing regimen of ondansetron as an anti-emetic treatment for the indications of PONV and CINV. The safety and efficacy of ondansetron in pediatric patients was evaluated in clinical trials, post-marketing studies and literature review. The worldwide search confirms that pediatric cancer patients ≥ 4 years old and surgical patients ≥ 2 years old tolerated ondansetron well and no new specific safety and efficacy issues were identified.

7.2.3 Adequacy of Overall Clinical Experience

Zofran has been previously approved for CINV and PONV in the United States since 1991 and is approved for use in children as young as two years old. The regimen used in the indications proposed are already approved and are being used in older pediatric patients although off-label use is common in younger patients due to a lack of alternative drug. Overall, there is an adequate clinical experience with Zofran.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new animal data was submitted in this NDA.

7.2.5 Adequacy of Routine Clinical Testing

The sponsor performed the appropriate safety monitoring and clinical testing for patients in this study.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Biopharmaceutics Review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not applicable

7.2.8 Assessment of Quality and Completeness of Data

The studies submitted with this sNDA are in response to a Pediatric Written Request issued to the sponsor; these studies fairly meet the requirements of the Written Request.

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions or safety update data submitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

One patient (1%) in Study S3A40320 experienced an AE, skin rash, classified as moderate, for which the investigator considered a relationship to study medication possible. No detail information or narrative was included in this submission regarding this adverse event.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not Applicable.

7.4.2 Explorations for Predictive Factors

There is no new significant information regarding predictive factors that would affect the safety of the drug that is submitted in this NDA

7.4.3 Causality Determination

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen below is similar to the current recommendations in older children for the prevention of CINV (4 to 18 years old) and prevention of PONV (2 to 12 years of age). The safety and efficacy of these doses have been demonstrated in older children. The dosing regimen proposed by the sponsor is appropriate for the indication being sought.

Prevention of Chemotherapy-Induced Nausea and Vomiting (6 months to 48 months old)

Three doses of *0.15 mg/kg/dose* IV. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy. Subsequent doses should be administered 4 hours and 8 hours after the first dose. The drug should be infused over 15 minutes.

Prevention of Postoperative-Induced Nausea and Vomiting (1 month to 24 months old)

Weight ≤ 40 kg: Single dose of *0.1-mg/kg IV*.
Weight > 40 kg: Single dose of *4-mg IV*.
The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes.

In adults, the mean elimination half-life of Zofran is 5.7 hours; for those age 15 years and younger, half-life is about 2.4 hours. PK study S3A40319 submitted by the sponsor in this sNDA indicates that Zofran clearance and volume of distribution were dependent on body weight and age. Clearance of Zofran in surgical patients 1 to 4 months old is lower than patients who are >4 to 24 months old, but comparable to weight-normalized clearance in patients aged 3 to 12 years. The half-life in surgical patients aged >4 to 24 months was similar to the half-life in surgical patients aged 3 to 12 years (mean=2.9 hr). For patients who are 1 to 4 months old, half-life was 6.7 hours (~ 2.5-fold longer than the >4 to 24 months patients). This is may be a reflection of age-related changes in metabolic systems. See Dr. Suliman Al-Fayoumi's Biopharmaceutics Review of this NDA for details. No dose adjustment is necessary for patients aged 1 to 4 months since only a single dose of IV Zofran is recommended for the prevention of PONV; however, clinicians should be made aware that clearance in this age group is lower, half-life is longer and therefore they should be monitored more closely. This should be reflected in the label of this drug.

8.2 Drug-Drug Interactions

The concomitant use of apomorphine with drugs of the $5HT_3$ antagonist class (including ondansetron, granisetron, dolasetron, palonosetron, and alosetron) is contraindicated.
This is based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

Ondansetron (Zofran®) is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs. This is reflected in the current label of Zofran.

8.3 Special Populations

The population evaluated in this NDA are surgical patients who are 1month to 24 months old and post-chemotherapy patients who are 6 months to 48 months old. The number of patients for each age group satisfied the requirements of the Written Request. No new information regarding other patient population was submitted in this NDA; therefore, this reviewer refers to the current prescribing information of Zofran.

In adults patients with impaired hepatic function (Child-Pugh score ≥ of 10), a single maximum dose of 8 mg infused over 15 minutes for PONV is recommended. No dosage adjustment is recommended in renally-impaired or geriatric patients.

Ondansetron is excreted in the breast milk of rats but it is not known whether it is excreted in human milk. Caution should be exercised when this drug is administered to a nursing woman because many drugs are excreted in human milk.

Ondnasetron is currently listed as Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and no evidence of impaired fertility or harm to the fetus have been revealed. There are no adequate and well-controlled studies in pregnant women; therefore, it should be used during pregnancy only if clearly needed.

8.4 Pediatrics

This NDA efficacy supplement was submitted in response to the Written Request issued to the sponsor and the studies fairly meet its requirements.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

The sponsor submitted a list of references/articles from peer reviewed journals and published articles. This reviewer also searched the literature for information on Zofran and incorporated this information in the review.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan for this NDA.

8.8 Other Relevant Materials

Not Applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Study S3A403020 supports the approval of Zofran IV for the indication of prevention of chemotherapy-induced nausea and vomiting (CINV) in cancer patients 6 months to 48 months

old receiving moderately to highly emetogenic chemotherapy. This study has proven that three doses of 0.15 mg/kg/dose of Zofran IV is safe and efficacious when administered 30 minutes before the start of an emetogenic chemotherapy. Fifty-six percent (56%, 42/75) of the patients had a complete response (no emetic episode), which is comparable to the complete response rate of 58% in cancer patients older than 48 months old. S3A403020 replicates the efficacy results of Zofran studies conducted in the United States in pediatric cancer patients 48 months and older.

Study S3A403023 supports the approval of the indication of prevention of postoperative-induced nausea and vomiting (PONV) in surgical patients 1 month to 24 months old who are undergoing general anesthesia. This study shows that a single dose of 0.1 mg/kg of Zofran IV (maximum of 4 mg/dose) is significantly better than placebo in preventing nausea and vomiting; 89% (297/335) of patients had a complete response (no emetic episode) compared to placebo (72%, 242/335). This well-conducted trial provides useful information and is sufficient in establishing the efficacy of Zofran in preventing PONV in surgical patients as young as 1 month old.

The proposed dosing regimen for the intended indications have been well studied and proven to be safe and effective in older pediatric patients ($\geq$ 4 years old). The results of the studies in this sNDA have shown that Zofran is effective in preventing nausea and vomiting regardless of opioid use; and its efficacy when compared to placebo is consistent among countries, race, gender, age, ASA[4] and most surgery types. Further, these studies submitted have not identified any new safety concerns and the safety results were consistent with Zofran's current safety profile as described in the current prescribing information.

It is well-known to clinicians that Zofran is widely used off-label in younger population outside its currently indicated age group. No anti-emetic agent is approved in children younger than 2 years old for either CINV or PONV. It will beneficial to pediatric patients to have an FDA approved drug available for use in children as young as 1 month old that has a wide margin of safety and few adverse effects.

The much needed information obtained from this sNDA will be very beneficial to clinicians in providing optimal care to pediatric cancer patients receiving chemotherapy as young as 6 months old, and pediatric patients undergoing routine surgery under general anesthesia as young as 1 month old who are at high risk of developing an emetic episode.

Lastly, there is substantial evidence that if Zofran is safe and efficacious in older children for the above indications; therefore, there is little doubt that it will provide similar therapeutic and safety effect in younger children.

9.2 Recommendation on Regulatory Action

Intravenous Zofran® (ondansetron hydrochloride) is recommended for approval by this Medical Officer for the following indications:

4 American Society of Anesthesiologists

- Prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric cancer patients 6 months to 48 months old who are receiving moderately to highly emetogenic chemotherapy
- Prevention of postoperative-induced nausea and vomiting (PONV) in pediatric patients 1 month to 24 months old who are undergoing routine surgery under general anesthesia.

For the indication of prevention of CINV, three doses of 0.15 mg/kg/dose of IV Zofran is recommended. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, and subsequent doses should be administered 4 hours and 8 hours after the first dose. The drug should be infused over 15 minutes.

For the prevention of PONV, a single dose of 0.1-mg/kg IV Zofran for patients weighing ≤ 40 kg, with a maximum single dose of 4-mg for patients > 40 kg is recommended. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Meidcal Officer's Labeling Review located in the Appendix section of this review and the NDA team's labeling recommendations.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management steps are recommended.

9.3.2 Required Phase 4 Commitments

There are no Phase 4 commitments recommended.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests in this NDA.

9.4 Labeling Review

The following are my recommendations for labeling changes to the sponsor's proposed label:

A. In the **"CLINICAL STUDIES"** section, under subsection **Chemotherapy Induced Nausea and Vomiting,** the following paragraph should be revised:

Pediatric Studies: …

(b) (4)

The new paragraph should read:

(b) (4)

ZOFRAN was administered intravenously over 15 minutes in three doses of 0.15 mg/kg. The first dose was administered 30 minutes before the start of chemotherapy, the second and third doses were administered 4 and 8 hours after the first dose, respectively. Eighteen patients (25%) received routine prophylactic dexamethasone (i.e. not given as rescue). Of the 75 evaluable patients, 56% had a complete response (no emetic episodes) on day 1. (b) (4)

Comments: Demographic information should be included in the description of the study, as well as how the drug was actually administered during the trial.

B. In the **"CLINICAL STUDIES"** section, under subsection **Postoperative Nausea and Vomiting**, the following paragraph should be revised:

Pediatric Studies: …

(b) (4)

The new paragraph should read:

(b) (4)

A single 0.1 mg/kg I.V. dose of ondansetron administered within five minutes following induction of anesthesia was significantly more effective than placebo in preventing vomiting. In the placebo group, 28% of patients experienced (b) (4) compared to 11% of subjects who received ondansetron. Overall, 32

(10%) of placebo subjects and 18 (5%) of patients who received ondansetron received antiemetic rescue medication(s) (or prematurely withdrew from the study).

Comments: Demographic information should be included in the description of the study, as well as how the drug was actually administered during the trial. (b) (4)

C. In the "**PRECAUTIONS"** section under subsection **Pediatric Use,** the following line should be revised:

Pediatric Use*:* (b) (4)

The new paragraph should read:

Pediatric Use: (b) (4)

Comments: This sentence was revised to make it easier to read and to add clarity to it.

In addition, in this "**PRECAUTIONS"** section, the following information should be added:

The clearance of (b) (4) in pediatric patients 1 month to 4 months old is slower and the half-life is ~2.5 fold longer than patients who are >4 to 24 months old. As a precaution, it is recommended that patients less than 4 months old receiving this drug be closely monitored.

Comments: Clinicians should be made aware of this important pk information when prescribing this drug.

