

Recommendations:

Several additional non-clinical questions have been raised by these studies:

1. Can the degenerative effects of PRAM be replicated by a clinically relevant dopaminergic agonist? Although using disk-shedding/phagosome number as a marker represents a shorter term study, assessing microscopic changes is probably a more appropriate index of degeneration since inhibition of the disk-shedding mechanism is hypothetical at this point.
2. How does pigmentation protect against PRAM-induced retinal degeneration? Does PRAM (or constant light) **not** inhibit the disk-shedding mechanism in pigmented animals? If strain differences were found, the validity of inhibition of disk-shedding as a degenerative mechanism would be supported.
3. Although strain differences in exposure levels may be a remote possibility as a contributing factor to the differences in response to pramipexole, they cannot be discounted and should be evaluated.
4. Is the effect of PRAM in pigmented and non-pigmented animals a sensitivity or selectivity issue? Does pigmentation merely prolong the latency to degeneration? Why were albino mice in the 2-year carcinogenicity not affected by pramipexole?
5. The timing of PRAM administration in these studies should be reevaluated. By administering the drug at the time of peak shedding (7-8 am), conditions are favorable for observing a drug effect by disrupting the normal circadian pattern, but do not accurately reflect the conditions under which the initial degenerative effects were observed/produced (drug-in-diet).

Appropriate experiments to address these issues should be considered to solidify the contention that pramipexole does not represent a serious risk of irreversible retinal degeneration in humans, which may lead to blindness.

/S/ 11/20/96

/S/

Thomas D. Steele, Ph.D.

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Summary and Evaluation:

This amendment contains six additional non-clinical toxicology studies of putative pramipexole (PPX) degradative products. Acute toxicity/lethality was studied in mice following intravenous administration, and mutagenicity was evaluated in a standard Ames assay. The degradative products were designated BIII 786, BIII 820, Product V, and Products Z₁ and Z₂. BIII 786 and BIII 820 were tested in separate and independent experiments. The photochemical degradation products V, Z₁ and Z₂ were tested by preparing a defined mixture of PPX and these components. The chemical structures are as follows:

According to the chemistry reviewer, Dr. Zarifa, these impurities were not found in the batches.

The only significant toxicological findings were obtained with BIII 786. The LD₅₀ of this compound was times lower than that of PPX, and the signs of toxicity by the two compounds were similar. In addition, BIII 786 evoked a positive response

at amounts ≥ 5000 $\mu\text{g}/\text{plate}$ in the Ames assay with activation by either rat or hamster S9 in strain TA98. The sponsor contends that the results demonstrate a "very weakly positive" mutagenic response. Whether the descriptive modifiers "very weakly" accurately characterize the mutagenic response is debatable since the mutagenic response to the positive control (2-aminoanthracene, 2-AA, 0.5 $\mu\text{g}/\text{plate}$) in the presence of rat S9 was only 3-fold higher than that produced by BIII 786. However, 2-AA produced a far greater mutagenic response than the test compound in the presence of hamster S9.

The acute toxicity of BIII 820 was approximately equivalent to that of PPX in terms of potency and symptomology, and a mixture of PPX with the photochemical degradative products was less toxic than the parent compound. No other positive mutagenic responses were obtained.

The Ames tests conducted with BIII 786 and BIII 820 were deficient in that a strain sensitive to A-T mutations (*E. coli* WP2 uvrA or *S. typhimurium* TA102) was not included in the screen as set forth in the OECD Guidelines.

Since these impurities are not present at a level greater than 0.1%, additional testing is not required at this time. In the event that batches are submitted in which levels exceed this value, the Ames test deficiencies should be addressed.

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Study Results:

1. Compound BIII 786 BR3:

Acute toxicity:

This compound was tested in mice (Ico:OF1), and compared to PPX according to the following dosage regimen:

1. SND 919 C12 Y

ANIMALS/DOSE		DOSE (mg/kg)	CONCENTRATION (g/100 ml)
male	female		
-	5	100	1
5	5	125	1.25
5	5	160	1.6

2. BIII 786 BR3

ANIMALS/DOSE		DOSE (mg/kg)	CONCENTRATION (g/100 ml)
male	female		
5	-	12.5	0.125
5	5	16	0.16
5	5	20	0.2
-	5	25	0.25

Animals were observed for 14 days following treatment. Mortality was as follows:

Dose	BIII 786		PPX		Dose
	M	F	M	F	
12.5	0/5	-	-	0/5	100
16	1/5	0/5	0/5	1/5	125
20	4/5	0/5	5/5	3/5	160
25	-	3/5			

Calculated LD₅₀s were:

	<u>BIII 786</u>	<u>PPX</u>
Males:	17.9	141.4
Females:	23.4	150.9

All deaths occurred within 30 min. Similar signs of toxicity were observed with either compound (prone/lateral position, dyspnea, tachypnea, tonic-clonic convulsions). No delayed deaths occurred, and no gross pathological changes were evident at autopsy.

These studies indicate that the degradation product is times more toxic than PPX following i.v. treatment in mice.

Mutagenicity:

The mutagenicity of BIII 786 was tested in a standard Ames test (plate incorporation method) at concentrations ranging from 10-7000 µg/plate in the absence and presence of rat and hamster S9. The strains used were TA1535, TA1537, TA100 and TA98.

In the absence of S9, there were no increased mutation frequencies by BIII 786. However, a positive response (greater than doubling of control mutation frequency) was noted in the presence of either rat or hamster S9 in strain TA98:

BIII 786 ER3 concentration (µg/plate)	Relative mutation frequency*	
	Rat S9	Hamster S9
1500	-	-
3000	-	-
5000	-	-
6000	2.8	3.0
7000	2.7	3.1

Of note, is the marked species difference between the two S9 fractions with respect to responsiveness to the positive control 2-aminoanthracene (Tab. 1). With rat S9, 2-AA causes about an 8-fold increase in mutation frequency whereas hamster S9 causes at least a 90-fold increase in mutation frequency. Interestingly, little or no species difference is evident in mutagenic response to BIII 786 as increases were noted with S9 fractions from either species.

Since this rate of mutation frequency meets the sponsor's own criteria for a positive response in the Statistics section of the report, and the response in the presence of the rat S9 is only about 3-fold lower than the positive control response, it is difficult to agree with the sponsor's conclusion that BIII 786 "was very weakly mutagenic."

