DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21438/S-013/S-014

SUPPLEMENT APPROVAL

GlaxoSmithKline
Attention: Willa Phyall
Associate Director
Global Regulatory Affairs
2711 Centerville Road
Suite 400
Wilmington, DE 19808

Dear Ms. Phyall:

Please refer to your Supplemental New Drug Applications (sNDA) dated April 16 (S-013) and June 14 (S-014), 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Innopran XL (propranolol hydrochloride) 80 mg and 120 mg Capsules.

These supplemental new drug applications provide for the following revisions to the package insert.

1. Under **CLINICAL PHARMACOLOGY, Special Populations,** *Renal Insufficiency,* a one-sentence paragraph was added at the end of the sub-section that reads: "Propranolol hydrochloride is not significantly dialyzable."

2. Under **CLINICAL PHARMACOLOGY, Drug Interactions,** *Interactions with Substrates, Inhibitors or Inducers of Cytochrome P450 Enzymes,* another one-sentence paragraph was added at the end of the sub-section that reads: "Plasma propranolol hydrochloride levels may increase with acute alcohol consumption and decrease upon chronic alcohol use."

3. Under **CLINICAL PHARMACOLOGY, Drug Interactions,** *Inducers of Hepatic Drug Metabolism,* the term, "and ethanol" was removed from the first sentence.

4. Under **WARNINGS**, a new subsection was added. It reads:

   Hypersensitivity and Skin Reactions:
   Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of propranolol hydrochloride (see **ADVERSE REACTIONS**).

Cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria, have been reported with use of propranolol hydrochloride (see **ADVERSE REACTIONS**).

5. Under **WARNINGS, Major Surgery:**

"The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures."

Was changed to read:

"Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery."

6. Under **PRECAUTIONS**, a new subsection was added. It reads:

Myopathy: Caution should be exercised when administering propranolol Hydrochloride to patients with underlying skeletal muscle disease. Isolated cases of exacerbation of myopathy and myotonia have been reported.

7. Under **PRECAUTIONS, Drug Interactions**, a new one-sentence paragraph was added at the end of the section that reads: "Plasma propranolol hydrochloride levels may increase with acute alcohol consumption and decrease upon chronic alcohol use."

8. Under **PRECAUTIONS, Cardiovascular Drugs**, *ACE Inhibitors,* the second sentence was deleted. It read: "Certain ACE inhibitors have been reported to increase bronchial hyperreactivity when administered with propranolol hydrochloride."

9. Under **PRECAUTIONS, Cardiovascular Drugs**, *Antiarrhythmics,* the third paragraph was deleted. It read:

"Disopyramide is a Type I antiarrhythmic drug with potent negative inotropic and chronotropic effects and has been associated with severe bradycardia, asystole, and heart failure when administered with propranolol hydrochloride."

10. Under **PRECAUTIONS, Cardiovascular Drugs**, *Antiarrhythmics,* the phrase, "β-blockers such as" was added into the paragraph beginning. "Amiodarone…" This paragraph now reads:

"Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with β-blockers such as propranolol hydrochloride."

11. Under **PRECAUTIONS, Cardiovascular Drugs**, *Reserpine,* the last sentence was deleted. It read: "Administration of reserpine with propranolol hydrochloride may also potentiate depression."

12. Under **PRECAUTIONS, Pregnancy,** *Pregnancy Category C*, the phrase, "small placentas, and congenital abnormalities have been reported" was added to the second paragraph. It now reads:

    There are no adequate and well controlled studies in pregnant women. Intrauterine growth retardation, small placentas, and congenital anomalies haves been reported for neonates whose mothers received propranolol hydrochloride during pregnancy. Neonates whose mothers received propranolol hydrochloride at parturition have exhibited bradycardia, hypoglycemia, and/or respiratory depression. Adequate facilities for monitoring such infants at birth should be available. Innopran XL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

13. Under **ADVERSE REACTIONS, Allergic**, the section was revised from:

    "Pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress."

    To read:

    "Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions; pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress."

14. Under **ADVERSE REACTIONS**, a new section was added. It reads:

    Skin
    Stevens-Johnson syndrome; toxic epidermal necrolysis; exfoliative dermatitis; Erythema multiforme; urticaria.

15. Under **ADVERSE REACTIONS**, a new subsection was added. It reads:

    Musculoskeletal: Myopathy, myotonia (see **PRECAUTIONS**).

We have completed our review of these supplemental applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (*i.e.*, a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Wachter, RN, BSN
Regulatory Health Project Manager
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Agreed-upon labeling text

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

/s/

MARY R SOUTHWORTH
12/14/2010