D. In the "**DOSAGE AND ADMINISTRATION"** section**,** under subsection**, "Prevention of Chemotherapy-Induced Nausea and Vomiting"** and "**Prevention of Postoperative Nausea and Vomiting",** the subtitle ***"Adult*** (b) (4)**"** should be added before the first line:

1) **Prevention of Chemotherapy-Induced Nausea and Vomiting:**
Adult (b) (4)**:** The recommended I.V. dosage of ZOFRAN for adults…….

2) Prevention of Postoperative Nausea and Vomiting:
Adult (b) (4)**:** The recommended I.V. dosage of ZOFRAN for adults is …….

Comments: This drug has different dosing regimen for different indications and different age groups. Therefore, the prescribing information should be easy to read and be very clear if the dosaging is for prevention of chemotherapy induced nausea

and vomiting in children or adults or if it is for the prevention of postoperative nausea and vomiting. Some healthcare providers who are very busy in this practice might not have enough time to read the entire label and would only read the portion of the label relevant to their patient. The addition of subtitles in this subsection will help clinicians discern easily if the dosaging information pertains to adult or pediatric patients, hopefully avoiding any potential medication dosaging error.

E. In the "**DOSAGE AND ADMINISTRATION"** section**,** under subsection**, Prevention of Chemotherapy-Induced Nausea and Vomiting, Pediatric** (b) (4) the paragraph should be modified with additions in underlined text and deletions in strikethrough:

Pediatric (b) (4) *On the basis of the available information (see CLINICAL TRIALS: Pediatric Studies and CLINICAL PHARMACOLOGY: Pediatric Pharmacokinetics), the dosage in pediatric cancer patients 6 months to 18 years of age should be three 0.15 mg/kg doses*(b) (4) *The first dose* (b) (4) *–is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy* (b) (4) *d subsequent doses (0.15 mg/kg) are* (b) (4) *administered 4 and 8 hours after the first dose of ZOFRAN. The drug should be infused intravenously over 15 minutes. Little information is available about dosage in pediatric cancer patients younger than 6 months of age.*

F. In the "**DOSAGE AND ADMINISTRATION"** section**,** under subsection**, Prevention of Postoperative Nausea and Vomiting, Pediatric** (b) (4)**,** the paragraph should be modified with additions in underlined text and deletions in strikethrough:

Pediatric (b) (4) *The recommended I.V. dosage of ZOFRAN ~~for~~* (b) (4) *pediatric surgical patients (1 month to 12 years of age) is a single 0.1 mg/kg dose for* (b) (4) *-patients weighing 40 kg or less, or a single 4 mg dose ~~for~~* (b) (4) *patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes immediately prior to or following anesthesia induction, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Prevention of further nausea and vomiting was only studied in patients who had not received prophylactic Zofran.*

G. All tables should be appropriately labeled according to the population studied, i.e., adults or pediatric patients. If the table involves studies conducted in pediatric patients, then the age group should be specified.

9.5 Comments to Applicant

The sponsor should modify the label according to the above labeling recommendations.

10 APPENDICES

10.1 Review of Individual Study Reports

Clinical Trial S3A40323

A Randomized, Double-blind, Placebo-controlled, Multi-center Study of Intravenous Ondansetron Hydrochloride 0.1 mg/kg for the Prevention of Postoperative Emesis in Pediatric Surgical patients Ages 1 Month to 24 Months Who Are Undergoing Routine Surgery Under General Anesthesia

Ethics

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the 1996 version of the Declaration of Helsinki.

Objectives

- To evaluate the efficacy of a single 0.1 mg/kg dose of intravenous Zofran administered prophylactically over at least 30 seconds (or as slowly as possible, given the small volume) to pediatric patients ages 1 month to 24 months who were undergoing routine surgical procedures under general anesthesia.

- To evaluate the safety and tolerability of a single 0.1 mg/kg dose of intravenous Zofran administered prophylactically over at least 30 seconds (or as slowly as possible, given the small volume) to pediatric patients ages 1 month to 24 months who were undergoing routine surgical procedures under general anesthesia.

Study Design

This was a randomized, double-blind, placebo-controlled, multi-center study in inpatient and outpatient pediatric patients 1 month to 24 months undergoing routine surgery under general anesthesia.

A single 0.1 mg/kg intravenous (IV) dose of Zofran administered prophylactically over at least 30 seconds (or as slowly as possible) compared to placebo. Efficacy was assessed by the number of emetic episodes, the time to the first emetic episode, the use of rescue antiemetic medications, and the time to administration of rescue antiemetic medications. In addition, the parent/guardian was asked to rate overall satisfaction with study medication in preventing postoperative vomiting.

Patients were evaluated during the Screening, Pre-treatment, Intraoperative, 24-Hour

Assessment, and Follow-up Phases. See Time and Events table below.

Table A-1: Time and Events Table
(S3A40323)

				24-Hour Assessment Phase		
	Screening Visit [1]	Pre-treatment Phase[1] (Day of Surgery)	Intraoperative Phase	Inpatient Period	Outpatient Period	Follow-up Telephone Call (within 2 hours after the end of the 24-Hour Assessment Phase)
Informed Consent [2]	X					
History & Physical	X					
Vital Signs [3]		X	X	X		
Notification of Surgeon	X					
Concomitant Medications	X[4]	X[4]	X	X	X	X
Inclusion/Exclusion Criteria [1]	X	X				
Emesis Assessment		X	X	X	X	X
LFTs [5]		X[5]				
Anesthesia Premedication and Induction		X				
Administration of Study Medication			X			
Adverse Event Assessment		X[6]	X	X	X	X
Dispense Diary [7]				X		
Parent/Guardian Global Assessment [8]				X	X	
Follow-up Phone Call [9]						X

Adapted from sponsor's electronic submission S3A40323

1. Screening was permitted within 21 days of the day of surgery or the same day as surgery. If screening was done on a day other than the day of surgery, the inclusion/exclusion criteria were to be re-evaluated to confirm that the patient continued to be eligible.
2. Written informed consent was provided by patient's parent or legal guardian prior to initiation of any study-specific procedures.
3. Blood pressure and heart rate were obtained after admission but prior to induction of anesthesia, within 5 minutes after administration of study medication, and again at the time of discharge or the end of the 24-Hour Assessment Period, whichever occurred first.
4. Medications taken within 48 hours prior to study medication administration were recorded.
5. ALAT (SGOT), ASAT (SGPT), total bilirubin, alkaline phosphatase. Specimen was obtained before administration of study medication, but it was permitted to be obtained after induction of anesthesia.
6. If Screening assessments were done on a day other than the day of study medication administration/surgery, the patient was to be re-assessed to determine if any new conditions had emerged. If so, serious events were recorded on the SAE form; otherwise, the Current Medical Conditions form was updated with non-serious events.
7. Diary dispensed only to parent/guardians of outpatients at the end of the Inpatient Period prior to departing from facility.
8. At the end of the 24-Hour Assessment Phase, the parent/guardian was asked to rate the overall satisfaction with study medication for prevention of postoperative vomiting
9. Outpatients only

Study Population

Inclusion Criteria

- Male or female patients ages 1 month to 24 months who were scheduled to undergo

surgery on inpatient or outpatient basis.

- Weight ≥ 3 kg.
- Estimated post-conceptual age of ≥ 44 weeks
- Scheduled to undergo procedures requiring general anesthesia (including, but not limited to, tonsillectomy, adenoidectomy, strabismus repair, orchidopexy, herniorrhaphy, hydrocelectomy, myringotomy, plastic surgery, orthopedic and dental procedures).
- American Society of Anesthesiologists (ASA) physical classification of 1, 2, or 3 as defined in the protocol.
- Signed and dated written informed consent provided by parents or legal guardians.
- For outpatients, parent(s) or legal guardian(s) must have been able to understand how to complete the diary and agree to be available by telephone within 2 hours after the end of the 24-Hour Assessment Phase.

Exclusion Criteria

- ASA physical classification 4 or 5 as defined in the protocol.
- Experienced emesis (retching and/or vomiting) in the 24 hours prior to surgery.
- Previously diagnosed with gastroesophageal reflux disease (GERD).
- Life-threatening conditions requiring immediate surgical intervention.
- Scheduled to undergo cardiac or neurosurgical procedures.
- patients scheduled to receive halothane or propofol as a component of the anesthetic regimen (i.e., for induction or maintenance of anesthesia).
- Expected to require postoperative mechanical ventilation or the insertion of a nasogastric tube.
- patients who received phenothiazines, metoclopramide or systemic corticosteroids within 48 hours of administration of study medication. (Topical or inhaled corticosteroids were permitted.)
- Patients with severe concurrent illness that the investigator believed to might interfere with the conduct of the study or confound the results of the study.
- Patients who had received any investigational product within 30 days or 5 half-lives (whichever was longer) prior to administration of study medication or were scheduled to receive an investigational product other than study medication during the course of this study.
- Hypersensitivity or contraindications to Zofran or other selective 5-HT3 receptor antagonists (e.g., granisetron, dolasetron).
- Patients who had participated previously in this study.

Medical Officer Comments: The inclusion and exclusion criteria are adequate for this study. IV Zofran is already approved by the Agency for prevention of postoperative nausea and vomiting (PONV) in pediatric surgical patients who are two years and older.

Withdrawal from the Study

A parent or legal guardian could voluntarily withdraw his or her child from this study at any time. The investigator could also, at his or her discretion, withdraw the patient from participating in this study at any time.

Patients who received rescue medication were to remain in the study and all efficacy assessments and safety assessments were to be continued and documented through the end of the 24-Hour Assessment Phase, unless the patient was withdrawn from the study at the parent/guardian's or investigator's discretion.

Study Drug

Dose: patients received either a single dose of 0.1 mg/kg of Zofran IV (ondansetron hydrochloride injection 2 mg/mL) or an equivalent volume of placebo (normal saline).

Administration: Study medication was administered within five minutes following induction of anesthesia and was injected intravenously in not less than 30 seconds (or as slowly as possible, given the small volume). If administered through an indwelling line, a sufficient volume of fluid was to be used to flush the lines.

Dose Rationale: The dose selected for this study was based on the results from the pharmacokinetic study of Zofran in pediatric patients (Study S3A40319), the current prescribing information for pediatric patients, and a search of the worldwide literature.

Blinding and Unblinding: This was a double-blind, placebo-controlled, randomized study design. A third party (e.g., pharmacist, nurse, or other qualified and authorized personnel) who was not associated with the study prepared the study drug and was not blinded.

The investigator was permitted to unblind a patient's treatment assignment in case of an emergency if necessary. GSK was to be notified immediately of the unblinding incident without revealing the patient's study treatment assignment.

Treatment Assignment: patients were randomized in a 1:1 ratio and received either single IV dose of 0.1 mg/kg of Zofran or placebo (normal saline) in accordance with a randomization schedule that was generated by the Biostatistics and Data Management (BDM) Department at GSK. Treatment assignment was stratified according to anticipated opioid usage as part of the anesthetic technique or for postoperative analgesia.