An apparent oversight in this study was the omission of a strain sensitive to A-T mutations (*S. typhimurium* TA102 or *E. coli* WP2 uvrA) as recommended in the OECD Guidelines.

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Table 8. Induction of mutations in the presence of a stabilizing system;
Experiment 3 (MUT 268/5, /6)

Substance ^a	Conc. (µg/pl.)	S9 ^b	Number of revertants per plate ^c		
			T198 S9 Rat	S9 Ham	
Solvent control (dist. water, 140 µl/pl.)		+	28	28	
			19	28	
			<u>14</u>	<u>29</u>	
			20 MY	28 MY	
			7 SD	1 SD	
BIII 786 BR3	10	+	n.t.	23	
				31	
				<u>26</u>	
				27 MY	
				4 SD	
	100	+	n.t.	27	25
					<u>26</u>
					26 MY
					1 SD
500	+	n.t.	26	39	
				<u>36</u>	
				34 MY	
				7 SD	
1500	+	n.t.	47	47	
				<u>49</u>	
				48 MY	
				1 SD	
3000	+	n.t.	60	50	
				<u>53</u>	
				58 MY	
				7 SD	
5000	+		45	73	
			37	66	
			<u>32</u>	<u>80</u>	
			40 MY	73 MY	
			4 SD	7 SD	
6000	+		68	85	
			49	78	
			<u>47</u>	<u>90</u>	
			55 MY	84 MY	
			12 SD	6 SD	
BIII 768 BR3	7000	+	41	90	
			69	95	
			<u>48</u>	<u>77</u>	
			53 MY	87 MY	
			15 SD	9 SD	
21A	0.5	+	162	>2500	
			152	>2500	
			<u>157</u>	>2500	
			157 MY	MY	
			5 SD	SD	
Titer of the bacterial suspension (x10 ⁸ /ml)			2.6 (248, 246, 271) ^d	2.7 (288, 243, 276) ^d	

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2. Compound BIII 820 BS:

Acute toxicity:

This compound was tested in mice (Ico:OF1) according to the following dosage regimen:

ANIMALS/DOSE		DOSE (mg/kg)	CONCENTRATION (g/100 ml)
male	female		
5	5	100	1.0
5	5	150	1.5
-	5	200	2.0

Mortality was as follows:

Dose	BIII 820	
	M	F
100	0/5	0/5
150	3/5	1/5
200	-	3/5

Calculated LD₅₀s were:

Males: 144.0
Females: 186.8

All deaths occurred within 3 min. Signs of toxicity were similar to those observed with PPX (prone/lateral position, dyspnea, tachypnea, tonic-clonic convulsions). There were no delayed deaths and no gross pathological findings in any animals at autopsy.

These studies indicate that the degradation product is approximately equipotent in acute toxicity to PPX following i.v. treatment in mice.

Mutagenicity:

The mutagenicity of BIII 820 was tested in a standard Ames test (plate incorporation method) at concentrations ranging from $\mu\text{g}/\text{plate}$ in the absence and presence of rat and hamster S9. The strains used were TA1535, TA1537, TA100 and TA98.

No cytotoxic or genotoxic effects were produced by BIII 820 under any conditions. As in the preceding study with BIII 786, a strain sensitive to A-T mutations (*S. typhimurium* TA102 or *E. coli* WP2 uvrA) was not tested.

3. Photochemical Degradation Products V, Z₁ and Z₂ in combination with PPX

For these experiments, a special compound mixture containing PPX and its photochemical degradative products was prepared. The final composition of the material on a percent basis was:

PPX (dihydrochloride salt)	-	83.1
Product V	-	9.5
Product Z ₁	-	2.5
Product Z ₂	-	4.9

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The rationale for this composition was not provided.

Acute toxicity:

The material was dissolved in saline and administered intravenously to mice (Ico:OF1) at doses of 150 and 225 mg/kg (5/sex/dose). Animals were observed for 14 days.

Three animals of each sex died within 2 minutes of receiving the 225 mg/kg dose. Signs of toxicity were prone/lateral position, tachypnea, exophthalmia, saltatory convulsions, and tremor. There were no delayed deaths and no gross pathological findings in any animals at autopsy. The calculated LD₅₀ was 216 mg/kg.

These studies indicate that the photochemical degradation products in this composition are less acutely toxic than PPX following i.v. treatment in mice.

Mutagenicity:

The mutagenicity of the photochemical degradative product mixture was tested in a standard Ames test (plate incorporation method) at concentrations ranging from 10-10000 µg/plate in the absence and presence of S9 from rat and hamster. The strains used were *S. typhimurium* strains TA1535, TA1537, TA100 and TA98, and *E. coli* WP2 uvrA.

No cytotoxic or genotoxic effects were produced by the mixture under any conditions.

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Recommendations

1. Since the potential impurities characterized in these studies have not been detected in batches at a level greater than 0.1%, additional testing is not required at this time. In the event that batches are submitted in which levels exceed this value, the Ames test deficiencies should be addressed.

/S/

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Thomas D. Steele, Ph.D.
Pharmacologist/Toxicologist

Original NDA 20667

cc.: /Division File, HFD-120
/G. Fitzgerald, Ph.D.
/J. Feeney, M.D.
/J. Purvis
/T.D. Steele, Ph.D.

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APPENDIX

Pathologist's Review of Retinal Degeneration Findings

Conducted by:

T.P. O'Neill, D.V.M., Ph.D
Armed Forces Institute of Pathology
Washington, D.C. 20306-0001



Memorandum

Date: 13 February 1996

From: Glenna Fitzgerald, Ph.D. /S/
Pharmacology Team Leader
Division of Neuropharmacological Drug Products

Subject: Consultative review of rodent retinal degenerative findings; NDA 20-667

To: Timothy O'Neill, D.V.M., Ph.D.
Dept. of Veterinary Pathology
Armed Forces Institute of Pathology
Building 54
16th and Alaska Ave., NW
Washington, D.C. 20306-6000

Thank you so much for agreeing to review the drug-induced retinal degeneration findings that you have discussed with Dr. Lois Freed. Enclosed please find several documents we would like evaluated.

