

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-007 / SE5-035

Generic Name: Zofran[®] Injection

Active Ingredient: Ondansetron

Sponsor: GlaxoSmithKline

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Efficacy Supplement for
Pediatric Labeling

Proposed Indications: Prevention of post-operative nausea and vomiting in surgical patients aged 1 month to 24 months and prevention of chemotherapy-induced nausea and vomiting in cancer patients aged 6 months to 48 months who receive moderately to highly emetogenic chemotherapy

Submission Date: 9/28/04

Related Submissions: IND (b) (4)

ORM Division: GI & Coagulation
Drug Products

OCPB Division: DPE II

Team Leader: Suresh Doddapaneni, Ph.D.

Proposed Dosage Regimen: In pediatric cancer patients aged 6 months to 48 months, 0.15 mg/kg is administered Q 4 hours for 3 doses

In pediatric surgical patients aged 1 month to 12 years, a single 0.1 mg/kg dose is administered to patients weighing 40 kg or less, or a single 4 mg dose for patients weighing more than 40 kg.

I. **Executive Summary**

Zofran[®] (ondansetron) I.V. (NDA 20-007) is currently approved for marketing in the US for the prevention of (1) chemotherapy-induced nausea and emesis (CINV) in adult cancer patients and in pediatric cancer patients 4-18 yrs of age and (2) post-operative nausea and vomiting (PONV) in adults and children 2 to 12 yrs of age.

A pediatric Written Request (PWR) for ondansetron was issued on 6/26/01 to obtain pediatric information in younger age groups. The PWR consists of three studies assessing pharmacokinetics (PK), exposure, and safety. Study 1 is a pharmacokinetic study evaluating one or more dose levels of ondansetron in pediatric patients aged 1 month to 24 months who are undergoing surgery. Study 2 assesses the safety, tolerability and ability to prevent post-operative nausea and vomiting in pediatric patients aged 1 to 24 months who are undergoing surgery, while study 3 assesses the safety, tolerability, pharmacokinetics (PK) and ability to prevent nausea and vomiting in pediatric cancer patients aged 6 months to 48 months with moderately to highly emetogenic chemotherapy.

Supplement SE5-035 to NDA 20-007 is submitted in support of the use of ondansetron in pediatric surgical patients aged 1 month to 24 months, and pediatric cancer patients aged 6 months to 48 months who receive moderately to highly emetogenic chemotherapy.

The submission consists of three studies; studies S3A40319, S3A40323, and S3A40320 corresponding to studies 1, 2, and 3 of the PWR. This review does not address the findings of study S3A40323 as the study did not evaluate the PK of ondansetron.

The findings of study S3A40319 indicate that for pediatric surgical patients aged 1 to 4 months, clearance (CL) of was lower and half-life was prolonged compared to patients aged > 4 to 24 months. Despite an increase in half-life by more than 2-fold in pediatric patients aged 1 to 4 months, no dosage adjustment is warranted in pediatric patients since Zofran I.V. is administered as a single dose for the treatment of PONV (i.e., no accumulation is projected with single dose administration of ondansetron). However, those patients should be monitored carefully in view of higher plasma levels.

The population PK analysis using combined data from studies S3A40319 and S3A40320 indicated that administration of a dose of I.V. Zofran 0.15 mg/kg every 4 hours for 3 doses in cancer patients aged 6 to 48 months results in systemic exposure levels similar to those achieved in older cancer patients (4 to 18 years; study S3A-150) at similar doses.

Taken altogether, the findings of studies S3A40319 and S3A40320 support the use of the weight-based dosing regimens for prevention of PONV and CINV in younger pediatric patients similar to those currently approved for older pediatric patients.

A. Recommendations

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 20-007 / S-035 is **acceptable** provided that a mutually satisfactory agreement can be reached between the sponsor and Agency. See Appendix A for the sponsor's proposed package insert.

From a Clinical Pharmacology perspective, the sponsor has adequately fulfilled the studies outlined in the Pediatric Written Request (PWR) for Zofran[®].

B. Phase IV Commitments

None.

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C. Summary of CPB Findings

NDA 20-007/S-035 consists of three studies; study **S3A40319** (a multi-center, two-arm, single dose PK study of I.V. Zofran in pediatric surgical patients aged 1 to 24 months), study **S3A40323** (a randomized, double-blind, placebo-controlled, multi-center study of I.V. ondansetron 0.1 mg/kg for the prevention of postoperative emesis in pediatric surgical patients aged 1 to 24 months who are undergoing routine surgery under general anesthesia) and study **S3A40320** (an open-label, multi-center study of the safety, PK and anti-emetic effect of 0.15 mg/kg I.V. ondansetron administered for 3 doses to pediatric cancer patients aged 6 to 48 months who are receiving moderately to highly emetogenic chemotherapy).

The current review solely addresses the Clinical Pharmacology and Biopharmaceutics-related results in the submission (i.e., studies 3A40319 & 3A40320).

The results of the study S3A40319 indicate that clearance of ondansetron was reduced and half-life was prolonged in 1-4 month old pediatric surgical patients relative to > 4-24 month old pediatric patients.

The results of the population PK analysis which used combined data from studies S3A40319 and S3A40320 demonstrate that administration of I.V. Zofran 0.15 mg/kg every 4 hours for 3 doses in cancer patients aged 6 to 48 months results in systemic exposure levels similar to those achieved in older cancer patients (4 to 18 years; study S3A-150) at similar doses.