Medical Officer Comments: The proposed dose is acceptable as this dose is already being used in pediatric surgical patients who are two years and older and was based on the results of pharmacokinetics study (*S3A40319).*

Concomitant Medications

Permitted

Normally prescribed medications for the care of the patient were permitted (unless prohibited). All concomitant medications taken during the study were recorded in the eCRF with indication, dose information, and date(s) and time(s) of administration. Rescue antiemetic medication, including Zofran, was permitted.

Prohibited

- Halothane and propofol as components of the anesthetic regimen
- Phenothiazines (e.g., prochlorperazine), metoclopramide, and systemic corticosteroids during the 48 hours prior to administration of study medication and until after completion of the 24-Hour Assessment Phase, except when used as rescue antiemetic medication. (Topical and inhaled corticosteroids were permitted, at any time.)

Rescue Antiemetic Medications

The first dose of rescue antiemetic medication (specifically given for the treatment of emesis during the 24-Hour Assessment Phase) was permitted if clinically indicated, if three emetic episodes occurred within a 15-minute period, at physician discretion, or at any time upon patient/parent/guardian request. The choice of rescue antiemetic medication was at the discretion of the investigator; Zofran was permitted as a rescue antiemetic medication. Unblinding of the patient's study medication was not permitted for the purpose of selecting rescue antiemetic medication.

Although nausea was not specifically addressed, it was felt that the patients were too young to adequately report nausea. However, it became apparent that investigators used their discretion to administer antiemetic medications for treatment or prophylaxis of nausea. Hence, these medications were taken into consideration in the efficacy analyses.

Efficacy

Assessment of the number of emetic episodes, time of emetic episodes, use of rescue antiemetic medication and time of rescue antiemetic medication were made during the 24-Hour Assessment Phase and recorded on the Subject's Diary and/or the eCRF.

An emetic episode was defined as a single vomit* or retch* or any number of continuous vomits and/or retches, and separated by the absence of both vomiting and retching for at least three minutes.

* Vomiting was defined as expulsion of any stomach contents through the mouth or nose.

The parent/guardian was also asked to rate overall satisfaction with study medication in preventing postoperative vomiting, using the following 5-point scale ranging from very satisfied to very dissatisfied at the end of the 24-Hour Assessment Phase.

Primary efficacy endpoint

Proportion of patients who experienced an emetic episode during the 24-hour Assessment Phase

Note: A patient is considered to have had an emetic episode if prematurely withdrawn, or if received rescue medication in the absence of emesis.

Secondary efficacy endpoint(s)

Time to first emetic episode
The time between the termination of anesthesia and the first emetic episode observed during the 24-Hour Assessment Phase. Where the first emetic episode occurred after receipt of study medication but before discontinuation of anesthesia, time of emesis was set to zero.

Time to rescue medication
The time between the termination of anesthesia and administration of the first rescue medication or withdrawal. Where the first rescue medication was administered after receipt of study medication but before discontinuation of anesthesia, time of emesis was set to zero.

Incidence of emetic episodes
Categorized as: Complete response = 0 emetic episodes
Partial response = 1 – 2 emetic episodes
Therapeutic failure ≥ 3 emetic episodes or
requiring rescue or
severity of vomiting resulting in withdrawal or
withdrawal due to other reasons

Proportion of patients who receive rescue medication during the 24-Hour (postoperative) Assessment Phase
All patients with either rescue medication use or withdrawal as the numerator and all randomized and treated subjects as the denominator.

Proportion of patients with one or more emetic episodes after the administration of the first rescue medication
All patients with either rescue medication use or withdrawal were used as the numerator and all randomized and treated patients were the denominator.

Other efficacy endpoint(s)
The parent/guardian's satisfaction with study medication for the prevention of postoperative vomiting was rated using a 5-point scale:

1 = Very satisfied
2 = Somewhat satisfied
3 = Neither satisfied nor dissatisfied
4 = Somewhat dissatisfied
5 = Very dissatisfied

The proportion of patients who had an emetic event was also categorized by surgery type.

Safety

The principal safety assessment consisted of evaluation of the patients for adverse events (AEs) and serious adverse events (SAEs). Parents or guardians provided input on the children's condition to the investigator and/or site staff. For outpatients, parents or guardians documented adverse events on a diary card and provided the information to study personnel in a telephone call at the end of the 24-Hour Assessment Phase. Parents/guardians were asked the following questions:
1. "Has your child had any other medical problems or seemed to act differently in any way since the surgery?"
2. "Has your child needed to take any medicines, other than those provided in this study, since his/her last assessment?"

The only laboratory evaluations that were required for this study were baseline assessments of LFTs, [ALT (SGOT), AST (SGPT)], total bilirubin, and alkaline phosphatase.

Blood pressure and heart rate were monitored after admission to the hospital before and immediately after administration of study medication (i.e., within 5 minutes) of study drug, at the end of the 24-Hour Assessment Phase and for outpatients, just prior to being discharged from the clinic.

Sample Size Considerations

Approximately 15% of children ages 24 months and under experience postoperative emesis in the absence of treatment.[5] It was anticipated that Zofran would provide a 50% reduction in the incidence of emesis to 7.5%.

A total of 600 patients, 300 per treatment group, was planned to provide 80% power to test the null hypothesis. The placebo group was assumed to have an underlying emetic rate of 15% and the Zofran group, 7.5%, using a two-sided type I error probability of 5%. A 15% dropout was assumed for a total sample size of 690 patients, in order to ensure the FDA's requirement of at least 300 completed Zofran patients. However, the dropout rate was

5 Schreiner MS, Nicolson SC, Martin T, Witney L. Should children drink before discharge from day surgery? Anesthesiology. 1992; 76: 528-533.

less than the estimated 15%. As a result, a total of 689 were randomized with 670 in the intent-to-treat (ITT) population.

Medical Officer Comments: The sample size is adequate for this study.

Population Analyzed

Intent-to-treat (ITT) population

- the primary population of interest
- includes all patients randomized who were randomized and who received study medication.

Safety population: Included patients in the group of the study medication they actually received.

Note: The ITT and Safety populations included all patients who were randomized and received the study medication.

Per-protocol (PP) population: These were patients who were randomized, received study medication, and met all important protocol requirements. Protocol violators were identified prior to unblinding of treatment assignment, patients with important deviations were excluded from the PP population.

STUDY RESULTS

Disposition of Patients

The tables below shows the number of patients in the Randomized, Intent-to-Treat (ITT), Per Protocol (PP), and Safety Populations.

Table A-2: Number and Distribution of patients

	Treatment Group		
Number of patients	**Placebo**	**Zofran**	**Total**
All Randomized	345	344	689
Randomized, Not Treated	10	9	19
ITT	335	335	670
PP	301	299	600
Safety	334	336	670

Adapted from sponsor's electronic submission S3A40323 p.38

One patient (Subject 35383.23460) was randomized to placebo but actually received ZOFRAN. Therefore, the number of subjects in the ITT and Safety populations differed by one.

Table A-3: Number and Percentage of patients Who Completed the Study or Were Withdrawn by the Reason for Study Withdrawal – ITT Population

	Treatment Group		
	Placebo	**Zofran**	**Total**
	(N=335)	(N=335)	(N=670)
	n (%)	n (%)	n (%)
Completed Study	321 (96)	323 (96)	644 (96)
Prematurely withdrawn[1]	14 (4)	12 (4)	26 (4)
Reason for Premature Withdrawal			
Adverse event	2 (<1)	0	2 (<1)
Lost to follow-up	9 (3)	10 (3)	19 (3)
Protocol violation	3 (<1)	2 (<1)	5 (<1)

Adapted from sponsor's electronic submission S3A40323 p.39

1 One investigator (#35581) reported that three patients (24353, 24364, and 24365) were withdrawn due to protocol violations; however, the time of withdrawal indicates that the patients completed the 24-Hour Assessment Phase. patients 24364 and 24365 were in the placebo group, opioid stratum, and patient 24353 was in the Zofran group, opioid stratum.

Table A-4: Major Protocol Deviations that Excluded patients from the PP Analysis

	Treatment Group	
	Placebo	**Zofran**
	(N=335)	**(N=335)**
Major Protocol Deviation	**n (%)**	**n (%)**
Any Major Deviation	34 (10)	36 (11)
Use of systemic corticosteroids	10 (3)	12 (4)
Use of metoclopramide	0	0
Use of phenothiazines	0	0
Diary data not collected	9 (3)	10 (3)
Use of propofol	5 (1)	5 (1)
Previous history of GERD	4 (1)	2 (<1)
Completion of study <22 hrs	1 (<1)	4 (1)
Received < 0.05 mg/kg study medication	1 (<1)	0
Received > 0.15 mg/kg study medication	2 (<1)[1]	1 (<1)
Use of halothane	2 (<1)	2 (<1)
Post-conceptual age < 44 wks	1 (<1)	1 (<1)
Age > 24 months	0	1 (<1)
Treatment blind was broken	1 (<1)	0
Received wrong study medication	1 (<1)	0
Unintentional receipt of extra **Zofran**	1 (<1)	0

Adapted from sponsor's electronic submission S3A40323 p.40

Table A-5: Demographic Characteristics – ITT Population

	Treatment Group	
	Placebo (N=335)	**Zofran (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 – Max[1]	1 – 24	1 – 42
Race		
Asian	9 (3)	8 (2)
Black	53 (16)	45 (13)
American Hispanic	42 (13)	42 (13)
White	210 (63)	220 (66)
Other	21 (6)	20 (6)
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

Adapted from sponsor's electronic submission S3A40323 p. 41

1. One patient (#35177.25033) in the Zofran group was 42 months of age.
2. Number of patients for whom height was measured was 308 in each group.

The treatment groups were well-balanced with regard to race, age, weight and sex distribution. Majority of the patients were males (74.5%). There were more white patients (64.5%) than any other racial group. In both the ITT and PP populations, in the Zofran group, minimum height was reported to be 27 cm. in the non-opioid stratum and 34 cm. in the opioid stratum while in the placebo group, minimum height was reported to be 48 cm in the non-opioid stratum and 52 cm in the opioid stratum. With regard to age distribution, half of the population were in the age range 1 to 12 months and half were age 13 to 24 months; the treatment arms were well-balanced with regard to age distribution.

In the Zofran group, opioid stratum, one patient who was 42 months old was enrolled into the study as opposed to the protocol's required upper limit of 24 months.

Table A-6: Baseline Characteristics – ITT Population

	Treatment Group			
	Placebo (N=335)		Zofran (N=335)	
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)

Adapted from sponsor's electronic submission S3A40323 p.42

Comments: Majority of the patients (73%) fall under Class 1 ASA Classification and are outpatients (85%). Baseline characteristics of treatment groups were well-balanced with regard to ASA Classification and surgical status.

