



NDA 20-357/S-026 and S-027

NDA 21-202/S-011 and S-013

Bristol-Myers Squibb  
Attention: Pamela Smith, M.D.  
Director, Metabolic & Endocrine Products  
P.O. Box 4000  
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your supplemental new drug applications dated June 19, 2003, received June 23, 2003, (for NDA 20-357/S-026 and NDA 21-202/S-011), and supplemental new drug applications dated September 26, 2003, received September 29, 2003 (for NDA 20-357/S-027 and NDA 21-202/S-011) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage® (metformin HCl), and Glucophage® XR (metformin HCl extended-release) Tablets.

We acknowledge receipt of your submission dated February 5, 2004, for supplements S-026 and S-011, and to your March 18, 2004, submission for the enclosed text for the merged package insert.

Your submission of February 5, 2004, for supplements S-026 and S-011 constituted a complete response to our December 23, 2003, action letter.

Supplemental new drug applications S-011 and S-026 provide for revisions to the **CLINICAL PHARMACOLOGY** section, **Special Population** subsection, and **OVERDOSAGE** sections of the package insert. The **CLINICAL PHARMACOLOGY** section, **Special Populations** subsection, pediatrics paragraph has been revised to read as follows:

After administration of a single oral GLUCOPHAGE 500 mg tablet with food, geometric mean metformin C<sub>max</sub> and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

The following 3 sentences have been added to the beginning of the **OVERDOSAGE** section:

“Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **WARNINGS**).

Supplements 027 and 013 provide for revising the boxed warning under the **WARNINGS** section to state that there have been no reports of lactic acidosis. The following sentence has been inserted into the second paragraph:

“In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis [1].

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling insert.

The final printed labeling (FPL) must be identical to the enclosed text for the package insert submitted on March 19, 2004. Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions “**FPL for approved NDA 20-357/S-026 and S-027, and FPL for approved NDA 21-202/S-011 and S-013.**” Approval of these submissions by FDA is not required before the labeling is used.

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

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II Center for Drug Evaluation

Enclosure (package insert text)

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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David Orloff  
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