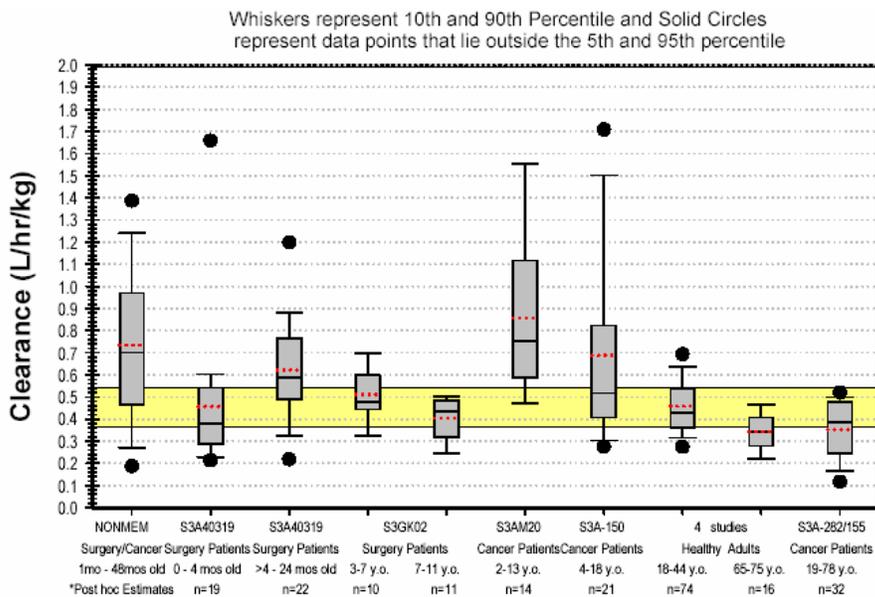


Fig. 1. Weight normalized ondansetron CL by type of patient and age

II. Question-Based Review

A. General Attributes

Ondansetron (Zofran[®]) is a 5-HT₃ receptor antagonist. It was first approved for marketing in the US on 1/4/1991.

Zofran[®] is currently approved for marketing in the US for the prevention of chemotherapy-induced nausea and emesis (CINV) in adult cancer patients and in pediatric cancer patients 4-18 yrs of age. It is additionally approved for the prevention of post-operative nausea and vomiting (PONV) in adults and children 2 to 12 yrs of age.

B. General Clinical Pharmacology

1. Are pediatric surgical patients aged 1 to 24 months and pediatric cancer patients aged 6 to 48 months who are receiving moderately to highly emetogenic chemotherapy comparable to older children on their PK/PD profiles of ondansetron?

Study S3A40319 evaluated the PK aspects of I.V. Zofran 0.1 mg/kg and 0.2 mg/kg in pediatric surgical patients aged 1 to 24 months. Forty six male and female pediatric surgical patients (stratified by age to two groups; 1-4 months and > 4-24 months) received either 0.1 mg/kg or 0.2 mg/kg single doses of I.V. Zofran. The study was conducted in a non-randomized, open label, two-arm, multi-center fashion. Blood samples were drawn for determination of ondansetron PK up to 8 hrs post-dose.

Table 1. Summary of the mean PK parameters (with 95% confidence intervals) for ondansetron I.V., 0.1 mg/kg and 0.2 mg/kg in pediatric patients aged 1-4 months and > 4-24 months (n = 41)

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

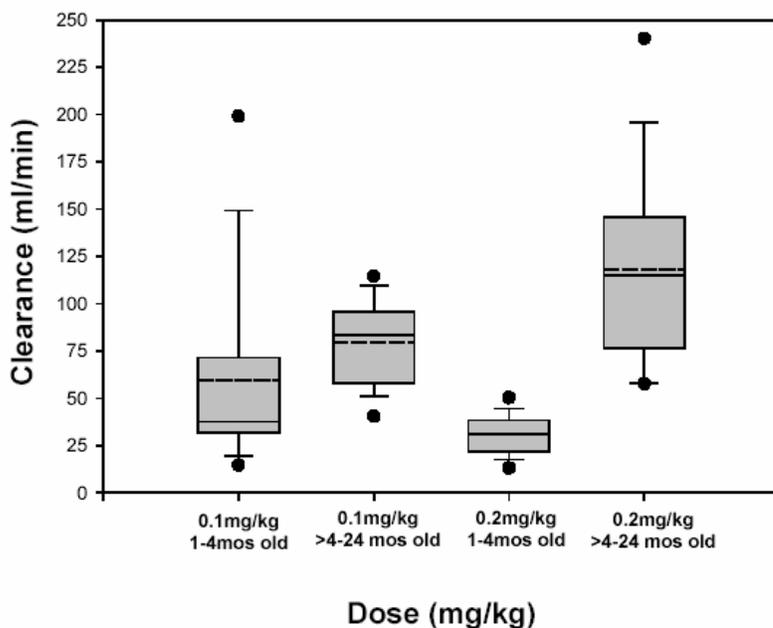


Fig. 2. Weight-normalized CL vs. dose for ondansetron

Following administration of I.V. ondansetron at doses of 0.1 mg/kg and 0.2 mg/kg to pediatric patients aged 1-4 months and > 4-24 months, mean C_{max} increased around 2-fold in both age groups. While $AUC_{0-\infty}$ was similar between the two age groups at the 0.1 mg/kg dose, $AUC_{0-\infty}$ values increased following administration of the 0.2 mg/kg dose by 2.5-fold and 1.4-fold in the 1-4 months and > 4-24 months groups, respectively (Table 1). The mean terminal half-life ($t_{1/2}$) of ondansetron in pediatric patients aged 4-24 months was 2.4-3.1 hrs following administration of 0.1 mg/kg and 0.2 mg/kg doses of I.V. ondansetron, while in patients aged 1-4 months, the mean terminal half-life of ondansetron was 5.9-6.2 hrs following administration of both doses of ondansetron. Despite an increase in half-life by more than 2-fold in pediatric patients aged 1 to 4 months, no dosage adjustment is warranted in pediatric patients aged 1 to 4 months since Zofran I.V. is administered as a single dose for the treatment of PONV.