To briefly summarize the issue, pramipexole is a relatively selective dopamine D2 receptor agonist under development by Upjohn for the treatment of Parkinson's disease. An unexpected finding in the two-year rat carcinogenicity study was retinal degeneration in mid- (2 mg/kg/day) and high- (8 mg/kg/day) dose rats. This finding was first made in premature decedents during weeks 76/78. The primary contention of the sponsor is that this finding is a species-specific effect in albino rats due to the lack of "protective" pigmentation. To support this contention, the sponsor has conducted a comparative study of retinal degeneration in non-pigmented (albino) and pigmented (Brown-Norway) rats. In addition, the sponsor has conducted a study on the possible mechanism by which pramipexole produces retinal degeneration in albino rats. According to their hypothesis, dopamine D2 receptor activation by pramipexole effectively mimics conditions of constant light, which is known to damage the retinae of albino rats. The sponsor's bottom line is that pigmented species (i.e., humans) should not be subject to similar retinal degenerative effects of pramipexole.

The following documents contain the material for review:

1. Boehringer Ingelheim Document #U93-0116 is a discussion of the initial retinal degeneration findings in the 2-year rat carcinogenicity study, and a literature review of retinal degeneration
2.
 - a. A literature review of retinal degeneration

- b. An Expert Panel Report regarding the drug-induced retinal degeneration findings and their possible relevance to humans
- c. A technical report (TR 7219-95-043) of a study in which a potential mechanism for drug-induced retinal degeneration (inhibition of disk shedding) was evaluated
- d. A technical report (TR 7219-95-049) of a study in which the degenerative effects of the drug were compared in pigmented and non-pigmented rats

Color photocopies from the Boehringer Ingelheim document (#93-0116, pages 32-34), and an original electron micrograph from the disk-shedding study (TR 7219-95-043) are provided. The histopathological evidence is rather limited, but according to the sponsor, this is the best they have at this point.

As you review the material, please consider the following questions:

1. In your opinion, has the sponsor provided convincing evidence that this is a species-specific effect that will occur only in non-pigmented animals? Bear in mind that albino mice did not show signs of retinal degeneration.
2. Are the retinal degeneration findings more likely a species-selective effect, as the sponsor contends, or a species-sensitive effect (i.e., does pigmentation merely prolong the latency for the degeneration)?
3. What are your recommendations for clinical monitoring for this effect, if any (type of monitoring, frequency)?
4. An issue that will arise during labeling is the description of the changes. The sponsor adamantly contends that the drug is not "retinotoxic", primarily citing the long latency for the changes. However, in the mechanistic and comparative studies, the retinal changes were produced in a much shorter period of time. Should the drug be considered retinotoxic? In non-pigmented rodents only?

If you have questions please contact me at (301) 594-5501, or speak directly to the pharmacology/toxicology reviewer of the NDA (who put this package together and knows the data better than anyone else) Thomas Steele, Ph.D., at (301) 594-5508.

cc: NDA 20-667
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THE REGISTRY OF COMPARATIVE PATHOLOGY

Armed Forces Institute of Pathology
Washington, D. C. 20306-0001

July 15, 1996

Glenna Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products
HFD-120
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Fitzgerald:

Thank you, once again, for the opportunity to assist the Division of Neuropharmacological Drug Products in the review of NDA 20-667. I very much appreciate the occasions to collaborate with your group in this and past reviews. I do, however, apologize for the delay in reporting this review summary to you, as my work here has been very demanding lately.

Enclosed along with this review of NDA 20-667 are the original documents sent to me for review on 15 Feb. 1996, to include:

1. Boehringer Ingelheim Document #U93-0116: discussion of the initial retinal degeneration lesions findings in the 2-year rat carcinogenicity study and literature review of retinal degeneration
2. containing:
 - a. Literature review of retinal degeneration
 - b. Expert Panel Report discussing the drug-induced retinal lesions and relevance to humans
 - c. Technical Report: TR 7219-95-043, SND 919 CL 2 Y:
- Influence on the Rod Outer Segment Disk Shedding Mechanism in the Retina of Albino Rats
 - D. Technical Report: TR 7219-95-049, Pramipexole (SND 919 CL 2 Y) influence on retinal degeneration in the albino rat with and without light as a cofactor

Phone: (202) 782-2440 ♦ Fax: (202) 782-9161/9150

Registry of Comparative Pathology activities are supported by a grant from the National Center for Research Resources, National Institutes of Health.



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3. Color photocopies and black and white photos of histological and electron microscopic images of control and drug-induced lesions in experimental animals.

The materials are returned in their entirety and original condition. In no instance was the material duplicated or reproduced and in no case was the proprietary nature of material disclosed.

As part of my review, in addition to review of the provided printed materials listed above, I conducted and reviewed information from fairly exhaustive MEDLARS[®] database searches from 1990 to the present on: retinal degeneration in rats and mice; dopamine and retina; dopamine receptors and retina; and dopamine or dopamine receptors and retinal degeneration. Moreover, I consulted with members of the Department of Ophthalmic Pathology, AFIP, on several questions I had regarding retinal pathology as they related to the lesions described in this NDA.

Before I specifically address the questions posed in your letter of 15 February 1996, I would like you to gain an appreciation for some of the assumptions I performed my review of the materials under. Defining these will aid in how I address these questions and arrived at my conclusions.

Firstly, The term retinal degeneration is ill defined in the documents. At times the term is applied to photoreceptor cell loss and at other times refers to, I assume, total loss of the retina.

Secondly, I did not find in the materials provided a detailed histological description of the retinal degeneration in the affected (treated) rats other than that described in the "Report of Expert Panel Evaluation...". In that report only a fairly general description of the light microscopic pathology was eluded to, i.e. "...loss of photoreceptor cells, inner layers of the retina had lesions and vessels penetrated the retinal pigment epithelium", and in TR 7219-95-049: "reduction of photoreceptor cell nuclei...". Little information regarding the genesis (e.g. the earliest lesion observed were nuclear pycnosis followed by cytoplasmic vacuolation, etc) of the photoreceptor cell loss was provided. Therefore, one has to assume these photoreceptor cells just disappeared without premonitory changes.

