DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019815/S-010

SUPPLEMENT APPROVAL

Shire Development LLC
Attention: Mihaela MacNair, Ph.D., M.Sc.
300 Shire Way
Lexington, MA 02421-2101

Dear Dr. MacNair:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on December 23, 2016, and your amendment dated and received on January 23, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ProAmatine (midodrine hydrochloride) Tablets, 2.5 mg, 5 mg, and 10 mg.

This "Changes Being Effected" supplemental new drug application provides for the following changes (additions are shown as underlined text and deletions are shown as ~~strike-through text~~):

1. Under **WARNINGS**, a new sentence was added to the end of the paragraph as follows:

   WARNINGS

   Supine Hypertension: The most potentially serious adverse reaction associated with ProAmatine® therapy is marked elevation of supine arterial blood pressure (supine hypertension). Systolic pressure of about 200 mmHg were seen overall in about 13.4% of patients given 10 mg of ProAmatine®. Systolic elevations of this degree were most likely to be observed in patients with relatively elevated pre-treatment systolic blood pressures (mean 170 mmHg). There is no experience in patients with initial supine systolic pressure above 180 mmHg, as those patients were excluded from the clinical trials. Use of ProAmatine® in such patients is not recommended. Sitting blood pressures were also elevated by ProAmatine® therapy. It is essential to monitor supine and sitting blood pressures in patients maintained on ProAmatine®. Uncontrolled hypertension increases the risk of cardiovascular events, particularly stroke.

2. Under **PRECAUTIONS/Drug Interactions**, the second paragraph has been changed as follows:

   (b) (4)

   (b) (4) The risk of hypertension increases with concomitant administration of drugs that increase blood pressure (phenylephrine, pseudoephedrine, ephedrine, dihydroergotamine, thyroid hormones, or droxidopa). Avoid concomitant use of drugs that increase blood pressure. If concomitant use cannot be avoided, monitor blood pressure closely.

   Avoid use of MAO inhibitors or linezolid with midodrine.

3. Under **HOW SUPPLIED**, the following changes were made:

   a. The first sentence has been changed as follows:

   [redacted]-2.5-mg, 5-mg and 10-mg tablets for oral administration.

   b. The NDC codes have been deleted as follows:

   2.5-milligram Tablets: [redacted] (Bottle of 100): Shire US no longer markets this product
   5.0-milligram Tablets: [redacted] (Bottle of 100): Shire US no longer markets this product
   10-milligram Tablets: [redacted] (Bottle of 100): Shire US no longer markets this product

   c. The "Manufactured for" information and revision dates have been updated as follows:

   [redacted]
   Shire US Inc., 300 Shire Way, Lexington, MA 02421, USA [redacted]
   [redacted]
   [redacted]
   © 2017 [redacted] Shire US Inc.
   Rev. 01[redacted]/17 [redacted]

   [redacted]

There were no other changes when compared with the last approved labeling supplement (S-007, approved on July 22, 2004).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. We remind you that your supplement submitted March 30, 2015 containing the results of studies intended to address the requirements under 21 CFR 314.510 to verify and describe clinical benefit of midodrine remains under review by the Agency. Approval of this labeling supplement does not constitute an Agency decision on the adequacy of those studies to verify clinical benefit.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 that include labeling changes for this NDA, including 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, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

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:
Content of Labeling

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
02/07/2017