Study S3A40320 was a multi-center, open-label study to evaluate the population PK of I.V. Zofran in pediatric cancer patients aged 6 to 48 months who were receiving moderately to highly emetogenic chemotherapy. Seventy six male and female pediatric cancer patients received three 0.15 mg/kg doses of I.V. ondansetron, beginning 30 min prior to emetogenic chemotherapy and at 4 and 8 hrs after the first dose. Blood samples were drawn for determination of ondansetron PK up to 8 hrs post-dose.

Population PK analysis was originally planned using data from pediatric cancer patients only (study S3A40320). However, due to difficulty in patient recruitment to meet the number of patients as specified in the ondansetron PWR, the PWR was amended per the sponsor's request to allow inclusion of PK data from 51 pediatric surgical patients (study S3A40319) in the population PK analysis.

Table 2. Mean (95% confidence interval) PK parameters for ondansetron in adult and pediatric cancer patients

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

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

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

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

Based on the population PK analysis, cancer patients aged 6 to 48 months who received I.V. Zofran doses of 0.15 mg/kg Q 4 hrs for 3 doses are expected to achieve systemic exposure levels similar to those achieved in older cancer patients (4 to 18 years; study S3A-150) at similar doses (Table 2).

Furthermore, in pediatric cancer subjects aged 2 to 18 years (n=35; Studies S3A-150 and S3AM20), it was determined that the AUC₉₀ (AUC required to achieve a 90% response) was around 250 ng·h/mL (Appendix C). In other words, pediatric cancer subjects with AUC_{0-∞} > 250 ng·h/mL had the best opportunity for a complete response (i.e. no emetic episodes). A similar exposure-response relationship was observed in study S3A40320, where at the model-predicted AUC_{0-∞} values > 250 ng·h/mL (26% of patients), there was complete control (no emetic episodes) in the majority of the subjects and only 2 patients had a partial response (1 emetic episode each). When model-predicted AUC_{0-∞} values were > 150 ng·h/mL¹ (68% of the patients), only one subject was classified as a therapeutic failure as they had more than one emetic episode and 9 subjects had partial responses (1 emetic episode each).

The results of study S3A40323 (a randomized, double-blind, placebo-controlled, multi-center study of I.V. ondansetron 0.1 mg/kg for the prevention of postoperative emesis in pediatric surgical patients aged 1 to 24 months who are undergoing routine surgery under general anesthesia) indicate that the proportion of patients who experienced an emetic episode corresponded to a total of 28% placebo and 11% Zofran patients, which is similar to the findings of study S3A40319 where 10% of Zofran patients experienced emesis.

Overall, pediatric surgical and cancer patients seem to have higher ondansetron CL and shorter half-lives relative to adults. In patients aged 1 to 4 months however, a longer half-life of ondansetron has been observed, mainly due to the higher volume of distribution relative to older pediatric patients and adults.

¹ Based on exposure/response data from studies S3A-150 and S3AM20, AUC₅₀ of the antiemetic effect of ondansetron in pediatric cancer patients was determined to be 170 ng·h/mL.

The PK and exposure/response findings of studies S3A40319 and S3A40320 for I.V. Zofran in pediatric surgical (aged 1 month to 24 months) and cancer (aged 6 month to 48 months) patients are generally comparable to those of older children and support the use of the weight-based dosing regimens for prevention of PONV and CINV in younger pediatric patients similar to those currently approved for older pediatric patients.

E. General Biopharmaceutics

None

F. Analytical Section

Plasma concentrations of ondansetron were determined using protein precipitation and a validated LC-MS/MS assay method (# RBMT-MET-255.00) over a range of 0.5 to 500.0 ng/mL. The lower limit of quantitation was established at 0.5 ng/mL.

At all validation sample concentrations examined, the % bias is less than $\pm 15\%$, while the maximum average % bias observed was -5.5% . In addition, the within- and between-assay precision are $\leq 15\%$ and the maximum average within- and between-assay precision observed were 7.3% and 7.4% , respectively.

Overall, the analytical assay method utilized in the submission was adequately validated.

III. Appendices

A. Proposed Package Insert (original and Agency proposed)

B. Individual Study Reviews

C. Exposure-Response Relationship for Ondansetron in Pediatric Cancer patients

D. Pediatric Written Request for Ondansetron

E. Cover Sheet and OCPB Filing/Review Form

Appendix A

Proposed Package Insert

18 Page(s) of Draft Labeling has been Withheld in Full as B4
(CCI/TS) immediately following this page

Appendix B

Individual Study Reviews

NDA: 20-007/ S-035 - Study S3A40319

Study Date: Jan 2002-May 2002

Type of Study: PK Study in Pediatric surgical Patients Aged 1 month to 24 months

The study is entitled,

“A PHASE IV, MULTI-CENTER, TWO-ARM, SINGLE DOSE PHARMACOKINETIC STUDY OF INTRAVENOUS ZOFRAN IN PEDIATRIC SURGICAL PATIENTS FROM 1 MONTH TO 24 MONTHS OF AGE”

Primary Objective(s)

- To assess the PK, safety and tolerability of I.V. Zofran in pediatric surgical patients aged 1 to 24 months.

Study Design

Non-randomized, multi-center, two-arm, single-dose PK and safety study

Subjects 46 pediatric patients (out of 51 enrolled patients)

Key Inclusion

Criteria

Male and female pediatric patients aged 1-24 months
Patients weighed ≥ 3 kg
Patients scheduled to undergo procedures requiring general anesthesia

Treatment

Patients stratified into two groups (1-4 months and > 4-24 months) were assigned to receive one of two single treatments: I.V. Zofran slow (30 sec) injection 0.1 mg/kg OR 0.2 mg/kg.