Thirdly, no mention was made of pathology secondary or ancillary to photoreceptor cell loss (i.e. retinal degeneration began with photoreceptor cell loss followed by inner nuclear layer cell loss, etc.), but rather terms such as "severe retinal degeneration" or "photoreceptor cells of the entire retina were completely degenerated". Therefore, one again assumes lesions were either restricted to photoreceptors or, as indicated, the entire retina (all layers) in the most severe form and were degenerated without a stepwise or pathogenesis to loss of the

other layers of the retina.

Lastly, the literature review and discussion material provided in the technical reports was at times confusing and contradictory in reference to dopamine action and metabolism and D2 (dopamine receptor) activation of the photoreceptor and inner nuclear layer cells. I gained ancillary information and clarification from the MEDLARS^R searches previously mentioned.

In response to your questions regarding my review, I provide the following responses:

1. Within the context of the studies conducted and reference materials included (or lack of information showing D2 agonist-induced retinal degeneration in other species), the sponsor has provided evidence to support their contention that this is a species and strain-specific effect in non-pigmented (albino) rats. Detailed information on the conduct of the histopathological examination for both affected and non-affected species is not available in the materials and, therefore, I cannot access what effort was put into looking for very early, inapparent or ultrastructural changes that may have been present in the other species/strains.
2. Again, within the context of the information provided or found, the absence of retinal degeneration in parallel 2-year studies in albino (non-pigmented) mice and pigmented rats would tend to support a strain-selective (i.e. Wistar rat) effect of the drug-induced retinal degeneration. As ultrastructural studies were not conducted in other species or 2-year studies using pigmented rats were not conducted the question of pigmentation prolonging latency of retinal degeneration cannot be answered.
3. Although this is not my area of expertise, I find the sponsor's plan for clinical monitoring of patients receiving the drug to be fairly inclusive of detecting untold effects on eyesight. A detailed clinical monitoring schedule to include parameters and periodicity of exams would be helpful.
4. From what I can conclude from the information on the drug, the drug is retinotoxic in Wistar rats. Albeit, the drug has not been shown to be retinotoxic in a limited number of other species of animals (including albino mice) or strains of rat, it is definitely toxic to the photoreceptor cells of the retina in Wistar rats.

In summary, after careful inspection and consideration of the provided and supplemental documentation I was able to retrieve on the subject matter, I conclude that the sponsor's claim: "that the retinal degeneration observed in association with pramipexole is species-specific and unique to albino rats" is correct within the limitations I have specified above. Without further information

regarding the histopathology of the retina in other species or future studies designed to better quantitate and characterize the effects of the drug on the retina in non-pigmented and pigmented species, I am unable to predict the effects of the drug in the human patient.

Once again, thank you very much for this opportunity to be of assistance to the FDA. Should you have any questions regarding this report or my conduct of the review, please do not hesitate to contact me directly at (202) 782-2442 or FAX at (202) 782-9150.

Respectfully Yours
/S/

Timothy P. O'Neill, D.V.M., Ph.D.
Chief Pathologist
Diplomate, American College of Veterinary Pathologists

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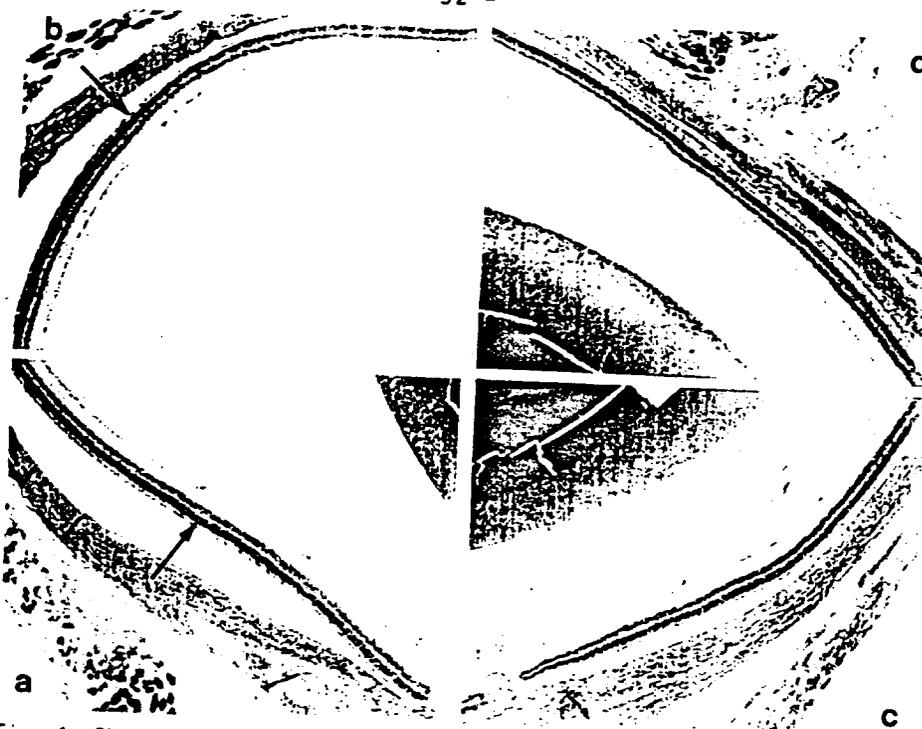


Fig. 1: SND 919 Cl 2 Y carcinogenicity study rat: control rat no. 0014
 a (central) and b (peripheral) represent one retinal hemisphere
 c (central) and d (peripheral) the second of the same eye, HE, 43 x
 —> = photoreceptor cell layer

