

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-667/S-008

ADMINISTRATIVE DOCUMENTS

Division of Neuropharmacological Drug Products

REGULATORY MANAGEMENT OFFICER REVIEW

Application Number: 20-667 / S-008

Name of Drug: Mirapex Tablets

Applicant: Pharmacia & Upjohn

Material Reviewed:

Submission Date: July 2, 2002

Receipt Date: July 3, 2002

Background and Summary

Pharmacia & Upjohn submitted this labeling supplement, which provides additional language about the findings in the pigmented rat study, as requested in a March 20, 2002 telecon. Due to unpaid user fees for other applications, the sponsor received an "UN" letter dated July 19, 2002. The user fee was paid on August 6, 2002, starting the review clock.

Review

NDA 20-667/S-008

CBE: No

Reviews: Clinical and Pharmacology (needed)

Provision:

This supplement provides labeling changes consisting of adding language about the findings in the pigmented rat study and updating the company logo.

Based upon a line track change (provided on pages 3-27) comparison of S007, the last approved label, and the proposed language in S-008, the following changes were found:

1. PRECAUTIONS section

Retinal pathology in albino rats: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats treated for 2 years, a thinning in the outer nuclear layer of the

retina was slightly greater in rats given drug compared with controls. Evaluation of the retinas of albino mice, pigmented rats, monkeys, and minipigs did not reveal similar changes.

2. ANIMAL TOXICOLOGY section, Retinal Pathology in Albino Rats subsection:

ANIMAL TOXICOLOGY

Retinal Pathology in Albino Rats

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans that received 1.5 mg tid). ~~Similar findings were not present in rats receiving 0.3 mg/kg/day (plasma AUC equal to 0.3 times the AUC in humans that received 1.5 mg tid).~~ In a similar study of pigmented rats with 2 years exposure to pramipexole at 2 or 8 mg/kg/day, retinal degeneration was not diagnosed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater than that seen in control rats utilizing morphometry.

Conclusions

The sponsor provided language regarding the rat findings as requested in a March 20, 2002 telecon. If the pharmacologist and clinical reviewer find the proposed language acceptable, then I recommend that an action letter issue approving this supplement.

Teresa Wheelous
Sr. Regulatory Management Officer

Supervisory Comment/Concurrence:

Robbin Nighswander
Chief, Project Management Staff

25 page(s) of draft
labeling has been
removed from this
portion of the review.

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/s/

Teresa Wheelous
4/10/03 12:32:34 PM
CSO

Robbin Nighswander
4/10/03 01:19:23 PM
CSO



NDA 20-667

Pharmacia & Upjohn
Attention: Roma Thomas
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Thomas:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Mirapex (pramipexole dihydrochloride) 0.125, 0.25, 1.0, 1.25, 1.5 mg Tablets.

You were notified in our letter dated July 19, 2003, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of August 6, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Supervisory Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robbin Nighswander
4/10/03 01:23:59 PM



NDA 20667/S-008

Pharmacia & Upjohn Company
Attention: Roma Thomas
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Thomas:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Mirapex

NDA Number: 20667

Supplement Number: S-008

Date of Supplement: July 2, 2002

Date of Receipt: July 3, 2002

We note that you are in arrears for payment of fees for products, or establishments, or previously submitted applications. Because an application is considered incomplete and can not be accepted for filing until all fees owed have been paid, review of the supplement referenced above may not begin at this time. Upon receipt of the outstanding fees, we will start the user fee clock and commence review of your application. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Jack Purvis

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