PK Sampling

Times

For determination of ondansetron plasma concentrations, blood samples were collected at the following time points:

0 (at end of slow injection), 1, 2, 4, 6 and 8 hrs post-dose.

Pharmacokinetic Analysis

The following PK parameters were determined: AUC_{0-last} , AUC_{0-inf} , C_{max} , t_{max} , $t_{1/2}$, CL & V_{dss} . The calculated PK parameters were summarized by dose group and by age group.

Results and Discussion

Table 1. Summary of the mean PK parameters (with 95% confidence intervals) for ondansetron I.V., 0.1 mg/kg and 0.2 mg/kg in pediatric patients aged 1-4 months and > 4-24 months (n = 41)

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

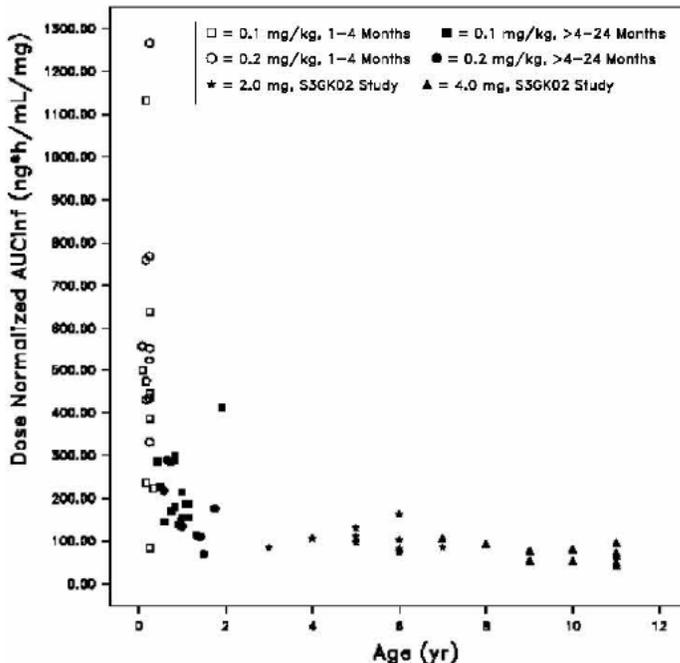


Fig. 1. Dose-normalized AUC_{0-inf} vs. age for ondansetron

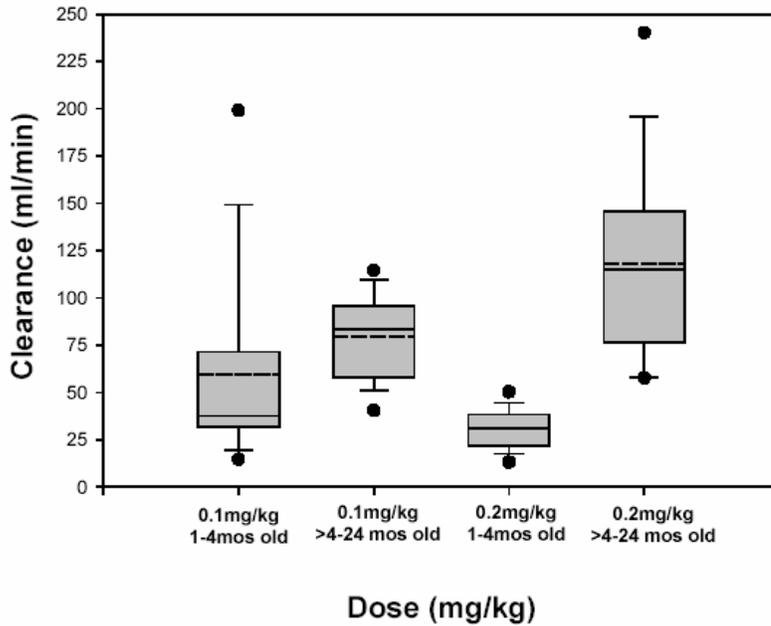


Fig. 2. Weight-normalized CL vs. dose for ondansetron

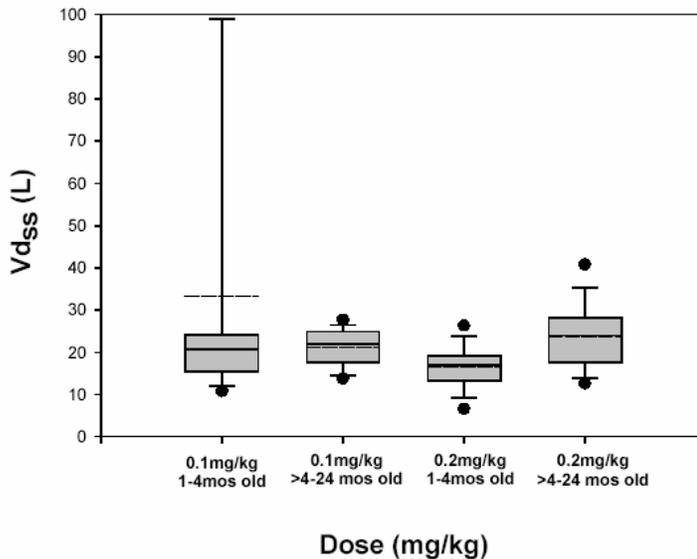


Fig. 3. Weight-normalized Vdss vs. dose for ondansetron

- Following administration of I.V. ondansetron at doses of 0.1 mg/kg and 0.2 mg/kg to pediatric patients aged 1-4 months and > 4-24 months, mean C_{max} increased around 2-fold in both age groups. However, C_{max} was around 20% greater in > 4-24 months group relative to the 1-4 months group at both doses (Table 1). While AUC_{0-∞} was similar between the two age groups at the 0.1 mg/kg dose, AUC_{0-∞} values increased following administration of the 0.2 mg/kg dose by 2.5-fold and 1.4-fold in the 1-4

months and > 4-24 months groups, respectively. This might be attributed to the relatively high PK variability observed in pediatric patients < 4 months of age compared to older pediatric patients, which in turn might be due to immaturity of hepatic metabolizing enzymes at this age, known to play a key role in the clearance of ondansetron (Fig. 1). However, individual ages of the pediatric subjects were not available in the study report to allow for an in-depth evaluation of the effect of age on the PK of ondansetron in the youngest of the patients participating in this study.

