CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-815/S-005

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-815/S-005

Shire Laboratories Inc.
Attention: Zohra E. Lomri
1550 East Gude Drive
Rockville, MD 20850

Dear Mr. Lomri:

Please refer to your supplemental new drug application dated April 12, 2001, received April 13, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ProAmatine (midodrine hydrochloride) Tablets, 2.5 mg and 5 mg.

This supplement proposes the following change: ProAmatine Tablets 10 mg as an additional strength to the existing 2.5 mg and 5.0 mg strengths.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Regarding specifications for ProAmatine Tablets:

In the specification tables for ProAmatine tablets, please also include the content of Midodrine HCl as a percentage.

Regarding *in vivo* Bioequivalence Waiver

In order to be considered for a waiver for the requirement of an in vivo bioequivalence study for the 10 mg strength of ProAmatine, please provide comparative dissolution data in two additional media (i.e. pH 4.5 and 6.8 buffers) and corresponding F_2 values (if appropriate).

Regarding Certificate of Analyses of ProAmatine tablets:

Please provide Certificate of Analyses for batches # 293011 and 293021 of ProAmatine 10 mg tablets.

Regarding the expiration date for ProAmatine tablets:

A review of the stability data for 2.5 mg and 5 mg tablets in your Annual Reports for this NDA indicates that both 2.5 mg and 5 mg tablets at storage conditions of [redacted] failed the specification limits in a few cases. The stability data for 5 mg tablets at storage conditions of [redacted] also did not meet the specifications at the [redacted] months testing interval. Because of these failing specifications, we recommend that you lower the expiration date of 2.5 mg and 5 mg ProAmatine tablets from [redacted] months to [redacted] months in a separate supplemental application.

In view of the stability failures of the approved strengths and since only [redacted] months data at [redacted] were provided for the 10 mg strength of ProAmatine, an expiration of only [redacted] months may be granted for this new strength.

Regarding labeling of the final product:

The description in the How Supplied Section of the Package Insert for the 10 mg tablet is written as:

[redacted]

This should be corrected to:

"and is scored on one side with" . . .

The container labels and package insert have the following storage statement:

[redacted]

The storage statement should be changed to:

"Store at 25ºC(77ºF)
Excursions permitted to 15-30ºC(59-86ºF) [see USP Controlled Room Temperature]"

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, call Edward Fromm, Regulatory Project Manager, at (301) 594-5313.

Sincerely,

{See appended electronic signature page}

/S/

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I for the
Division of Cardio-Renal Drug Products, (HFD-110)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Kasturi Srinivasachar
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