A total of 95% of patients in the placebo group and 96% in the Zofran group had at least one concurrent medical condition. There was no more than a 3% difference in incidence of conditions in any one body system between the treatment groups. The three most common body systems for which medical conditions were reported were ear/nose/throat (33% placebo, 36% Zofran group); urinary system (23% placebo, 22% Zofran group), and respiratory (20% placebo and 23% Zofran group). There was no clinically important differences identified across the opioid/non-opioid strata.

Other Factors Affecting Response to Therapy

Type of Surgery

In children, a high incidence of PONV might be expected after strabismus surgery, orchidopexy, middle ear surgery, otoplasty, herniorrhaphy, and tonsillectomy and adenoidectomy. See table below.

Table A-7: Summary of Surgical Procedures – ITT Population

	Treatment Group			
	Placebo (N=335)		Zofran (N=335)	
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)
Orthopedic	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)

Adapted from sponsor's electronic submission S3A40323 p. 44

As seen in the table above, the treatment groups were well-balanced with regard to surgical procedures. The groups were also similar with regard to history of anesthesia, intraoperative fluids, opioid use, analgesic and anesthetic use.

Most surgical procedures were categorized as Other. The procedures were reported to be extremely diverse, with at least 75% in each of the age and treatment stratified groups could not be categorized in the list. A total of 12 patients had a cleft palate repair, 5 had anorectoplasty or endorectal pull-through procedures. patients could also have a combination of procedures.

At the time of randomization, patients were stratified by anticipated opioid use in an effort to have balance in use of opioids across treatment groups. However, postrandomization events may have led to a change in the anticipated opioid treatment.

Systemic corticosteroids were prohibited during the study; 10 (3%) patients in the placebo group and 12 (4%) patients in the Zofran group were identified as protocol violators because they received systemic corticosteroids during the 24-Hour Assessment Phase.

EFFICACY RESULTS

Primary Efficacy Results

Emetic Episodes
The proportion of patients who experienced at least one episode of emesis during the 24-Hour Assessment Phase.

Table A-8: Summary of Emetic Episodes – ITT Population

	Treatment Group			
	Placebo		Zofran	
	(N = 335)		(N = 335)	
	n	(%)	n	(%)
0 Emetic Episodes	242	(72)	297	(89)
> 0 Emetic Episodes[1]	93	(28)	38	(11)
Odds Ratio	0.33			
95% CI for Odds Ratio	(0.22, 0.5)			
p-value for Odds Ratio	<0.0001			

Adapted from sponsor's electronic submission S3A40323 p. 47

1. Includes 10 (3%) patients in both the placebo group and Zofran groups who had incomplete/missing data.

Comments: As seen in the table above, 89% of patients in the Zofran group had complete response (no emetic episode) compared to the placebo group, 72%. The common odds ratio was 0.33, which suggests that the odds of having an emetic episode after administering Zofran is roughly one-third compared to after giving placebo. This was also statistically significant (p<0.0001). Zofran was significantly better than placebo regardless of opioid use. See also Statistics Review by Dr. Milton Fan.

Secondary Efficacy Results

1) *Median Time to First Emetic Episode* (between the termination of anesthesia and the first emetic episode observed during the 24-Hour Assessment Phase)

A total of 93 (28%) of patients in the placebo and 38 (11%) Zofran group experienced emesis (see previous table).

Table A-9: Median Time to first Emetic Event – ITT Population

	Treatment Group					
	Opioid Stratum		Non-Opioid Stratum		Overall	
	Placebo (N=194)	Zofran (N=196)	Placebo (N=141)	Zofran (N=139)	Placebo (N=335)	Zofran (N=335)
n (%)	57 (29)	26 (13)	36 (26)	12 (9)	93 (28)	38 (11)
Median Time (min)	132	264	149	135	135	207

Adapted from sponsor's electronic submission S3A40323 p. 50

As seen in this table, the overall median time to first emetic episode for patients in the placebo group was shorter compared to patients in the Zofran group (2.25 hours vs.

3.45 hours). It should be noted that patients in the Zofran group who are in the opioid stratum took a longer time (4.4 hours) before having their first emetic episode compared to the other strata.

2) Time to First Rescue Medication (or Withdrawal)

Overall, a total of 32 (~10%) of placebo and 18 (5%) of Zofran patients *received rescue* antiemetic medication(s) *or withdrew* from the study prematurely (see table A-10 below). Rescue medication times of zero were noted in a few patients due to the administration of rescue medication after the receipt of study medication but prior to discontinuation of anesthesia.

The next table shows the time to first rescue medication. The median time to first rescue medication was based on only those patients who received rescue medication or were prematurely withdrawn from the study.

Table A-10: Summary of Time to First Rescue Medication - ITT Population Stratified by Anticipated Opioid Use

	Opioid Placebo (N=194)	Opioid Zofran (N=196)	Non-Opio Placebo (N=141)	Non-Opio Zofran (N=139)	Total Placebo (N=335)	Total Zofran (N=335)
Patients						
Completed w/o rescue	172(89%)	185 (94%)	131 (93%)	132 (95%)	303 (90%)	317 (95%)
Receiving rescue med/s	14 (7%)	3 (2%)	7 (5%)	3 (2%)	21 (6%)	6 (2%)
Incomplete/ Missing data	8 (4%)	8 (4%)	3 (2%)	4 (3%)	11 (3%)	12 (4%)
Time to First Rescue Medication (Minutes)						
n	22	11	10	7	32	18
Median	81	150	103	35	91	85
Min.	0	50	0	0	0	0
Max.	1440	1442	475	324	1440	1442

Adapted and modified from sponsor's electronic submission S3A40323 p.152

Note that as shown in this table A-10, the median time to first rescue medication was based on only those patients who received rescue medication or were prematurely withdrawn from the study.

Comments: Fewer patients in the Zofran group required rescue medication, and overall, median time to first rescue/withdrawal was 91 mins. after placebo and 85 mins after Zofran. However, it appears that patients in the non-opioid stratum who received Zofran received rescue earlier (0.5 hrs) than those in the placebo group (1.7 hrs); this is the opposite in the opioid stratum in which patients who received Zofran received rescue after

2.5 hrs. It will be difficult to conclude from the results in this table because of the small number of patients in each stratum.

3) Incidence of Emetic Episodes During the 24-Hour Assessment Period

Table A-11: Incidence of Emetic Episodes – ITT Population (During the 24-Hr Assessment Period)

	Treatment Group			
	Placebo N=335		Zofran N=335	
	n	(%)	n	(%)
Complete Response	242	(72)	297	(89)
Partial Response	57	(17)	19	(6)
Therapeutic Failure	26*	(8)*	9*	(3)*
Incomplete/Missing Data	10	(3)	10	(3)

Adapted from sponsor's electronic submission S3A40323 p. 53

Note: Therapeutic failure was defined as ≥ 3 emetic episodes, use of rescue medication, or withdrawal from the study.
* Each of the two treatment groups had 10 (3%) patients for whom data were not available for assessment of the incidence of emesis. When these subjects with incomplete/missing data were included as therapeutic failures, the rate increased to 11% (placebo) and 6% (Zofran).

4) Proportion of subjects who receive rescue medication the 24-Hour (postoperative) Assessment Phase (all patients with either rescue medication use or withdrawal as the numerator and all randomized and treated subjects as the denominator.

Comments: Rescue medication was received by 21/335 (6%) patients in the placebo group and 6/335 (2%) patients in the Zofran group during the 24 hours following discontinuation of anesthesia (ITT Population). See table A-10. Rescue medications included dexamethasone, dimenhydrinate, dimeticone, dolasetron, metoclopramide, and ondansetron. It should be noted that none of these medications is approved for children younger than 2 years old.

It appears that among the rescue medications, ondansetron was the most frequently used by the investigators; 14 patients (4%) in the placebo group received Zofran as rescue compared to 2 (<1%) in the Zofran group.

5) Emesis Following Administration of Rescue Medication (ITT)
There were only a few patients in each treatment group (21, 6% placebo; 6, 2% ZOFRAN) who required rescue medication as originally defined by the protocol. Of these patients, 7 (33%) patients in the placebo group experienced between 1 and >5 emetic episodes after administration of rescue medication. On the other hand, no patient in the Zofran group experienced emesis after receiving rescue medication.

Other Efficacy Results

Other efficacy analyses were: emetic episodes by surgery type, emetic episodes after the 24-hour assessment period and parent/guardian satisfaction with study medication.

Emetic Episodes by Surgery Type – ITT Population

See table below.

Table A-12: Proportion of patients with Emetic Episodes by Surgery Type ITT Population[1]

Treatment Group				
Type Surgery	**Placebo (N=335)[2]**		**Zofran (N=335)[2]**	
	n/n[3]	**(%)**	**n/n[3]**	**(%)**
Tonsillectomy	1/4	(25)	2/4	(50)
Adenoidectomy	4/19	(21)	4/24	(17)
Dental procedure	0/3		1/6	(17)
Hydrocelectomy	0/4		1/6	(17)
Strabismus surgery	1/11	(9)	2/12	(17)
Myrignotomy	10/37	(27)	5/36	(14)
Orchidopexy	13/40	(33)	3/40	(8)
Other	45/189	(24)	12/186	(6)
Plastic surgery	10/38	(26)	2/42	(5)
Hernia repair	8/39	(21)	0/44	
Orthopedic	3/15	(20)	0/10	

Adapted from sponsor's electronic submission S3A40323 p. 55

1. Table 13 includes patients with emesis only, in contrast to Table 9 which includes patients with emesis, early withdrawal, rescue in the absence of emesis, or missing data.
2. Total number of surgeries is greater than 335 because some patients had multiple surgeries.
3. Denominator is the number of patients who underwent that particular surgical procedure and the numerator is the number of patients who experienced one or episodes of emesis.

Comments: Previous tabulations have shown that 28% of patients in the placebo group experienced at least one episode of emesis compared to only 11% in the Zofran group. See table A-8. *Certain types of surgeries are associated with a higher incidence of post-operative vomiting such as orchidopexy and herniorrhaphy. In general, patients in the Zofran group had less emesis episode, regardless of surgery type.*

Emetic Episodes After the 24-Hour Assessment Period

There were no reports of emesis after the end of the 24-Hour Assessment Period.

Parent/Guardian's Satisfaction with Study Medication – ITT Population

Parents were asked to evaluate his/her satisfaction with study medication in the prevention of POV using the following five-point scale: Parents/guardians in Zofran group reported the following (ITT population):

Very satisfied=92%
Somewhat satisfied=6%
Neither satisfied nor dissatisfied =2%
Somewhat dissatisfied <1%
Very dissatisfied=0

Within the opioid and non-opioid strata, parent/guardian satisfaction was similar compared to the total placebo and total Zofran groups.

Subgroup Analyses

Emetic Episodes by Age

The table below shows the summary of the number and percentage of patients who experienced any emetic episodes during the 24-Hour Assessment Phase.