- The mean terminal half-life ($t_{1/2}$) of ondansetron in pediatric patients aged 4-24 months was 2.4-3.1 hrs following administration of 0.1 mg/kg and 0.2 mg/kg doses of I.V. ondansetron. This is comparable to the reported mean half-life of ondansetron (2.5-3 hrs) in older pediatric patients aged 3-12 years. As for patients aged 1-4 months, the mean terminal half-life of ondansetron was 5.9-6.2 hrs following administration of both doses of ondansetron. Those findings are in agreement with the observed reduction in CL and increase in V_{dss} of ondansetron in the youngest pediatric patients (Table 1).

NDA: 20-007/ S-035 - Studies S3A40319 & S3A40320 Study Date: Mar 2003-Mar 2004

Type of Study: Population PK Analysis in Pediatric Patients Aged 1 month to 48 months

Population PK analysis was originally planned using data from pediatric cancer patients only (study S3A40320). However, due to difficulty in patient recruitment to meet the number of patients as specified in the ondansetron PWR, the PWR was amended per the sponsor's request to allow inclusion of PK data from pediatric surgical patients (study S3A40319) in the population PK analysis.

Primary Objective(s)

- To develop a PK model to characterize the population PK of ondansetron in pediatric cancer and surgical patients aged 1 to 48 months.

Study Design

Study S3A40319 was a multi-center, two-treatment arm, single dose, PK study in pediatric surgical patients aged 1 to 24 months. Study S3A40320 was a multi-center, open-label study in pediatric cancer patients aged 6 to 48 months who were receiving moderately to highly emetogenic chemotherapy.

Subjects 51 pediatric surgical patients (study S3A40319) and 76 pediatric cancer patients (study S3A40320). Of a total of 127 pediatric patients, data from 115 pediatric patients were included in the population PK analysis

Treatments In study S3A40319, patients were stratified into two groups (1-4 months and > 4-24 months) were assigned to receive one of two single treatments: I.V. ondansetron slow (30 sec) injection 0.1 mg/kg OR 0.2 mg/kg.

In study S3A40320, patients received three 0.15 mg/kg doses of I.V. ondansetron, beginning 30 min prior to emetogenic chemotherapy and at 4 and 8 hrs after the first dose

PK Sampling

Times For determination of ondansetron plasma concentrations, blood samples were collected at the following time points:

Study S3A40319: 0 (at end of slow injection), 1, 2, 4, 6 and 8 hrs post-dose.

Study S3A40320: Pre-dose # 2, 2-5 min post-dose # 2, 0.5-1.5 hrs post-dose # 2, 2-3 hrs post-dose # 2, pre-dose # 3, 2-5 min post-dose # 3 & 12-24 hrs post-dose # 3

Population Pharmacokinetic Analysis

The main objective of the population PK analysis was to develop a basic PK model that would describe the population PK of ondansetron in pediatric cancer and surgical patients aged 1 to 48 months. The initial model selected for this analysis was based on previous experience with ondansetron. Following an assessment of intersubject variability and residual error, the initial model was refined to the “base” model. Subsequent forward-addition and backward-elimination of covariates in the base model resulted in the final full model. Improvements to the model were assessed by the log likelihood ratio test (i.e., reduction in the objective function), improvements in the agreement between the observed and the predicted ondansetron serum concentrations and improvement in plots of the weighted residuals versus the predicted ondansetron concentrations and versus time.

Results and Discussion

Table 2. Summary of the PK parameter estimates of the base and final Population PK models

Parameter	Base Model Population Parameter	Std Error of Parameter Estimate	Inter Subject Variability, CV%	Final Model Population Parameter	Std Error of Parameter Estimate	Inter Subject Variability, CV%
CL (L/h) = θ_1	5.29	0.526	82%	5.67	0.333	78%
V1 (L) = θ_4	3.26	0.523	221%	5.65	0.749	167%
CLd (L/h) = θ_6	93.6	10.4	-	78.1	8.77	-
V2 (L) = θ_7	27.8	2.07	63%	31.2	1.66	48%
θ_2 (WT on CL)	-	-	-	0.759	0.107	-
θ_3 (AGE on CL)	-	-	-	-0.352	0.097	-
θ_5 (WT on V1)	-	-	-	0.641	0.088	-
θ_8 (WT on V2)	-	-	-	0.29	0.068	-
	Residual Variance	Std Error	Residual CV%	Residual Variance	Std Error	Residual CV%
σ^2 proportional	0.11	0.071	33%	0.127	0.055	36%
σ^2 additive	13.1	13.8	-	-	-	-

Table 3. Median and 95% confidence intervals for ondansetron PK parameters using the final population PK model

Parameter	Fixed-effect Parameter Estimate (SE) from Modeling	Bootstrap 95% CI
CL (L/h) = θ_1	5.67 (0.333)	5.01, 6.60
$\times e^{(\theta_2 \times \text{AWT})}$	0.759 (0.107)	0.41, 1.41
$\times e^{(\theta_3 \times \text{AAGE})}$	-0.352 (0.097)	-1.074, 0.034
V1 (L) = θ_4	5.65 (0.749)	3.6, 12.7
$\times e^{(\theta_5 \times \text{AWT})}$	0.641 (0.088)	0.0, 1.029
CLD (L/h) = θ_6	78.1 (8.77)	37.0, 95.2
V2 (L) = θ_7	31.2 (1.66)	24.1, 35.4
$\times e^{(\theta_8 \times \text{AWT})}$	0.29 (0.068)	0.137, 0.467

