DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 12-003/S-018/S-019/S-020/S-021
NDA 12-418/S-006/S-007/S-008/S-009

Knoll Pharmaceutical Company
Attention: Robert Ashworth, Ph.D.
Director, Regulatory Affairs
3000 Continental Drive-North
Mount Olive, NJ 07828-1234

Dear Dr. Ashworth:

Please refer to your supplemental new drug applications dated March 5, 1980 (12-003/S-018 & 12-418 S-006), May 1, 1980 (12-003/S-019 & 12-418 S-007), September 25, 1985 (12-003/S-020 & 12-418 S-008), and December 10, 1985 (12-003/S-021 & 12-418 S-009), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Akineton (biperiden HCl) 2 mg Tablets (NDA 12-003) and Akineton (biperiden lactate) Injection (NDA 12-418).

These supplemental applications provide for the following revisions to product labeling:

12-003/SLR-018
12-418/SLR-006
These supplements provide for draft revisions to the labeling to conform to a FR Notice dated June 26, 1979.

12-003/SLR-019
12-418/SLR-007
These supplements provide for final printed labeling of the draft labeling changes dated March 5, 1980 submitted under 12-003/SLR-018 and 12-418/SLR-006.

12-003/SLR-020
12-418/SLR-008
These supplements provide for draft revisions throughout the following sections in labeling: **DESCRIPTION**, **CLINICAL PHARMACOLOGY**, **CLINICAL PHARMACOLOGY-Pharmacokinetics and Metabolism**, **INDICATIONS AND USAGE**, **CONTRAINDICATIONS**, **WARNINGS**, **ADVERSE REACTIONS**, **OVEDOSAGE**, and **DOSAGE AND ADMINISTRATION**.

12-003/SLR-021
12-418/SLR-009
These supplements provide for final printed labeling of the labeling changes submitted as draft labeling under 12-003/SLR-020 and 12-418/SLR-008.

We have completed the review of these supplemental applications, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use. Accordingly, these supplemental applications are approved effective on the date of this letter.

Labeling changes of the kind which you have proposed under the above supplemental applications are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above NDA supplements, have been made.

Additionally, based upon our review of annual reports submitted to your NDA, we request that the following further changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

Under **ADVERSE REACTIONS**

[Double underline font denotes additions to the labeling.]

Atropine-like side effects such as dry mouth; blurred vision; drowsiness; euphoria or disorientation; urinary retention; postural hypotension; constipation; agitation; disturbed behavior may be seen. A case of generalized choreic movements has been reported in a Parkinson's disease patient when biperiden was added to carbidopa/levodopa. A reduction in rapid eye movement (REM) sleep, characterized by increased REM latency and decreased percentage of REM sleep, has been reported.

[Continue with remainder of section.]

We additionally note that Akineton Injection has not been manufactured since February 1989, and the last manufactured batch of drug expired in February 1994. Knoll does not intend to produce or market Akineton Injection in the future. However, there are several references to the injectable product in the labeling.

Since Akineton Injection is no longer marketed, we request that you delete all references to the injectable product in the **DESCRIPTION** and **DOSAGE AND ADMINISTRATION** sections along with the references to the injectable product in the storage statement and label title.

We additionally request that you replace the presently used storage recommendations for the tablet formulation under the **HOW SUPPLIED** section of labeling as well as the container labels with the following statement:

"Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature]."

Please submit the final printed labeling (FPL) revised exactly as specified above as a "Supplement - Changes Being Effected". The FPL should be submitted electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material. Please incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

This supplement should be submitted within 6 months from the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz

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