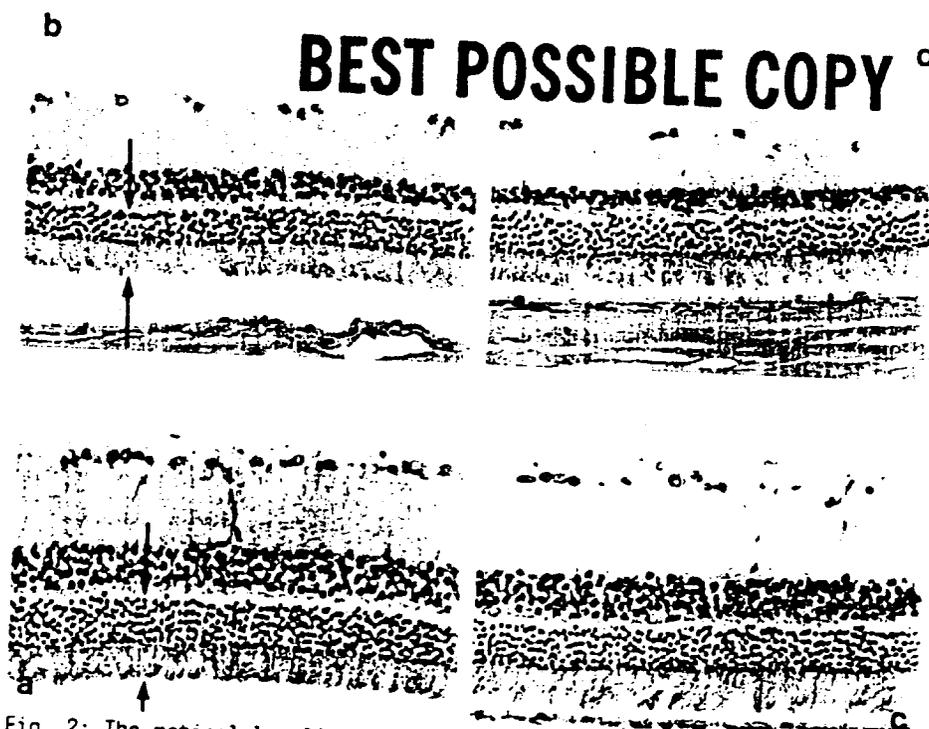


Fig. 2: The retinal localisations shown in Fig. 1 at higher magnification,
 HE, 260 x
 —> <— = photoreceptor cell layer

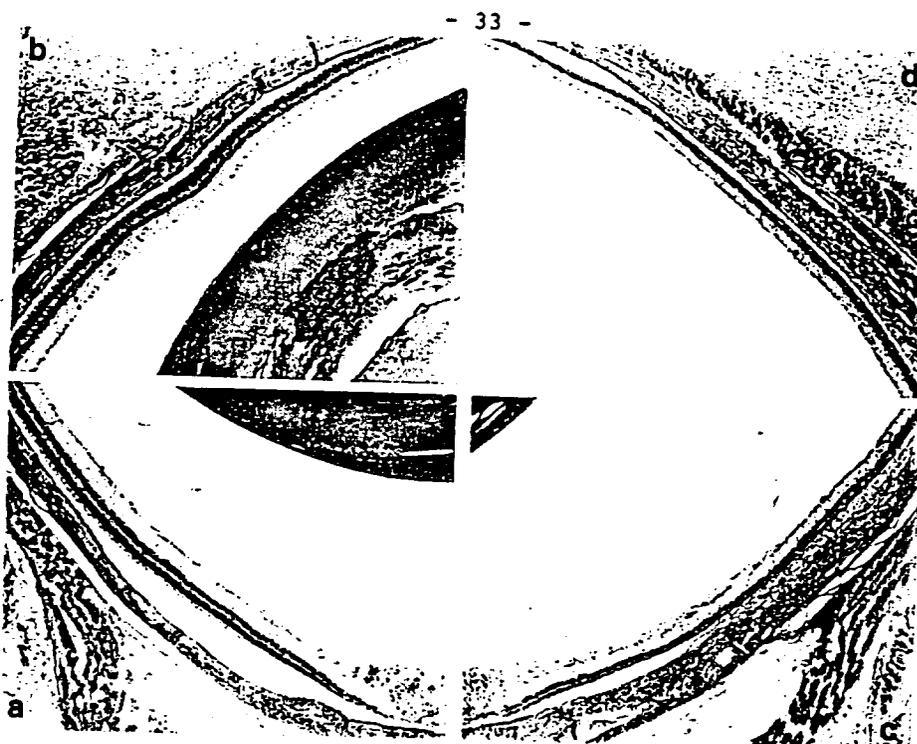


Fig. 3: SND 919 Cl 2 Y carcinogenicity study rat: high dose rat no. 3526
 a (central) and b (peripheral) represent one retinal hemisphere
 c (central) and d (peripheral) the corresponding, HE, 43 x,
 photoreceptor cell layer is present in one hemisphere
 nearly missing in the other one.

b

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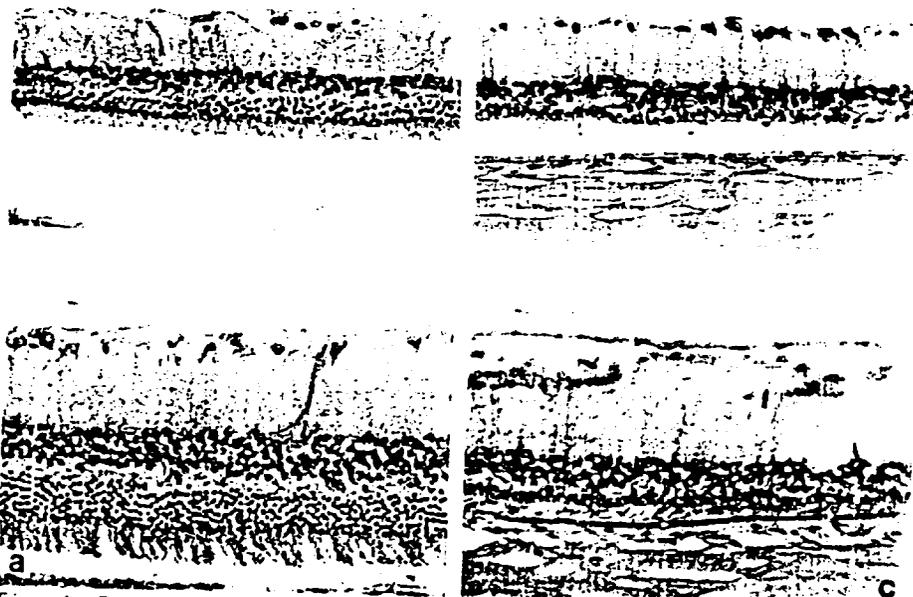


Fig. 4: The retinal localisations shown in Fig. 3 at higher magnification,
 HE, 260 x, intact and degenerated photoreceptor cell layer

