CLINICAL REVIEW

Application Type	NDA
Submission Number	20-007
Submission Code	S-035
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Reviewer Name	Lolita A. Lopez, M.D.
Medical Team Leader	Ruyi He, M.D.
Review Completion Date	February 15, 2005
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

EXECUTIVE SUMMARY

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 and the sNDA Team's labeling recommendations.

2 Recommendation on Postmarketing Actions

No postmarketing commitments are recommended for this sNDA.

3 Summary of Clinical Findings

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 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, 336 received Zofran.

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 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 old to claim for the indication of prevention of PONV as well as cancer patients 6 to 48 months old 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. 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.

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

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.

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.

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. 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 ≥ 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.

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.

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.

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/s/

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