Table A-13: Summary of Emetic Episodes – ITT Population by Age

	Treatment Group			
	Placebo (N = 335)		Zofran (N= 335)	
All patients	**n**	**(%)**	**n**	**(%)**
0 Emetic Episodes	242	(72)	297	(89)
> 0 Emetic Episodes	83	(25)	28	(8)
Missing/Incomplete Data	10	(3)	10	(3)
Age: 1 to 12 months	**169**	**(50)**	**162**	**(48)**
0 Emetic Episodes	123	(73)	149	(92)
> 0 Emetic Episodes	42	(25)	11	(7)
Missing/Incomplete Data	4	(2)	2	(1)
Age: 13 to 24 months	**166**	**(50)**	**172**	**(51)**
0 Emetic Episodes	119	(72)	147	(85)
> 0 Emetic Episodes	41	(25)	17	(10)
Missing/Incomplete Data	6	(4)	8	(5)
Age: > 24 months	**0**		**1**	**(<1)**
0 Emetic Episodes	0		1	(100)

Adapted from sponsor's electronic submission S3A40323 p. 57

Emetic Episodes by Gender

Table A-14: Summary of Emetic Episodes – ITT Populations by Gender

	Treatment Group			
	Placebo (N =335)		Zofran (N = 335)	
All patients	**n**	**(%)**	**n**	**(%)**
0 Emetic Episodes	242	(72)	297	(89)
> 0 Emetic Episodes	83	(25)	28	(8)
Missing/Incomplete Data	10	(3)	10	(3)
Males	**251**	**(75)**	**255**	**(76)**
0 Emetic Episodes	179	(71)	224	(88)
> 0 Emetic Episodes	65	(26)	22	(9)
Missing/Incomplete Data	7	(3)	9	(4)
Females	**84**	**(25)**	**80**	**(24)**
0 Emetic Episodes	63	(75)	73	(91)
> 0 Emetic Episodes	18	(21)	6	(8)
Missing/Incomplete Data	3	(4)	1	(1)

Adapted from sponsor's electronic submission S3A40323 p. 58

Overall, results of this study favors Zofran on "complete Response" and were consistent among race, gender, age, ASA and most surgery types.

SAFETY RESULTS

Exposure

In the Zofran group:

- 99% of patients received a dose between 0.09 and 0.12 mg/kg
- two patients received a dose of > 0.15 mg/kg and two (<1%) patients Zofran as rescue medication*
- *a total of 4 (1%) patients received > 0.15 mg/kg of Zofran.

In the placebo group 14 (4%) patients received Zofran as rescue medication, of whom:

- 9 (3%) received 0.9 to 0.12 mg/kg,
- 2 (<1%) received 0.13 to 0.15 mg/kg,
- 3 (<1%) received >0.15 mg/kg.

Adverse Events

All patients who received the study medication required by the protocol (N=670) were included in the evaluation of the safety data. Adverse events were also based upon comparisons of patient experience by study medication actually received.

There appears to be no clinically important differences in the frequency or types of events reported for each treatment group, regardless of opioid use. Overall, 18% of patients in both the placebo and Zofran groups experienced one or more adverse events (59/334 placebo, 62/336 Zofran). Most AEs were reported in 1% or fewer patients, see table below for exceptions.

Table A-15: Summary of Most Frequent Adverse Events (≥ 2% in either treatment group) – Safety Population

	Treatment Group			
Adverse Event	**Placebo (N = 334)**		**Zofran (N = 336)**	
	n	**(%)**	**n**	**(%)**
Any Event	59	(18)	62	(18)
Pyrexia	14	(4)	14	(4)
Bronchospasm	6	(2)	2	(<1)
Post-procedural pain	6	(2)	4	(1)
Diarrhea	3	(<1)	6	(2)

Adapted from sponsor's electronic submission S3A40323 p. 61

The AEs reported were generally of mild intensity except for three patients (<1%) in the placebo group each had one AE reported to be severe: exacerbated pain, laryngospasm, and irritability. In the Zofran group, one patient (<1%) experienced three severe events: hypercapnia, hypoxia, and nodal arrhythmia; all three of which were also reported as serious AEs.

With regard to age, gender, there was no clinically significant differences between treatment groups or across the opioid and non-opioid strata.

The black population reported up to 18% more AEs compared to the four other categories of race. There was a similar incidence of AEs within the black population, placebo (28%) and Zofran group (29%). In the American Hispanic population, 7% more patients reported AEs in the Zofran group than in the placebo group. The interpretation of these differences is limited due to the relatively small population in each group. Majority of the patients were white.

Serious Adverse Events

There were no deaths during the course of this study.

Non-fatal serious adverse events were experienced by less than 1% of patients in each treatment group (3/334 placebo, 2/336 Zofran). In the placebo group, the following SAEs were experienced: tachycardia (1 patient), bronchospasm (1 patient) and exacerbated pain (1 patient). The patients who experienced tachycardia and bronchospasm were withdrawn from the study prematurely due to the SAE. In the Zofran group, one patient had staphylococcal

infection and one patient experienced three events; nodal arrhythmia, hypocapnia, and hypoxia; the investigator assessed these SAEs as not caused by the investigational product. Both patients completed the study.

Other Relevant Adverse Events

Potential drug-specific safety considerations prospectively identified included constipation, extrapyramidal reactions, redness/inflammation at the injection site, rash, hypersensitivity reactions, and seizures. See table below.

Table A-16: Potential Drug-specific Safety Considerations – Safety Population

	Treatment Group			
Adverse Event	**Placebo N = 334**		**Zofran N = 336**	
Bronchospasm	6	(2)	2	(<1)
Laryngospasm	4	(1)	3	(<1)
Rash	2	(<1)	1	(<1)
Pruritus	1	(<1)	1	(<1)
Urticaria	1	(<1)	0	
Swollen Tongue	0		1	(<1)
Injection site reaction	0		1	(<1)
Feces hard	1	(<1)	0	
Constipation	0		0	
Extrapyramidal reaction/symptoms	0		0	
Hypersensitivity reaction	0		0	
Seizure/Convulsion	0		0	

Adapted from sponsor's electronic submission S3A40323 p. 65

The investigators judged these events as to be not caused by the study medication.

Comments: Drug-specific safety considerations which included constipation, extrapyramidal reactions, redness/inflammation at the injection site, rash, hypersensitivity reactions, seizures and liver function abnormalities. Among these identified concerns, patients in study S3A40323 reported constipation (1 patient), rash (2) and redness/inflammation at the injection site (1).

The sponsor only assessed baseline liver function tests (SGPT, SGOT, bilirubin and alkaline phosphatase); no follow-up assessment was done. The sponsor stated that (in S3A40323), it was anticipated that the vast majority of patients would be outpatients, making it logistically impractical to require that patients return to the clinic for follow-up laboratory assessments and a risk-benefit consideration was assessed and an effort was made to minimize the total amount of blood drawn from each patient and due to the lack of a randomized control group and polypharmacy, abnormalities would be difficult to interpret. The sponsor's were to repeat these laboratory tests if clinically indicated. None of the patients required a repeat liver function test due to an adverse event.

Clinical Laboratory Evaluations

The study did not require and clinical laboratory evaluations, with the exception of baseline liver function tests.

Other Safety Evaluations

No clinically significant differences were detected in blood pressure or heart rate between the treatment groups or across the opioid and non-opioid strata.

Clinical Trial S3A40320

An Open-label, Multicenter, Study of the Safety and Antiemetic Effect of 0.15 mg/kg Intravenous (IV) Ondansetron Hydrochloride Administered for Three Doses to Pediatric Cancer patients Aged 6 Months to 48 Months Who Are Receiving Moderately to Highly Emetogenic Chemotherapy

Date of Study and Centers

The study was conducted on March 4, 2003 to March 19, 2004

A total of 22 centers participated in the study, 16 in the United States, 2 in Spain and 1 each in Australia, Austria, Canada, and Israel. The number of patients enrolled at each site ranged from 1 to 12. The sample size was 76 patients. The number of patients enrolled at each site ranged from 1 to 12.

Ethics

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the 1996 version of the Declaration of Helsinki.

Objectives

- To obtain qualitative *efficacy* data on Zofran administered as three 0.15mg/kg IV doses prophylactically to pediatric cancer patients aged 6 months to 48 months receiving moderately to highly emetogenic cancer chemotherapy.

- To evaluate the *safety* and *tolerability* of Zofran administered as three 0.15mg/kg

IV doses prophylactically to pediatric cancer patients aged 6 months to 48 months receiving moderately to highly emetogenic chemotherapy.

- To determine ondansetron serum concentrations following three 0.15 mg/kg IV doses administered prophylactically to pediatric cancer patients aged 6 months to 48 months receiving moderately to highly emetogenic chemotherapy.

- To evaluate the effects of age and body weight on the clearance and volume of distribution of ondansetron administered to pediatric cancer patients aged 6 months to 48 months receiving moderately to highly emetogenic chemotherapy.

Study Design

This was a Phase III, multicenter, open-label, single arm study assessing three 0.15mg/kg doses of IV Zofran in pediatric patients aged 6 months to 48 months with cancer and receiving moderately or highly emetogenic chemotherapy.

Patients were evaluated during the Screening and 24-Hour Assessment Phases. Screening visit was done within 7 days prior to administration of study medication. The 24-Hour Assessment Phase began with the start of intravenous Zofran and continued for 24 hours after the initiation of the first dose of moderately- or highly-emetogenic chemotherapy. During this phase, safety, efficacy and pharmacokinetic data was collected. See the table below for Time and Events Schedule.

Table B-1: Time and Events Schedule

	Screening (within 7 days of study medication administration)[1]	**24-Hour Assessment Phase**
Informed Consent[2]	X	
History &Physical	X	
Vital Signs	X[3]	X[3]
Concomitant Medications	X[4]	X
LFTs[5]	X	
Inclusion/Exclusion (I/E)Criteria[6]	X	
Emesis Assessment	X[7]	X
Administration of Study		X[8]
Medication		
Adverse Event Assessment	X[9]	X
Pharmacokinetic Sampling[10]		X
Parent/Guardian Global		X
Assessment[11]		

Adapted from sponsor's electronic submission S3A40323 p. 16

1. Screening was done on the day that study medication was administered or within 7 days prior.

2. Written informed consent was provided by patient's parent or legal guardian.
3. Blood pressure and heart rate were obtained on the day that chemotherapy was administered prior to administration of the first dose of Zofran and again at the end of the 24-Hour Assessment Phase.
4. Medication taken within 48 hours prior to Zofran administration.
5. ALT (SGPT), AST (SGOT), total bilirubin, alkaline phosphatase.
6. If Screening assessments were done on a day other than the day that study medication and chemotherapy were administered, the I/E criteria were required to be reviewed prior to administration of study medication to assure that the patient continued to be eligible.
7. Patients who experience emesis (i.e., vomiting and/or retching) with 24 hours prior to administration of the first dose of Zofran were NOT eligible to participate in the study.
8. Zofran was required to be administered 30 minutes prior to administration of moderately/highly emetogenic chemotherapy and again four and eight hours after the first dose of Zofran.
9. If Screening assessments were done on a day other than the day that study medication and chemotherapy were administered, prior to administration of study medication, the patient was assessed to determine if any new conditions had emerged. If so, serious events were required to be recorded on the SAE form; otherwise, the Current Medical Conditions form was updated with non-serious events.
10. Six to seven blood samples were required for PK analysis.
11. At the end of the 24-Hour Assessment Phase, the parent/guardian was asked to rate the overall satisfaction with Zofran for prevention of chemotherapy-induced vomiting.