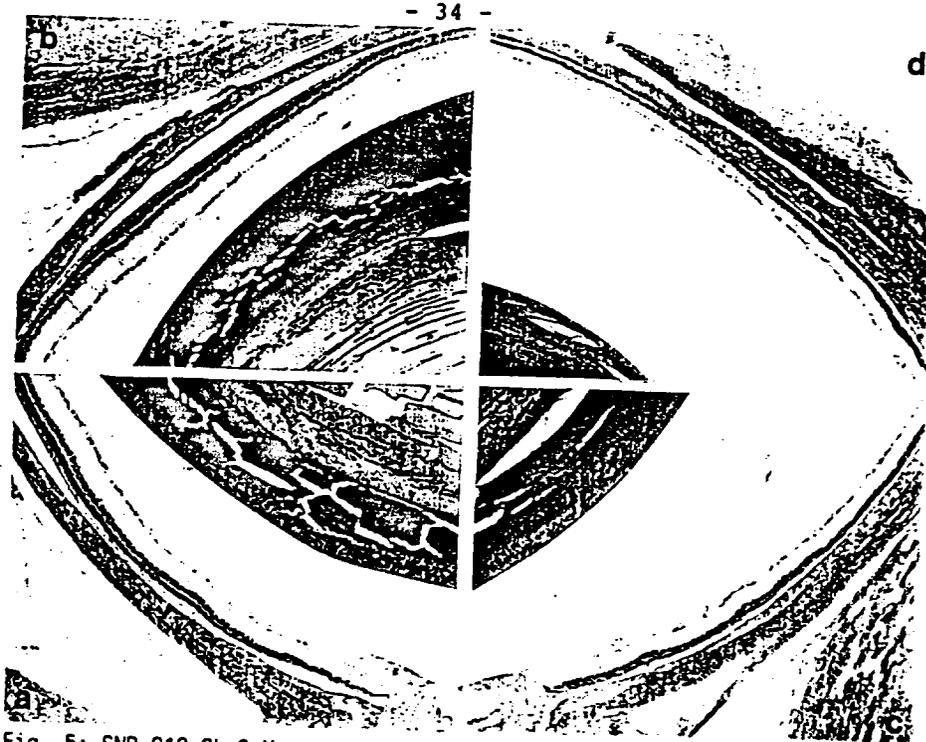


Fig. 5: SND 919 Cl 2 Y carcinogenicity study rat: high dose rat no. 3535
 a (central) and b (peripheral) represent one retinal hemisphere
 c (central) and d (peripheral) the corresponding, HE, 43 x,
 photoreceptor cell layer is present in one hemisphere
 nearly missing in the other one.

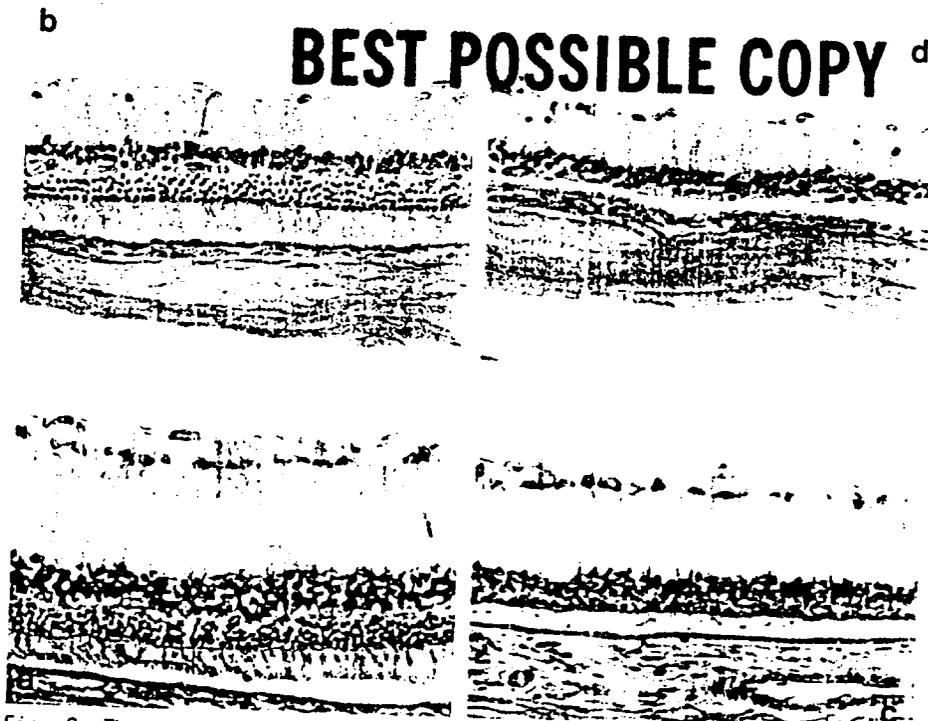


Fig. 6: The retinal localisations shown in Fig. 5 at higher magnification,
 HE, 260 x, intact and degenerated photoreceptor cell layer.