SE = standard error of the estimate

95%CI = 95% confidence interval

AWT = (WT-Mean_{WT})/SD_{WT}

AAGE = (AGE-Mean_{AGE})/SD_{AGE}

Table 4. Ondansetron PK parameter values predicted for the typical patient aged 20.5 months and weighing 10.8 kg

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

Table 5. Mean (95% confidence interval) PK parameters for ondansetron in adult and pediatric cancer patients

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

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

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

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

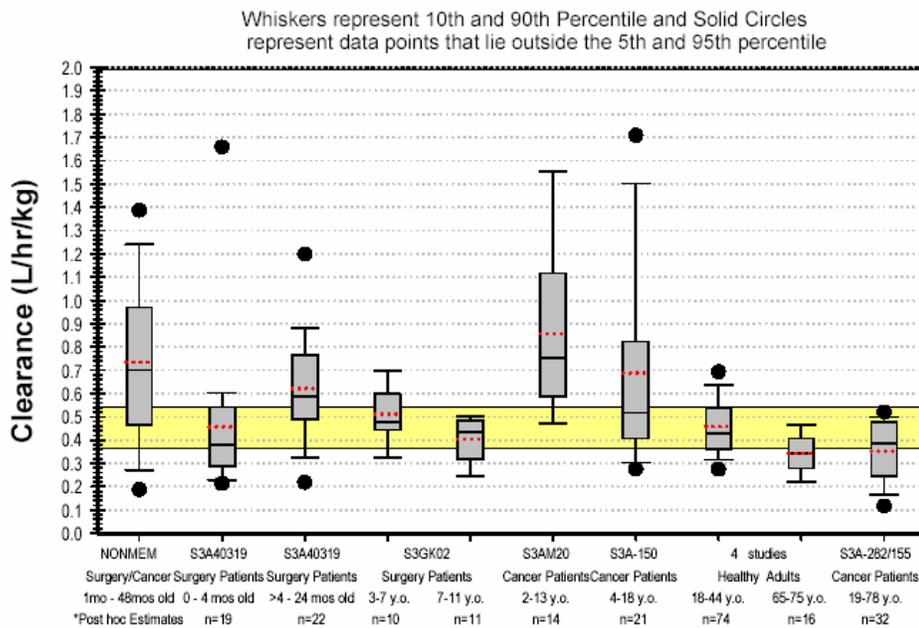


Fig. 4. Weight-normalized ondansetron CL by type of patient and age

- The PK of ondansetron in pediatric surgical and cancer patients were best characterized by a two-compartment model with a constant-rate infusion and first-order elimination.
- The results of the population PK analysis indicate that weight was a significant covariate for CL, V1 and V2, while age was only significant for CL.

- After adding weight and age to the model, the addition of other covariates such as height, BSA, gender, race, pre-dose liver function tests and co-existing disease did not improve the model, indicating that CL and V of ondansetron do not have a relationship with those covariates.
- The final model was validated using bootstrapping to estimate the confidence intervals of parameters (Table 3). Weight normalized CL in pediatric surgical and cancer patients aged 1 to 48 months was comparable to that observed in pediatric cancer patients aged 4 to 18 years.
- Based on the population PK analysis, cancer patients aged 6 to 48 months who received I.V. Zofran doses of 0.15 mg/kg Q 4 hrs for 3 doses are expected to achieve systemic exposure levels similar to those achieved in older cancer patients (4 to 18 years; study S3A-150) at similar doses (Table 5).
- In pediatric cancer subjects aged 2 to 18 years (n=35), it was determined that the AUC₉₀ (AUC required to achieve a 90% response) was around 250 ng·h/mL (Appendix C). In other words, pediatric cancer subjects with AUC_{0-∞} > 250 ng·h/mL had the best opportunity for a complete response (i.e. no emetic episodes). A similar exposure-response relationship was observed in study S3A40320, where at the model-predicted AUC_{0-∞} values > 250 ng·h/mL (26% of patients), there was complete control (no emetic episodes) in the majority of the subjects and only 2 patients had a partial response (1 emetic episode each). When model-predicted AUC_{0-∞} values were > 150 ng·h/mL (68% of the patients), only one subject was classified as a therapeutic failure as they had more than one emetic episode and 9 subjects had partial responses (1 emetic episode each).

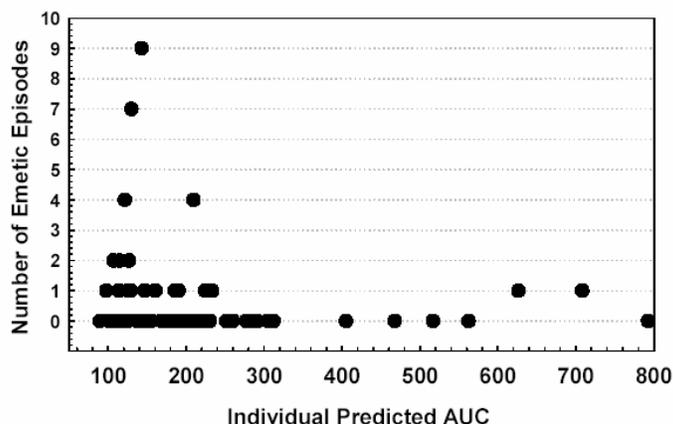


Fig. 2. Number of emetic episodes vs. model-predicted AUC_{0-∞} in cancer patients aged 6 to 48 months (study S3A40320)

The results of study S3A40323 (a randomized, double-blind, placebo-controlled, multi-center study of I.V. ondansetron 0.1 mg/kg for the prevention of postoperative emesis in pediatric surgical patients aged 1 to 24 months who are undergoing routine surgery under general anesthesia) indicate that the proportion of patients who experienced an emetic episode corresponded to a total of 28% placebo and 11%

Zofran patients, which is similar to the findings of study S3A40319 where 10% of Zofran patients experienced emesis.