Study Population

Inclusion Criteria

- Pediatric patients (male or female) aged 6 months to 48 months, with a diagnosis of cancer.
- In-patients who were to receive one or more cycles of moderately/highly emetogenic chemotherapy.
- Patients who, in the opinion of the investigator, were expected to receive Zofran or another 5-HT_3-receptor antagonist as prophylaxis for chemotherapy-induced nausea and vomiting.
- Parents or legal guardians provided written informed consent for their children to participate in the study.

Exclusion Criteria

- Patients with pre-existing etiologies for emesis including but not limited to gastrointestinal obstruction, active peptic ulcer disease, increased intracranial pressure, hypercalcemia, meningeal leukemia, or central nervous system primary or secondary tumors.
- Experienced emesis (retching and/or vomiting) in the 24 hours before receiving moderately/highly emetogenic chemotherapy.
- Score of less than 60 on the Lansky Performance Status Scale.
- Severe concurrent illness (other than neoplasia) or who had evidence of clinically significant disorders, or medical conditions that the investigator believed might interfere with the conduct of the study.

- Receipt of abdominal or pelvic irradiation within 48 hours prior to administration of study drug or who were scheduled to receive such radiotherapy during the 24-Hour Assessment Phase.
- Active, or a recent (in the opinion of the investigator) history of hepatic disease including known liver metastases.
- Receipt of phenothiazines or metoclopramide within the 48 hours prior to receiving study medication.
- Participated in a clinical trial with an investigational drug during the previous 30 days or who were scheduled to receive an investigational drug during the study period (from the time of giving consent until completion of the 24-Hour.
- Hypersensitivity or contraindications to Zofran as indicated in the Prescribing Information.
- Previously participated in this study.

Dosages and Administration

Dosage: three 0.15 mg/kg doses of IV Zofran diluted in 10 to 50 mL of 5% dextrose injection or 0.9% sodium chloride, to be infused over 15 minutes.

1st dose: administered 30 minutes before the start of moderately/highly emetogenic chemotherapy.
2nd dose: administered at 4 hours after the first dose
3rd dose: administered at 8 hours after the first dose

The intravenous (IV) line was required to be flushed immediately after the Zofran infusion with an adequate amount of fluid to assure that the line was clear of Zofran.

Concomitant Medications

Prohibited Medications

- Phenothiazines were prohibited during the 48 hours prior to drug administration and until after completion of the 24-Hour Assessment Phase.
- Metoclopramide was prohibited during the 48 hours prior to administration of study medication; however, it was permitted as rescue antiemetic medication.
- Zofran and other 5-HT_3 receptor antagonists were not permitted to be used as a rescue antiemetic medication.
- Drug that are specified in the exclusion Criteria

Rescue Antiemetic Medication

Rescue antiemetic medication was given specifically for the treatment of emesis during the 24-Hour Assessment Phase. It could be administered if three emetic episodes occurred within a 15 minute period, at physician discretion, or at any time upon parent/guardian request. The choice of rescue antiemetic medication was left to the discretion of the investigator.

Dexamethasone is standard of antiemetic care; its prophylactic use was permitted during the study. However, because of its antiemetic properties, routine use of dexamethasone (i.e., not given as rescue) administered within two hours prior to the administration of the first dose of study medication and during the study was identified and taken into consideration in the efficacy analyses.

Efficacy

The number and time of emetic episodes (defined below), use of rescue antiemetic medication, and time to rescue antiemetic medication were assessed beginning with the start of administration of moderately/highly emetogenic chemotherapy and throughout the 24-Hour Assessment Phase.

In the event the patient experienced any emetic episodes in the interval between administration of Zofran and moderately/highly-emetogenic chemotherapy, details of the event were reported under Emesis Assessments in the CRF.

An emetic episode was defined as:

- a single vomit or retch or any number of continuous vomits and/or retches*
- an emetic episode was, by definition, separated by the absence of both vomiting or retching for at least three minutes.

* An episode of vomiting was defined as expulsion of any stomach contents through the mouth or nose. Passive regurgitation, i.e., vomiting without associated retching, was NOT considered an episode of vomiting nor expected loss of small amounts of food or liquid from the mouth around feeding.

Retching was defined as an attempt to vomit that was not productive of any stomach contents. Continuous vomiting and/or retching was defined as two or more vomits and/or retches that occur within three minutes of each other.

The parent/guardian was also asked to rate the overall satisfaction with Zofran for prevention of chemotherapy-induced vomiting using a 5-point scale ranging from very satisfied to very dissatisfied.

<u>The following are the Co-Primary Efficacy Endpoint</u>

- The incidence of emetic episodes during the 24-Hour Assessment Phase;
- Proportion of patients receiving rescue antiemetic medication during the 24-Hour Assessment Phase
- Time to first rescue antiemetic medication
- Parent/guardian's overall satisfaction with Zofran in preventing chemotherapy induced vomiting; and
- Time to first emetic episode (post hoc).

Safety

The principal safety assessment consisted of evaluation of the patient for adverse events (AEs) and serious adverse events (SAEs). Due to the young age of the patients (6 to 48 months), parents or guardians provided input on the children's condition to the investigator and/or site staff. The protocol required that study personnel inquire about adverse events by asking the following standard questions of the parent/guardian:

1. "Has your child had any other medical problems or seemed to act differently in any way since the surgery?"
2. "Has your child needed to take any medicines, other than those provided in this study, since his/her last assessment?"

The investigator made an assessment of intensity (mild, moderate or severe) for each AE and SAE reported during the study.

The only laboratory evaluations that were required for this study were baseline assessments of LFTs, including ALT (SGOT), AST (SGPT), total bilirubin, and alkaline phosphatase.

Blood pressure and heart rate were required to be measured on the day that chemotherapy was administered prior to administration of the first dose of Zofran and again at the end of the 24-Hour Assessment Phase.

Pharmacokinetic Assessments

In order to determine ondansetron serum concentrations and estimates of ondansetron clearance and volume of distribution, six to seven 1 mL blood samples were required to be collected from all patients at the following times relative to the doses of Zofran:

1. Just prior to the administration of the **second** Zofran infusion dose,
2. 2 to 5 minutes after the end of infusion of the **second** Zofran dose,
3. Between 0.5 and 1.5 hours after the **second** Zofran dose
4. Between 2 and 3 hours after the **second** Zofran dose,
5. Just prior to the administration of the **third** Zofran dose,
6. 2 to 5 minutes after the end of the infusion of **third** Zofran dose, and
7. Between 12 to 24 hours after the **third** Zofran dose*

* This last sample was only required from patients who had not been prematurely withdrawn and discharged prior to this time.

If only the **first** dose of Zofran was administered and the patient had not been discharged from the hospital, three 1 mL blood samples were to be collected at the following times relative to the first and only dose of Zofran:

- 4 to 5 hours after the first Zofran dose,

- 6 to 8 hours after the first Zofran dose, and
- 12 to 24 hours after the first Zofran dose or at discharge, which ever occurs first.

If the first and second doses of Zofran were administered but the third dose was not, the PK samples were to be obtained as follows:

- Samples 1 to 4 were to be obtained as described above
- Sample 5 was to be obtained when the **THIRD** dose of Zofran was scheduled to be administered (approximately 4 to 5 hours after the second dose).
- Sample 6 was not required.
- Sample 7 was to be obtained between 12 and 24 hours after the **SECOND** Zofran dose (i.e., the last dose administered), if the patient had not been discharged from the hospital.

Sample Size Considerations

It was estimated that 75 patients would be enrolled to obtain 60 evaluable patients, including at least 20 patients between the ages of 6 months and 12 months. The sample size was based on enrollment feasibility rather than formal statistical criteria due to the lack of Zofran experience in the proposed population and the variability associated with the incidence of emesis of different chemotherapy regimens.

Comments: Due to difficulty in recruiting pediatric cancer patients 6 months to 12 months old and refusal of parents to subject their children to a study because of their very young age, the sponsor requested to include data from surgical patients to be included in the population PK analysis of this study. The Agency found this to be acceptable.

Population Analyzed

Intent-to-Treat Population (ITT)

- considered the primary population
- used for reporting all efficacy endpoints
- included all patients who received any study medication and moderately/highly emetogenic chemotherapy

Per-Protocol Population(PP):

- all patients who received at least one dose of study medication, moderately/highly emetogenic chemotherapy, and met all important protocol requirements.
- was used for reporting all efficacy endpoints, except for the post-hoc analysis of time to first emetic episode, and was considered the secondary population.

Safety Population:

- Patients who received any study medication regardless of whether or not chemotherapy was administered

- A patient was excluded from this population if there was documented evidence that no study medication was administered.

Examination of subgroups

Analyses by age (6 to 12 months and 13 to 48 months), gender, and race were performed for adverse event data and the following co-primary efficacy endpoints:
• Incidence of emetic episodes
• Proportion of patients who received rescue antiemetic medication

Premature discontinuation and missing data

All premature discontinuations from the study were tabulated by reason for discontinuation. If a patient did not remain in the study for the full 24 hours after administration of emetogenic chemotherapy, but the investigator indicated that the patient completed the study, the patient was included in the ITT analysis but not in the PP analysis, if the patient did not complete at least 22 hours. Withdrawal reports were generated based on both the ITT and Safety populations. If withdrawn from the trial without having an emetic episode, then this were considered to have had at least one emetic episode.

Derived and transformed data

The incidence of emetic events was categorized as follows:
Complete Response group
- Patients who did not experience emetic events,
- Receive rescue antiemetic medication, or
- Withdrawn from the study prematurely

Partial Response category
- Patients who experienced 1-2 emetic episodes, but did not receive antiemetic medications or withdrawal from the study prematurely were included in the Partial Response category.

Therapeutic Failure
- Patients who either experienced at least 3 emetic episodes or received rescue medication, or withdrew from the trial for any reason.

STUDY RESULTS

Disposition of patients

The ITT population included all patients who received at least one dose of study medication *and* moderately or highly emetogenic chemotherapy.

The PP population included patients who received study medication, moderately or highly emetogenic chemotherapy, and who met all important protocol requirements, i.e., did not have any major protocol deviations.