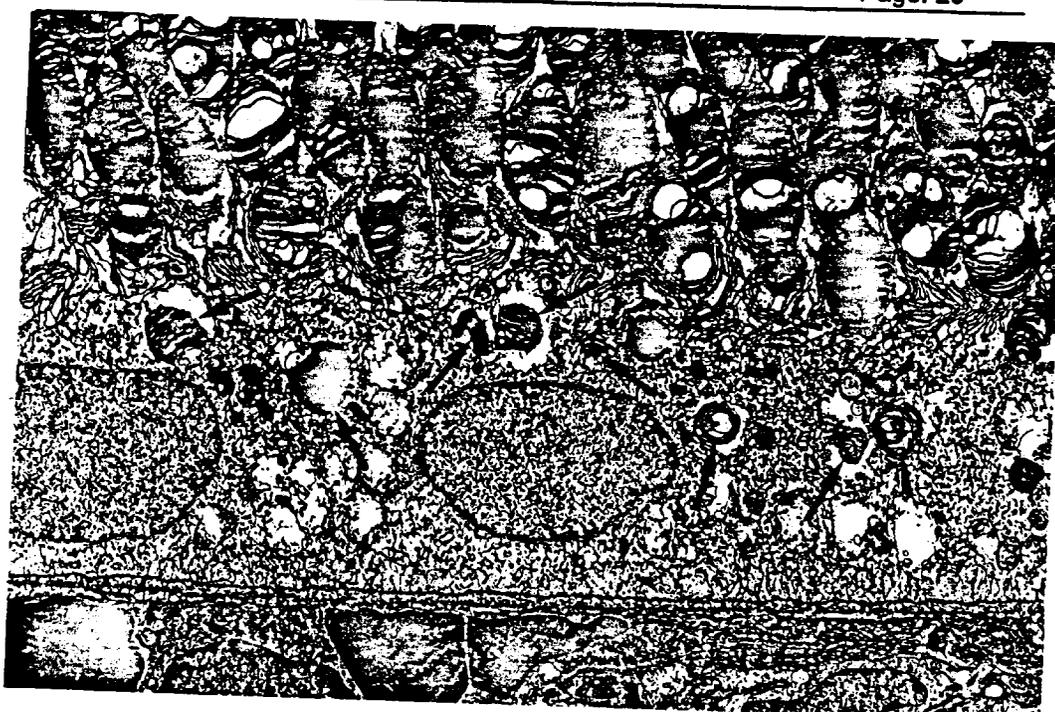


Figure 8: Electron micrograph of rod outer segments (ROS) and retinal pigment epithelium cells (RPE) from a control rat sacrificed at 8 am (early light phase). The RPE cells contain numerous phagosomes (←), magnification 5400 x

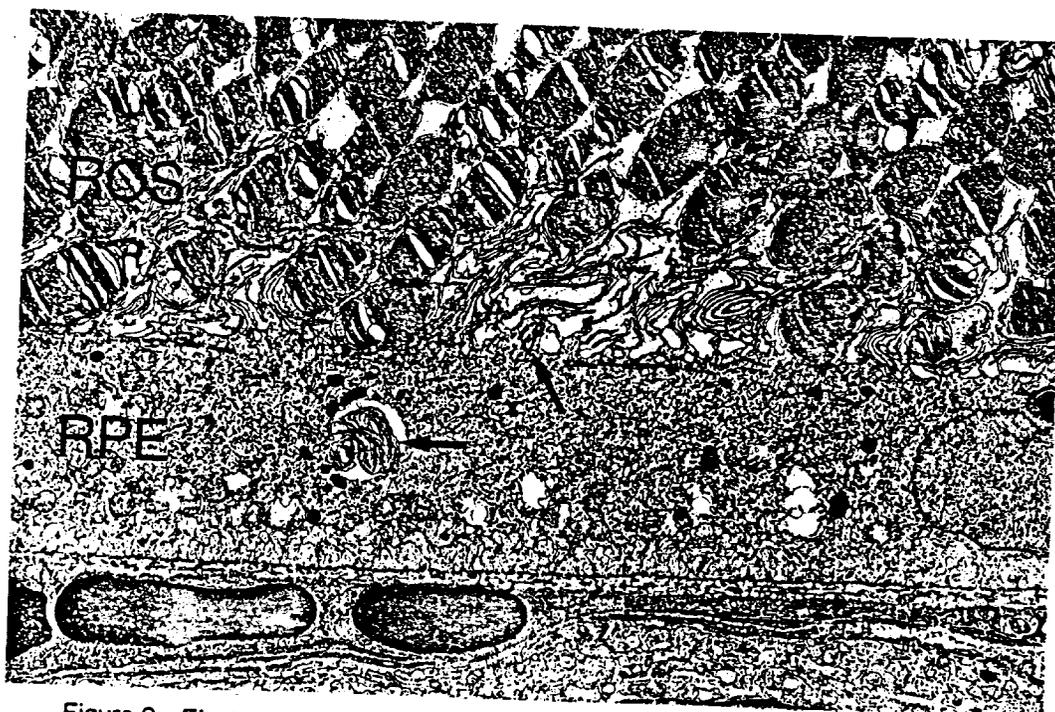


Figure 9: Electron micrograph of rod outer segments (ROS) and retinal pigment epithelium cells (RPE) from a SND 919 CL 2 Y-treated rat sacrificed at 8 am (early light phase). The RPE cells are nearly devoid of phagosomes (←), magnification 5400 x

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**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Amendments 039, 040, 043, 044**

NDA No.: 20667

Submission Date: 1/27/97

Drug: MIRAPEX (pramipexole) Oral Compressed Tablets

Sponsor: The Upjohn Co.
7000 Portage Rd.
Kalamazoo, MI 49001-0199

Reviewer: T.D. Steele

Indication: Parkinson's disease

Pharmacologic Class: Dopamine agonist

Background:

This amendment is revised labeling for MIRAPEX. Some of the revisions were in amendments 39, 40 and 43; thus, this review pertains to all these amendments.

Sponsor's text that should be deleted is indicated by ~~strikeout~~. Reviewer's revisions are redlined.

Review of Revised Labeling:

1. Page 1...Under **CLINICAL PHARMACOLOGY**

"Pramipexole is a nonergot dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the D₂ subfamily of dopamine receptors.

"The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiological studies in animals that have demonstrated that pramipexole influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum. Animal studies have also shown that pramipexole depresses dopamine synthesis, release, and turnover

Comments:

- a. Inclusion of "full intrinsic activity" - According to the sponsor, pramipexole is distinct from other currently available dopamine agonists (bromocriptine, pergolide) by virtue of its "full intrinsic activity". Four of the five

studies cited by the sponsor to support this statement were electrophysiology studies, primarily assessing inhibition of neuronal cell firing in the substantia nigra pars compacta. Electrophysiology studies with dopamine agonists are not the best models for demonstrating full intrinsic activity because of the complexity of the neural pathways involved. *In vitro* studies assessing inhibition of adenylate cyclase by D₂ receptor agonists may be a more appropriate model. Nonetheless, the results were consistent with the conclusion that pramipexole possesses full intrinsic activity. Administration of bolus (but not cumulative) injections of pergolide suggested that this compound also possesses full intrinsic activity. Bromocriptine did not completely suppress cell firing, and was therefore not considered a full agonist. Bromocriptine has been considered a full agonist and a partial agonist in the literature. The lack of full intrinsic activity in the electrophysiology studies may have been due activation of other receptors by bromocriptine, which counteracted the effects of D₂ receptor activation. Thus, it is not clear from these studies that pramipexole is distinct from pergolide, and possibly bromocriptine, on the basis of full intrinsic activity. However, the sponsor's contention that pramipexole possesses full intrinsic activity appears accurate, and may be included in the label.