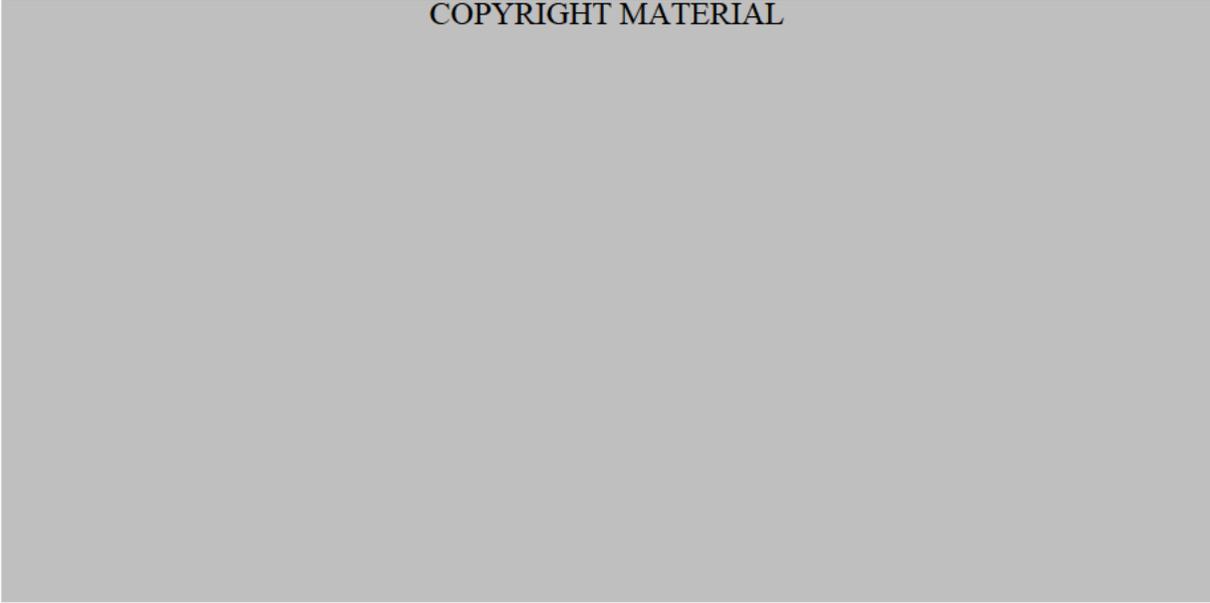
- Overall, pediatric surgical and cancer patients seem to have higher ondansetron CL and shorter half-lives relative to adults. In patients aged 1 to 4 months however, a longer half-life of ondansetron has been observed, mainly due to the higher volume of distribution relative to older pediatric patients and adults (Fig. 4).

Appendix C

Exposure-Response Relationship for Ondansetron in Pediatric Cancer Patients

EVALUATION OF THE EXPOSURE-RESPONSE RELATIONSHIP FOR ONDANSETRON IN PEDIATRIC CANCER PATIENTS. LJ Haberer, Ph.D.^{1*} and JL Palmer, M.Sc., LRSC.^{2*}: ¹Clinical Pharmacology, Glaxo Research Institute, RTP, NC & ²Glaxo Research and Development Ltd, Greenford, Middlesex, UK.

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Appendix D

PWR for Ondansetron



NDA 20-007

Glaxo Wellcome Inc.
Attention: Craig A. Metz, Ph.D.
Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. Metz:

Reference is made to your Proposed Pediatric Study Request submitted on July 28, 2000 for Zofran (ondansetron) Injection to NDA 20-007.

To obtain needed pediatric information on ondansetron, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

• **Type of studies:**

Study 1: A pharmacokinetic (PK) assessment of one or more dose levels of ondansetron in pediatric patients aged one month up to two years who are undergoing surgery. Either a traditional PK or population PK approach may be used. This study should be done prior to studies 2 and 3 below (see Objectives for study 1 in the next section below).

Study 2: A study of ondansetron's safety, tolerability, and ability to prevent post-operative nausea and vomiting (PONV) in pediatric patients aged one month up to two years who are undergoing surgery.

Study 3: A study of ondansetron's safety, tolerability, and ability to prevent nausea and vomiting in pediatric cancer patients aged six months up to four years undergoing treatment with moderately to highly emetogenic chemotherapy. Characterization of ondansetron PK should be performed in a subpopulation of the study patients, or alternatively, in a separate study of pediatric cancer patients. Either a traditional PK or population PK approach may be used.

• **Indication(s) to be studied (i.e., objective of each study):**

Study 1: Objective includes:

- To determine the PK parameters of ondansetron in pediatric surgical patients. This study is to be completed and the results submitted to the Agency for review and comment before proceeding with studies 2 and 3.

Study 2: Objectives include:

- To evaluate the safety and tolerability of ondansetron administered as single and/or repeated doses in pediatric patients.
- To obtain qualitative efficacy data of the effects of ondansetron on initial and further PONV in pediatric patients.

Study 3: Objectives include:

- To evaluate the safety and tolerability of ondansetron in pediatric cancer patients being treated with moderately to highly emetogenic chemotherapy.
 - To obtain qualitative efficacy data of ondansetron for preventing chemotherapy-induced nausea and vomiting in pediatric cancer patients being treated with moderately to highly emetogenic chemotherapy.
 - To characterize the PK of ondansetron in pediatric cancer patients.
- **Age group in which studies will be performed:**

Study 1: Patients:

- Patients will be aged one month up to two years.