The safety population included all patients who received study medication

Table B-2: Number and Distribution of Patients

Population	Number of patients
ITT	75
PP	46
Safety	76

Adapted from sponsor's electronic submission S3A40320 p.37

One patient (site #009292, patient #25116) was included in the safety population and not the ITT population because the patient was withdrawn for an adverse event, vascular access complication, prior to receiving chemotherapy.

Table B-3: Patients Who Completed the Study or Were Withdrawn (ITT Population)

	Zofran (N=75)
Intent-to-Treat (ITT)	75 (100%)
Completed Study	73 (97%)
Per-Protocol (PP)	46 (61%)
Prematurely Discontinued From Study	2 (3%)
Reason for Premature Withdrawal	
Consent withdrawn	1 (1%)
Other	1 (1%)

Adapted from sponsor's electronic submission Protocol S3A40320 p. 38

Table B-4: Major Protocol Deviations that Excluded patients from the PP Analysis

Major Protocol Deviation	N	(%)
Any Major Deviation	29	(39)
Use of ondansetron[1]	11	(15)
Use of metoclopramide	2	(3)
Pre-existing etiologies for emesis	3	(4)
No diagnosis of cancer[2]	1	(1)
Did not receive all 3 doses of study medication	2	(3)
Study duration < 22 hours	16	(21)

Study medication received > 2 hours prior to 1st dose of mod/highly emetogenic chemotherapy	5	(7)

Adapted from sponsor's electronic submission S3A40320 p. 39

1. Subject 25154 was identified as having received additional ondansetron and was included as having had a major PD. This was not technically a protocol deviation because it was received 3 ½ hours prior to study start and prior use of ondansetron was not prohibited by the protocol. Three additional patients received ondansetron as rescue after they competed the study (i.e., early completion) but prior to the 24 hours following the first moderately or highly emetogenic chemotherapy.
2. Subject 25076 was diagnosed with beta-zero thalassemia, undergoing bone marrow transplantation following emetogenic chemotherapy.

Table B-5: Safety Population

	Zofran (N=76)
Completed Study	73 (96%)
Safety (SP)	76 (100%)
Per-Protocol (PP)	46 (61%)
Prematurely Discontinued From Study	3 (4%)
Reason for Premature Withdrawal	
Adverse event	1 (1%)
Consent withdrawn	1 (1%)
Other (venous access problem)	1 (1%)

Adapted from sponsor's electronic submission S3A40320 p. 65

Demographics and Other Baseline Characteristics

Table B-6: Demographic Characteristics – ITT Population

	Zofran (N = 75)
	N (%)
Sex	
Female	43 (57)
Male	32 (43)
Age (months)	
Mean ± SD	27.1 ± 12.6
Min – Max	6 - 48
Race	
Black	11 (15)
American Hispanic	14 (19)
White	50 (67)
Other	
Height (cm)	
Mean ± SD	87.1 ± 11.9
Min – Max	61 – 125
Weight (kg)	
Mean ± SD	12.6 ± 3.1
Min – Max	6 - 20

Adapted from sponsor's electronic submission S3A40320 p. 40
Subject number 25116 who received the initial dose of Zofran, but was not included in the ITT population because he did not receive chemotherapy, was a 31 month old, American Hispanic male whose weight was 13.8 kg and height was 92 cm.

Comments: There were more females (57%) than males (43%), the mean age of patients was 27 months, with age ranging from 6 to 48 months. There were more white patients (67%) than either Black (15%) or Hispanic (19%) patients.

Table B-7: Primary Site of Cancer – ITT Population

Primary Site	**Zofran (N = 75)**
	n (%)
Head and Neck	5 (7)
Genito-urinary	7 (9)
Gynecologic	1 (1)
Hematopoietic/Immunologic	21 (28)
Bone and Soft Tissue	8 (11)
Other	33 (44)

Adapted from sponsor's electronic submission S3A40320 p. 40

Prior chemotherapy-induced emesis may increase a patient's risk of emesis during subsequent courses of chemotherapy. The numbers and percentages of patients who received prior chemotherapy and who had emesis following prior chemotherapy are displayed below.

Table B-8: Prior Cytotoxic Chemotherapy

	Zofran (N=75)
Received Prior Cytotoxic Chemotherapy	**n (%)**
Yes	65 (87)
No	10 (13)
Prior Emesis following Prior Chemotherapy	
Yes	48 (74)
No	17 (26)

Adapted from sponsor's electronic submission S3A40320 p. 42

Comments: Majority of the patients received cytotoxic chemotherapy in the past and had emesis after chemotherapy. Therefore, these patients appear to have the highest risk of emesis post-chemotheraphy and would benefit most from an antiemetic.

Concomitant Medications

Table B-9: Summary of Cytotoxic Chemotherapy Medication by Emetogenicity - ITT Population

Patients Receiving Chemotherapy	**Zofran (N=75)**
Any Chemotherapy	75(100%)
Emetogenicity: Low	
Any Chemotherapy	57 (76%)
VINCRISTINE	27 (36%)
ETOPOSIDE	15 (20%)
VP-16	9 (12%)
METHOTREXATE	6 (8%)
CYCLOPHOSPHAMIDE	3 (4%)
CYTARABINE	2 (3%)
MERCAPTOPURINE	2 (3%)
6-THIOGUANINE	1 (1%)
ARA-C	1 (1%)
E-COLI ASPARAGINASE	1 (1%)
ETOPOPHOS	1 (1%)
ETOPOSID	1 (1%)
L-ASPARAGINASE	1 (1%)
PREDNISONE	1 (1%)
THIOGUANINE	1 (1%)
THIOTEPA	1 (1%)
VP16	1 (1%)

Emetogenicity: Moderate	
Any Chemotherapy	**71 (95%)**
CARBOPLATIN	17 (23%)
DOXORUBICIN	12 (16%)
CYTOXAN	9 (12%)
CYCLOPHOSPHAMIDE	7 (9%)
IFOSFAMIDE	7 (9%)
METHOTREXATE	6 (8%)
CISPLATIN	5 (7%)
CYTARABINE	4 (5%)
ACTINOMYCIN D	3 (4%)
ADRIAMYCIN	3 (4%)
MELPHALAN	3 (4%)
ACTINOMYCIN	2 (3%)
CYTOSAR	2 (3%)
DACTINOMYCIN	2 (3%)
DAUNORUBICIN	2 (3%)
ETOPOSID	2 (3%)
ARA-C	1 (1%)
BUSULFAN	1 (1%)
DAUNOMYCIN	1 (1%)
DOXORUBICINE	1 (1%)
ETOPOSIDE	1 (1%)
IDARUBICIN	1 (1%)

Emetogenicity: High	
Any Chemotherapy	**18 (24%)**
CYCLOPHOSPHAMIDE	5 (7%)
CYTOXAN	4 (5%)
CISPLATIN	2 (3%)
DOXORUBICIN	2 (3%)
MELPHALAN	2 (3%)
BUSULFAN	1 (1%)
CARBOPLATIN	1 (1%)
CYTARABINE	1 (1%)
FLUDARABINE	1 (1%)
METHOTREXATE	1 (1%)

Adapted from sponsor's electronic submission S3A40320 p. 85 to 88

Ninety-five percent (95%) of patients received at least one moderately emetogenic chemotherapeutic agent and 24% received at least one highly emetogenic agent. The most common moderately emetogenic chemotherapy agents in this trial were carboplatin (23%), doxorubicin/doxorubicine/Adriamycin (21%), and Cytoxan™/cyclophosphamide (21%). The most common highly emetogenic agents was Cytoxan/cyclophosphamide (12%).

Treatment Compliance

- All three doses of study medication were received by 96% of patients
- 2 doses were received by 1%
- 1 dose was received by 3% of patients.

The first dose of study medication was had to be administered 30 minutes prior to the first chemotherapy. If the study medication was administered greater than 2 hours prior to the first dose of moderately or highly emetogenic chemotherapy, this was prospectively identified as a major protocol deviation that excluded patients from the per protocol analysis. Five (7%) patients were identified as having such a protocol deviation.

EFFICACY RESULTS

Complete response: no emetic episodes
Partial response: 1 to 2 emetic episodes.
Therapeutic failure: ≥ 3 emetic episodes, use of rescue medication, or withdrawal from the study for any reason.

More than half of patients had a complete response to study medication (ITT and PP), see table below.

Table B-10: Incidence of Emetic Episodes – ITT and PP Populations

	ITT (N = 75)	**PP (N = 46)**
	n (%)	n (%)
Complete Response (0 emetic episode)	42 (56)	28 (61)
Partial Response (1-2 emetic episodes)	8 (11)	8 (17)
Therapeutic Failure (≥3 emetic episodes)	25 (33)	10 (22)

Adapted from sponsor's electronic submission S3A40320 p. 44
Therapeutic failure is defined as > 2 emetic episodes, use of rescue medication, or withdrawal from the study for any reason.

Table B-11: Alternative Summary of Incidence of Emesis During 24-Hour Assessment Phase-ITT Population (Patients who received prophylactic dexamethasone were considered as therapeutic failures)

	Zofran
	(N=75)
Incidence of Emesis	
Complete Response (0 emetic episodes)	34 (45%)
Partial Response (1-2 emetic episodes)	7 (9%)
Therapeutic Failure [1]	34 (45%)

Adapted from sponsor's electronic submission S3A40320 p. 108

1 Therapeutic failure is defined as either having at least three emetic episodes, or receiving rescue antiemetic medication, or withdrawing due to any reason.
Note: Rescue antiemetic medication includes: a) Prophylaxis for emesis and/or nausea including systemic dexamethasone and b) all antiemetic medication for the treatment of emesis and/or nausea including systemic dexamethasone.

When patients who received prophylactic dexamethasone were considered as therapeutic failures, the complete response rate in the ITT population was decreased to 45% and the therapeutic failure rate increased to 45%. It appears that patients on both Zofran and dexamethasone have a higher therapeutic rate compared to ondansetron alone. However it will be difficult to draw any meaningful conclusion from these dat as there is no control and the numbers are small.

Proportion of patients Who Received Rescue Antiemetic Medications

The majority of patients in both the ITT and PP populations did not require rescue antiemetic medication.

Table B-12 Summary of Patients Who Received Rescue Medication ITT and PP Populations

	ITT Population (N = 75)	PP Population (N = 46)
Subject Received Rescue Medication	N (%)	n (%)
NO	52 (69)	38 (83)
YES[1]	23 (31)	8 (17)

Adapted from sponsor's electronic submission S3A40320 p. 45

1. Includes all patients who received any rescue antiemetic and all patients who received emesis prophylaxis, excluding dexamethasone.

