Executive Summary of 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 28,856

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.

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.

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