DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 four 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 Vd_{ss}. 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 Vd_{ss}.

- **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

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

/s/

Victor Raczkowski

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