Time to First Rescue Antiemetic Medication

Table B-13: Summary of Time to First Rescue Medication - ITT Population Rescue for Treatment of Emesis and/or Nausea

	Zofran (N=75)
Patients:	
n	75
Censored, follow-up ended	52 (69%)
Received Rescue medication	23 (31%)
Time to First Rescue Medication (minutes)	
n	23
Median	955
Min.	0
Max.	1380

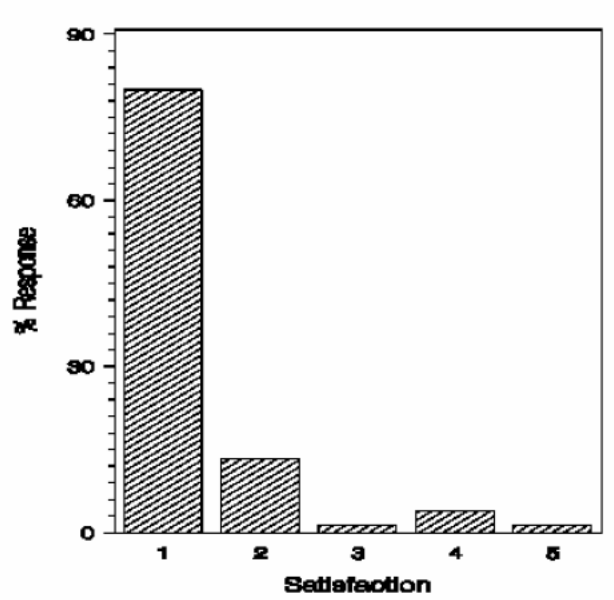
Adapted from sponsor's electronic submission S3A40320 p. 106

A total of 23 (31%) patients received rescue antiemetic medication(s) (not including prophylactic dexamethasone). The median time to first medication was 955 minutes (~16 hours).

Parent/Guardians Overall Satisfaction with Study Medication

A graphical representation of parent/guardian satisfaction for the ITT population is displayed in the figure below.

Figure B-1: Parent/Guardian Satisfaction with Study Medication



1. Very satisfied = 80%
2. Somewhat satisfied = 13%
3. Neither satisfied nor dissatisfied = 1%
4. Somewhat dissatisfied = 4%
5. Very dissatisfied = 1%

Comments: Majority of parents/guardians (93%) were either very satisfied or somewhat satisfied with the use of Zofran IV.

Time to First Emetic Episode

Table B-14: Summary of Time to First Emetic Episode - ITT Population

	Zofran (N=75)
Patients:	
n	75
Censored, follow-up ended	54 (72%)
Emetic Event Occurred	21 (28%)
Time to First Emetic Episode (minutes)	
n	21
Median	625
Min.	10
Max.	1432

Adapted from sponsor's electronic submission S3A40320 p. 118

A total of 21 patients experienced at least one emetic episode. For these 21 patients, median time to first emetic episode was 625 minutes (~10 hours) with a minimum of 10 minutes and a maximum of 1432 minutes (~24 hours). The median time includes only patients who experienced and emetic event.

Subgroup Analyses

Table B-15: Incidence of Emesis by Age, Gender, and Race – ITT Population

Subgroup	Complete Response[1]		Partial Response[1]		Therapeutic Failure[1]	
	n	(%)	n	(%)	n	(%)
Age						
6 to 12 months (N=10)	7	(70)	0		3	(30)
13 to 48 months (N=65)	35	(54)	8	(12)	22	(34)
Gender						
Female (N=43)	27	(63)	2	(5)	14	(33)
Male (N=32)	15	(47)	6	(19)	11	(34)
Race						
Black (N=11)	9	(82)	0		2	(18)
American Hispanic (N=14)	7	(50)	2	(14)	5	(36)
White (N=50)	26	(52)	6	(12)	18	(36)

Adapted from sponsor's electronic submission S3A40320 p. 49

1. Complete Response = 0 emetic episodes; partial response = 1-2 emetic episodes; therapeutic failure = ≥3 emetic episodes, or receiving rescue antiemetic medication, or withdrawing due to any reason

As shown above, a greater percentage of females (63%) and younger patients (6 months to 12 months of age; 70%) experienced complete response than did males and older patients (13 months to 48 months of age). The black subgroup had a higher percentage of patients who experienced complete response, the percentages American Hispanics who experienced complete response, partial response and therapeutic failure were comparable to the white subgroup.

Comments: Although the number of patients in each subgroup are too small to be able to make meaningful conclusions, it can be safely said that at least 50% of patients in each subgroup had a complete response.

Table B-16: Summary of Patients Who Received Rescue Antiemetic Medication

Subgroup	Received Rescue		Did Not Receive Rescue	
	n	(%)	n	(%)
Age				
6 to 12 months (N=10)	3	(30)	7	(70)
13 to 48 months (N=65)	20	(31)	45	(69)
Gender				
Female (N=43)	12	(28)	31	(72)
Male (N=32)	11	(34)	21	(66)
Race				
Black (N=11)	1	(9)	10	(91)
American Hispanic (N=14)	5	(36)	9	(64)
White (N=50)	17	(34)	33	(66)

Adapted from sponsor's electronic submission S3A40320 p. 50

Comments: As shown on the table above, the percentage of patients who received rescue antiemetic was similar across age and gender groups, approximately around a third of the patients. The black subgroup had a higher percentage of patients who did not require rescue medication.

SAFETY RESULTS

Extent of Exposure

A total daily dose of 0.45 mg/kg, three doses of Zofran 0.15 mg/kg/dose were prescribed. Zofran was used as rescue medication in 13 patients, although was not permitted to use as a rescue medication. Three of these patients completed the study early and the additional Zofran was administered after study completion, but within the 24-hour assessment window. These patients were included in the Summary of the Extent of Exposure.

Three (4%) patients received 0.36 mg/kg or less of the 0.45 mg/kg total daily dose of Zofran prescribed by the protocol, while 54 (71%) received between 0.37 and 0.45 mg/kg, and 19 (25%) received 0.46 to 0.54 mg/kg. When Zofran given as rescue antiemetic medication was included in the total daily dose, 13 (17%) received >0.54 mg/kg, ranging from 0.61 mg/kg to 1.97 mg/kg.

Of the 13 who received >0.54 mg/kg, 5 experienced adverse events which the investigator considered as not related to the study drug.

Table B-17: Summary of Extent of Exposure of Zofran - Safety Population

	Zofran
Zofran Dosage (mg/kg)	**(N=76)**
Total Treatment	
< 0.27	2 (3%)
0.27 - 0.36	1 (1%)
0.37 - 0.45	54 (71%)
0.46 - 0.54	19 (25%)
> 0.54	0
Total Rescue[1]	
None Given	63 (83%)
< 0.27	0
0.27 - 0.36	0
0.37 - 0.45	4 (5%)
0.46 - 0.54	4 (5%)
> 0.54	5 (7%)
Total Exposure	
None Given	0
< 0.27	1 (1%)
0.27 - 0.36	1 (1%)
0.37 - 0.45	47 (62%)
0.46 - 0.54	14 (18%)
> 0.54	13 (17%)

Adapted from sponsor's electronic submission S3A40320 p. 122
The dose administered is determined by: Actual Dose (mg) administered / weight (kg)
[1] Total Rescue reflects doses of Zofran given for the treatment of emesis and/or nausea

Adverse Events

All patients who received any ondansetron study medication (N=76) were included in the safety evaluation. Below is a summary of all reported adverse events during the study.

Table B-18: Summary of All Adverse Events During the Study - Safety Population

System Organ Class Preferred Term	Zofran (N=76)	
ANY EVENT	**21 (28%)**	
Gastrointestinal disorders		
ANY EVENT	**8**	**(11%)**
Nausea	**5**	**(7%)**
Stomach discomfort	**2**	**(3%)**
Constipation	**1**	**(1%)**
Teething	**1**	**(1%)**
Injury, poisoning and procedural complications		
ANY EVENT	**5**	**(7%)**
Contusion	**1**	**(1%)**
Excoriation	**1**	**(1%)**
Fall	**1**	**(1%)**
Post procedural nausea	**1**	**(1%)**
Vascular access complication	**1**	**(1%)**
Psychiatric disorders		
ANY EVENT	**4**	**(5%)**
Irritability	**3**	**(4%)**
Aggression	**1**	**(1%)**
Skin and subcutaneous tissue disorders		
ANY EVENT	**3**	**(4%)**
Palmar erythema	**1**	**(1%)**
Rash	**1**	**(1%)**
Skin ulcer	**1**	**(1%)**
General disorders and administration site conditions		
ANY EVENT	**1**	**(1%)**
Pain	**1**	**(1%)**
Metabolism and nutrition disorders		
ANY EVENT	**1**	**(1%)**
Decreased appetite	**1**	**(1%)**
Musculoskeletal and connective tissue disorders		
ANY EVENT	**1**	**(1%)**
Pain in extremity	**1**	**(1%)**
Respiratory, thoracic and mediastinal disorders		
ANY EVENT	**1**	**(1%)**
Cough	**1**	**(1%)**
Nasal congestion	**1**	**(1%)**

Adapted from sponsor's electronic submission S3A40320 p. 123-125

A total of 28% of patients experienced one or more adverse events. Each of the AEs reported occurred in only 1 (1%) patient, with the following exceptions occurring ≥ 2%: nausea (5,7%) irritability (3, 4%), and stomach discomfort (2, 3%).

Rash (n=1, 1%) was the only AE that was considered by the investigator to be related to the trial drug. AEs reported were mostly severe, no AE was reported to be severe.

No clinically important differences in the nature of AEs was detected between age groups, race or gender.

One patient, 25116, withdrew from the trial at the mother's request due to a vascular access complication prior to receiving chemotherapy.

Serious Adverse Events

There were no deaths or other serious adverse events were reported during the study.

Other Relevant Adverse Events

The Written Request prospectively identified potential drug-specific safety considerations which included constipation, extrapyramidal reactions, redness/inflammation at the injection site, rash, hypersensitivity reactions, and seizures. Below is a table of similar adverse events.

Table B-19: Potential Drug-specific Safety Considerations – Safety Population

	Zofran	
Adverse Event	(N = 76)	
	n	(%)
Rash	1	(1)
Palmer erythema	1	(1)
Constipation	1	(1)

Adapted from sponsor's electronic submission S3A40320 p. 54

Symptoms Suggestive of Liver Function Abnormalities

The sponsor states that the extensive safety record of Zofran does not indicate that liver function abnormalities would be of particular concern with the administration of Zofran. The risk-benefit consideration was assessed and in an effort to minimize the total amount of blood drawn from each patient, only baseline LFTs were required. Any observed abnormalities would be difficult, if not impossible to explain due to the lack of a randomized control group and the administration of polypharmacy, Follow-up of AEs including additional laboratory tests were to be done when clinically indicated. No reports of additional LFTs were volunteered.

Other Safety Evaluations

Heart rate and blood pressure were measured prior to study medication administration and at the end of the 24-Hour Assessment Phase. No clinical laboratory evaluations were required, except for baseline liver function tests.

Line-by-Line Labeling Review

See section 9.4

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/s/

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