DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-103/S-023, 20-605/S-007, 20-781/S-007

GlaxoSmithKline
Attention: Anne-Margaret Martin
U.S. Regulatory Affairs, Oncology
2301 Renaissance Boulevard, Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Ms. Martin:

Please refer to your supplemental new drug applications dated May 19, 2004 received May 24, 2004 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA 20-103/S-023	Zofran® (ondansetron hydrochloride) Tablets
NDA 20-605/S-007	Zofran® (ondansetron hydrochloride) Oral Solution and,
NDA 20-781/S-007	Zofran® (ondansetron hydrochloride) Orally Disintegrating Tablets.

These supplemental new drug applications provide for the revision of the package insert in order to add to and strengthen the PRECAUTIONS and related sections of the label as well as minor editorial changes.

We also refer to your supplemental new drug applications submitted May 19, 2004, received May 24, 2004 providing for the same changes noted above, for the following:

NDA 20-007/S-034	Zofran® (ondansetron hydrochloride) Injection and,
NDA 20-403/S-013	Zofran® (ondansetron hydrochloride) Injection, Premixed,

for which a separate action letter will be sent.

We completed our review of these supplemental new drug applications. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) identified as "May 2004, RL-2082) submitted electronically on May 19, 2004.

Comments:

Although not required, in order to further harmonize the oral formulation label with the parenteral formulation label; inasmuch as is possible, you may wish to make the following minor editorial revisions at your next printing.

1) In the **PHARMACOKINETICS** section, in the oral formulation package insert, the following sentence reads with the clause in question italicized:

   a. "Ondansetron is extensively metabolized in humans, with approximately 5% of radiolabeled dose recovered *from the urine as the parent compound*,"

whereas in the parenteral package insert, the same sentence reads:

   b. "Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered *as the parent compound from the urine*."

Comment: For consistency between labels as much as is possible, use the same word order for the subordinate clause above (in *intalics*).

2) Also in the **PHARMACOKINETICS** section, in the oral formulation package insert, starting with line #112 (sentence describes clearance in mild-to-moderate hepatic impairment), the sentence reads (with the items in question in *italics*):

a. "In patients with mild-to-moderate hepatic impairment, clearance is reduced *2-fold* and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (*Child-Pugh*[2] *score* of 10 or greater), clearance is reduced *2-fold* to *3-fold* and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours."

whereas in the parenteral package insert, the same sentence reads:

b. "In 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 patients with severe hepatic impairment (*Child-Pugh score*[2] 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."

Comment: For consistency between labels as much as is possible, use of numeric or alpha description is appropriate (2-fold or two-fold), however it is noted that the text twofold and threefold are compound words and should be written two-fold and three-fold respectively. The reference number "2" for Child-Pugh should appear after "Pugh" and not "score".

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Betsy Scroggs, Pharm.D., Consumer Safety Officer at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Division Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment

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

/s/

Joyce Korvick
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