DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-414

Commanding General
U.S. Army Medical Research and Materiel Command
Attn: Colonel Jeffrey A. Gere
504 Scott Street
Fort Detrick, MD 21702-5012

Dear Colonel Gere:

Please refer to your March 4, 1994 new drug application (NDA) and to your resubmission dated January 3, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for pyridostigmine bromide tablets, 30 mg.

We also acknowledge receipt of the following amendments:

January 7, 2003
January 14, 2003
January 16, 2003
January 30, 2003
February 4, 2003

This new drug application provides for the use of pyridostigmine bromide for prophylaxis against the lethal effects of Soman nerve agent poisoning. We note that your resubmission asks that this application be reviewed under the provisions of Subpart I of the new drug regulations [21 CFR 314.600-650].

We have completed our review of this application, as amended, and it is approved effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 20-414**." Approval of this submission by FDA is not required before the labeling is used.

Subpart I Approval Requirements

We note that we are taking this regulatory approval action under the provisions of 21 CFR Part 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible). An approval under this subpart is subject to three requirements:

(1) *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical.

We note that you have included in your application a plan or approach for these postmarketing study commitments (see discussion of Subpart I Confirmatory Studies below). We ask that you submit detailed protocols to address this requirement within 1 month of the date of this letter. We would be happy to meet with you to discuss the design of these protocols prior to their submission.

(2) *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that pyridostigmine can be safely used without restrictions on distribution or use and note your commitment to continue your internal educational program for soldiers similar to that proposed for use under the IND contingency protocol (allowed to proceed on January 22, 2003).

(3) *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart.

We have concluded that the Patient Package Insert provided as an attachment to this letter meets the requirements of this subsection. We remind you that the patient labeling must be available with the product to be provided prior to administration or dispensing of the drug product for the use approved under this subpart, if possible.

Rx Only

We remind you that under § 503(b)(1) of the FD&C Act, pyridostigmine bromide is a prescription drug which is limited to use under the professional supervision of a practitioner licensed by law to administer such drug.

Proprietary Name

We note that you have not proposed a proprietary name for your product. If you choose to use a proprietary name for this product, the name and its use in the labeling must conform to 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

Dissolution Method and Specification

Please adopt the following dissolution method and specification for pyridostigmine 30 mg tablets.

Table 1: Final Regulatory Dissolution Method and Specification

Parameter	Description	
Apparatus type:	USP Apparatus II (paddle)	
Media:	Water	
Volume (ml):	900 ml	
Temperature:	37 ± 0.5 °C	
Speed of rotation (rpm):	50 rpm.	
Sample times (hours):	60 minutes	
Specifications: (% of Label Claim)	Q = 80% at 60 minutes	Acceptance criteria as per USP XXV – NF 20 <711> Dissolution Acceptance Table

Specifications and Testing for Certain Stockpiled Lots

We note that your February 4, 2003 amendment includes a list of certain lots in DOD inventory. We remind you that all lots must meet applicable specifications before being dispensed. In particular we note that:

1. Lot PYA558 may not be distributed since the data submitted to the NDA indicate that this lot failed under accelerated (room temperature) stability testing conditions.

2. With regard to the lots manufactured in 1991, you will be testing each of these lots for degradants prior to dispensing and will be testing the lots identified as "sister" lots for dissolution and content in addition to degradants. We also note your plan to send a "global medical materiel quality control message" to the field, suspending and quarantining these lots from use pending the results from these tests.

Post-Marketing Study Commitments

We remind you of your postmarketing study commitments in your submission dated January 14, 2003. These commitments are listed below.

1. Chemistry, Manufacturing and Controls (CMC): We note your agreement to provide the methods validation package one month from the date of this letter.

2. CMC: We note your agreement to provide, within one month from the date of this letter, a stability protocol for initiation of a long-term (10 years) stability study. This protocol

should provide for yearly testing of each batch of drug product, including assays, related substances, and dissolution.

3. CMC: We note your commitment to provide, within one month of the date of this letter, a detailed description of the final packaging configuration including Letters of Authorization for all pertinent Drug Master Files of all packaging assembly components.

4. Subpart I Confirmatory Studies: We note your commitment to provide, within 1 month of the date of this letter, detailed protocols to address the requirement to conduct postmarketing studies, such as field studies, to verify and describe pyridostigmine's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. We would be happy to meet with you to discuss the design of these protocols prior to their submission.

5. Additional Animal & Human Studies: We note your commitment to provide, within three months of the date of this letter, a detailed plan for the conduct, completion, and submission of final study reports for additional animal and human studies. We will be happy to meet with you to discuss the design of those studies yet to be conducted.

Submit clinical and animal protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Promotional Materials

We note that no preapproval review of promotional materials was conducted because you have stated that you do not plan to promote this product. Should you choose to promote this product, you must comply with the requirements of 21 CFR 314.640. Submit all proposed materials in draft or mock up form, not final print. Send one copy to the Division of Neuropharmacological Drug Products (HFD-120) and two copies of the promotional materials along with the package insert directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

Methods Validation

As noted above under Post-Marketing Commitments, you have not submitted a methods validation package. Therefore, we have not initiated nor completed validation of your regulatory methods. We expect your continued cooperation to resolve any problems that may be identified.

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, call Mr. Robbin Nighswander, M.S., Supervisory Regulatory Health Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures
- Package Insert
- Patient Package Insert
- Carton/Container Labels

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

/s/

Robert Temple
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