

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020667**

**CHEMISTRY REVIEW(S)**

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS  
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

**NDA 20,667**

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-DEC-95	29-DEC-95	01-JAN-96	15-JUL-96
AMENDMENTS:	15-MAY-96	20-MAY-96	22-MAY-96	15-JUL-96
	26-JUN-96	28-JUN-96	12-JUL-96	15-JUL-96

CHEMIST REVIEW: # 1

SPONSOR: PHARMACIA & UPJOHN

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 7000 Portage Road  
 Kalamazoo, Michigan 49001-0199

**PRODUCT NAME:**

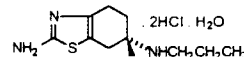
Proprietary: To be established  
 USAN: NA  
 INN: **PRAMIPEXOLE**  
 Code Name/Number: SND 919 CL 2 Y; U-98528E

DOSAGE FORM/ROUTE OF ADMINISTRATION: 0.125-mg, 0.25-mg, 1-mg, 1.25-mg, and 1.5-mg compressed tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Parkinson's Disease

**STRUCTURAL FORMULA & CHEMICAL NAME:**

$_{10}H_{21}Cl_2N_3OS$  Mol. Wt. 302.27



(S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

REMARKS: The n.d.s. is freely soluble in water.

The bulk drug is stable but the tablets are susceptible to photo degradation and have to be protected from light. In general, the CMC information is adequate except for specific information that appears to be missing/unclear and needs to be provided or clarified.

**CONCLUSIONS & RECOMMENDATIONS:** RECOMMEND THAT NDA 20-667 FOR PRAMIPEXOLE TABLETS IS APPROVABLE CONTINGENT UPON RECEIPT AND REVIEW OF REQUESTED INFORMATION. INSPECTION OF THE FACILITIES WAS DONE AND AN ACCEPTABLE RECOMMENDATION FROM COMPLIANCE WAS RECEIVED (SEE ATTACHED EER). AN EXPIRY DATE OF 18-MONTHS APPEARS REASONABLE AT THE PRESENT TIME.

cc: ORIG: NDA  
 HFD-120/Div. File  
 HFD-120/JPurvis  
 HFD-120/SBlum/MZarifa  
 HFD-810/CHoiberg (cover page, def.list only)  
 INIT:

APPEARS THIS  
 ON ORIGINAL

*/S/*  
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 Mona Zarifa, Ph.D., Chemist

filename: N020667.000

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*/ name = MIRAPEX*

APPEARS THIS  
 ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS  
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,667

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-DEC-95	29-DEC-95	01-JAN-96	15-JUL-96
AMENDMENT:	06-SEP-96	09-SEP-96	11-SEP-96	16-SEP-96

CHEMIST REVIEW: # 2

SPONSOR: PHARMACIA & UPJOHN

OCT 15 1996

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 7000 Portage Road  
Kalamazoo, Michigan 49001-0199

PRODUCT NAME:

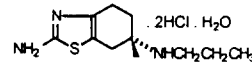
Proprietary: MIRAPEX  
USAN: NA  
INN: PRAMIPEXOLE  
Code Name/Number: SND 919 CL 2 Y; U-98528E

DOSAGE FORM/ROUTE OF ADMINISTRATION: 0.125-mg, 0.25-mg, 1-mg, 1.25-mg, and 1.5-mg compressed tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Parkinson's Disease

STRUCTURAL FORMULA & CHEMICAL NAME:

$H_{21}Cl_2N_3OS$  Mol. Wt. 302.27



(S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

REMARKS: In this amendment the sponsor responds to the CMC deficiencies telefaxed to them on August 12, 1996. All missing/unclear information is now provided/ clarified or will follow as requested (see Telecon. Report 9/13/96). Updated 18-month stability data are provided.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT NDA 20-667 FOR PRAMIPEXOLE TABLETS IS APPROVED CONTINGENT UPON RECEIPT OF THE AGREED UPON REQUESTED INFORMATION. INSPECTION OF THE FACILITIES WAS DONE AND AN ACCEPTABLE RECOMMENDATION FROM COMPLIANCE WAS RECEIVED (SEE CMC REVIEW 1). THE REQUESTED EXPIRY DATE OF 24 MONTHS IS NOW ACCEPTABLE.

cc: ORIG: NDA  
HFD-120/Div. File  
HFD-120/JPurvis  
HFD-120/SBlum/MZarifa  
HFD-810/CHoiberg (cover page, def.table only)  
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APPEARS THIS WAY  
ON ORIGINAL

/S/

Mona Zarifa, Ph.D., Chemist

filename: N020667.001

/S/ 10/11/96

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ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS  
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

OCT 11 6 1996

NDA 20,667

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-DEC-95	29-DEC-95	01-JAN-96	15-JUL-96
AMENDMENT:	07-OCT-96	08-OCT-96	11-OCT-96	11-OCT-96

CHEMIST REVIEW: # 3

SPONSOR: PHARMACIA & UPJOHN

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 7000 Portage Road  
Kalamazoo, Michigan 49001-0199

PRODUCT NAME:

Proprietary: MIRAPEX  
USAN: NA  
INN: PRAMIPEXOLE  
Code Name/Number: SND 919 CL 2 Y; U-98528E

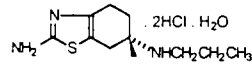
DOSAGE FORM/ROUTE OF ADMINISTRATION: 0.125-mg, 0.25-mg, 1-mg, 1.25-mg, and 1.5-mg compressed tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Parkinson's Disease

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{10}H_{21}Cl_2N_3OS$

Mol. Wt. 302.27



(S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

REMARKS: In this amendment the firm provides the information agreed upon in the Telecon dated 9/13/96.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT NDA 20-667 FOR PRAMIPEXOLE TABLETS IS APPROVED as was recommended in CMC Review #2.

cc: ORIG: NDA  
HFD-120/Div. File  
HFD-120/JPurvis  
HFD-120/SBlum/MZarifa  
HFD-810/CHOibera (cover page, def.table only)  
INIT:

APPEARS THIS WAY  
ON ORIGINAL

/S/

Mona Zarifa, Ph.D., Chemist

filename: N020667.002

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10/11/96

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ON ORIGINAL