Study 2: Patients:

- Patients will be aged one month up to two years.

Study 3: Patients:

- Patients will be aged six months up to ²four years.

• **Number of patients to be studied:**

Study 1:

- Sufficient numbers of patients will be enrolled to characterize the single-dose pharmacokinetics of ondansetron. If a population PK approach is used, at least 24 patients are needed for each ondansetron dose level that is being studied. In addition, if a population PK approach is used, approximately 3 to 4 blood samples per patient will be collected in 3 to 4 time brackets (instead of collection of blood samples at 3 to 4 fixed time points). Timing of blood samples should be such that the entire time course of plasma concentrations can be accurately captured.
- Patients will be approximately uniformly distributed in each administered dose level and within each of the following age ranges: one month up to four months; four months up to two years.

Study 2:

- At least 300 pediatric PONV patients will complete the study.

Study 3:

- At least ⁶⁰ pediatric cancer patients undergoing treatment with moderately to highly emetogenic chemotherapy will complete the study and a sufficient number of patients should be enrolled to adequately characterize the PK of ondansetron in this patient population. If a population PK approach is used, please refer to the comments on Study 1 (above, in this section) for the sampling scheme.
- If a traditional PK approach is used, at least 10 patients should be in the age range of six months up to one year. Alternatively, if a population PK approach is used, at least 20 patients should be in the age range of six months up to one year.
- **Study endpoints:**

Study 1: PK endpoints will include PK parameters such as C_T (at end of infusion), AUC, $t_{1/2}$, clearance, and V_d . Adverse events should be recorded.

Study 2: Clinical endpoints will include:

- Adverse events
- Number of emetic episodes experienced by patients during the treatment period
- Use of rescue antiemetic medication
- Time to rescue
- Incidence of adverse events

Study 3: Clinical endpoints will include:

- Adverse events
- Number of emetic episodes experienced by patients during the treatment period
- Use of rescue antiemetic medication
- Time to rescue
- Incidence of adverse events

Also provide PK parameters such as C_T (at end of infusion), AUC, $t_{1/2}$, clearance, and V_d .

- **Drug information:**

- **dosage form:** Studies 1, 2 and 3: Injection
- **route of administration:** Studies 1, 2, and 3: Intravenous
- **regimen:**

Study 1: Select appropriate doses of ondansetron and administer a single dose of ondansetron at each dose level.

Study 2: The dose level(s) should be selected based on the results from Study 1 and other data on the use of ondansetron for PONV in pediatric patients and adults (e.g., medical literature). Patients will receive a single initial dose which can be repeated if necessary. If emesis occurs, rescue with ondansetron is permitted.

Study 3: The dose level(s) should be selected based on the results of study 1 and other data on the use of ondansetron in pediatric and adult cancer patients undergoing treatment with moderately to highly emetogenic chemotherapy (e.g., medical literature). Patients will receive a single initial dose which can be repeated if necessary. If emesis occurs, rescue with ondansetron is permitted.

- **Drug specific safety concerns:** Constipation, rash, extrapyramidal reactions, redness/inflammation at the injection site, hypersensitivity reactions, seizures, and liver function abnormalities.
- **Statistical information, including power of study and statistical assessments:**

Study 1: Provide appropriate analyses and descriptive statistics of single dose PK data.

Study 2:

- Provide descriptive statistics for clinical outcome measures and safety results.
- Perform a thorough search of the world literature on the use of ondansetron in this pediatric population and provide a critical summary.

Study 3:

- Provide descriptive statistics for clinical outcome and safety results.
- Provide appropriate analyses and descriptive statistics of PK data.
- Perform a thorough search of the world literature on the use of ondansetron in this pediatric population and provide a critical summary.

- **Labeling that may result from the studies:**

Studies 1, 2, and 3: Appropriate sections of the label may be changed to incorporate the findings of the studies.

- **Format of reports to be submitted:** Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.
- **Timeframe for submitting reports of the studies:** Reports of the above studies must be submitted to the Agency on or before June 30, 2004. Please keep in mind that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the

submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Melodi McNeil, Regulatory Project Manager, at (301) 827-7310.

Sincerely yours,

Victor F.C. Raczkowski, M.D., M.S.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Appendix E

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-007/SE5-035	Proposed Brand Name	Zofran
OCPB Division (I, II, III)	II	Generic Name	Ondansetron
Medical Division	GI & Coagulation	Drug Class	5-HT ₃ antagonist
OCPB Reviewer	Suliman Al-Fayoumi	Indication(s)	Anti-emetic
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	I.V. Solution
		Dosing Regimen	Single doses of 0.1 mg/kg in pediatric surgical patients < 40 kg & three 0.15 mg/kg doses in pediatric cancer patients
Date of Submission	9/28/04	Route of Administration	I.V.
Estimated Due Date of OCPB Review	2/20/05	Sponsor	GlaxoSmithKline
PDUFA Due Date	3/28/05	Priority Classification	Priority
Estimated Division Due Date	2/28/05		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1	1	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				

Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses –				
Data rich:				
Data sparse:	X	1	1	
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	X	2	2	
Filability and QBR comments				
	"X" if yes	Comments		
<u>Application filable ?</u>	X			
<u>Comments sent to firm ?</u>	Not needed at this time			
QBR questions (key issues to be considered)	1. Are pediatric surgical patients aged 1 to 24 months and pediatric cancer patients aged 6 to 48 months who are receiving moderately to highly emetogenic chemotherapy comparable to older children on their PK/PD profiles of ondansetron?			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Suliman Alfayoumi
3/9/05 12:38:19 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/9/05 01:26:47 PM
BIOPHARMACEUTICS