- b. D₃ receptor activity - As recognized by the sponsor, a full appreciation of the significance of D₃ receptors is currently lacking. This is particularly true in primates where a relatively low density of D₃ receptors is found. In view of the questionable clinical relevance of this pharmacological activity, references to it should be deleted.
- c. Reduction of neuronal degeneration - As detailed in the original review, this statement is of questionable clinical relevance and should be deleted.

2. Page 6... Under **PRECAUTIONS**

"Retinal degeneration in albino rats: Retinotoxicity (loss of photoreceptor cells, degeneration of retinal pigment epithelium) was observed in albino rats in the 2-year carcinogenicity study (see ANIMAL TOXICOLOGY). The significance of this effect in humans is not known, but cannot be disregarded since disruption of a universal vertebrate mechanism (i.e., disk-shedding) may be involved. If visual disturbances are suspected, a comprehensive ophthalmological examination including ERG and EOG should be conducted."

Comments:

- a. In the original labeling, the sponsor used "retinal degeneration" to describe the lesions in the 2-year rat carcinogenicity study. As recommended by the FDA consultant, Dr. Tim O'Neill, the term "retinotoxicity" was used in FDA Draft Labeling. The sponsor reinserted "retinal degeneration" for "retinotoxicity", claiming that this term is more descriptive of the lesion. The present revision

incorporates both views by parenthetically describing the nature of retinotoxicity with the same descriptions used by the sponsor's Expert Study Panel.

- b. An additional line incorporates the suggestions of the study panel regarding the use of ERG and EOG to detect retinal damage in humans.
3. Page 7... Under "Information for Patients":

"Because animal teratogenicity information and human experience with MIRAPEX is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy)."

Comments:

- a. The original Pharmacology/Toxicology review detailed the inadequacies of the rat Segment II study in terms of its limited teratology information. The sponsor has not submitted any additional teratogenicity data to supplement their claim that pramipexole is not teratogenic in rats. The current revision is a slight modification of the FDA Draft Labeling.
4. Page 7... Under "Drug Interactions"...

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent K_i of 30 μM , indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid).

Dopamine antagonists: Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of MIRAPEX."

Comments:

- a. The sponsor has adequate data to support the claims that MIRAPEX does not inhibit cytochrome P450 isozymes at clinically relevant concentrations, and that dopamine antagonists may diminish the effectiveness of MIRAPEX.
5. Page 8...

"Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to Chbb:NMRI mice at doses of 0.3, 2, and 10 mg/kg/day (0.5,

3.4, and 17.2 times the highest recommended clinical dose [1.5 mg tid] on a mg/m² basis). In mice dosed at these levels, the plasma levels were at least 0.1, 0.49, and 4.4 times the observed C_{max} in humans dosed 1.5 mg tid. Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (0.8, 5, and 20 times the highest clinical dose on a mg/m² basis). In rats dosed at these levels, the plasma AUC was 0.3, 2.5, and 12.5 times the AUC in humans dosed at 1.5 mg tid.

Comments:

- a. The sponsor has modified the dosage conversions using factors from Casarett & Doull's Toxicology. The original dosage conversions (by the reviewer) were according to FDA standard conversions and based on a 50 kg body weight for humans. The sponsor's conversion is based on 70 kg human body weight. When the same human body weights (70 kg) were used for the conversion by both methods, the same values were obtained for rats, monkeys, and rabbits. Values for mice were slightly lower using the FDA conversion as compared to the sponsor's conversion. Thus, the conversions conducted by the sponsor are acceptable for all species.

"Testicular Leydig cell adenomas were found in male rats as follows: 13 of 50 control group A males, 9 of 60 50 control group B males, 17 of 50 males given 0.3 mg/kg/day, 22 of 50 males given 2 mg/kg/day, and 22 of 50 males given 8 mg/kg/day.

Leydig cell adenomas were not observed in mice after 2 years of treatment with MIRAPEX. Leydig cell hyperplasia and increased numbers of adenomas

in rats are of questionable significance in humans because of their high background incidence in rats, the absence of similar changes in mice, and the probable involvement of endocrine mechanisms that are not relevant to humans."

Comments:

- a. The Leydig cell tumor findings were omitted from FDA Draft Labeling because these tumors were not significant according to Agency criteria. The sponsor wishes to describe the tumor findings, and has reinserted them in the present labeling. This is acceptable to the reviewer. The text on the mechanism is modified since the sponsor has not clearly demonstrated that this mechanism applies to pramipexole.
- b. In line 2, the sponsor indicated (as in the initial submission) that 60 males were in control group B. The reviewer has been unable to identify the additional 10 animals claimed by the sponsor. The sponsor will need to clarify this discrepancy.

"Pregnancy: Pregnancy Category B C. When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (6.2 times the highest clinical dose on a mg/m² basis). In rats dosed at 2.5 mg/kg/day, the plasma levels were 19.3 times the observed C_{max} in humans dosed 1.5 mg tid. Administration of 1.5 mg/kg/day (3.7 times the highest clinical dose on a mg/m² basis) of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos

The plasma AUC in rats dosed at this level was 4.3 times the AUC in humans dosed at 1.5 mg tid. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of MIRAPEX could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day (47.2 times the highest clinical dose on a mg/m² basis) to pregnant rabbits during organogenesis. In rabbits dosed at 10 mg/kg/day, the plasma AUC was 71 times that in humans dosed at 1.5 mg tid. Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the highest clinical dose on a mg/m² basis) or greater during the latter part of pregnancy and throughout lactation. In pregnant rats dosed at 0.5 mg/kg/day, the plasma AUC was 1.5 times the AUC in humans dosed at 1.5 mg tid.

"There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus."

Comments:

- a. The sponsor deleted text from the FDA Draft labeling that indicated the inadequacies of the rat teratogenicity data. This text has been reinserted. The sponsor has argued that pramipexole should be labeled similar to bromocriptine as Pregnancy category B because the two drugs cause similar effects on early rat pregnancy. However, bromocriptine is labeled as B because substantial human experience exists with bromocriptine, and no reproductive or teratogenic effects have been associated with its use. It is also noted that the sponsor has identified pharmacological properties of pramipexole that are distinct from bromocriptine (i.e., full intrinsic activity, D₃ receptor selectivity). It is possible that these unique pharmacological properties of pramipexole may also convey unique toxicities to the compound.
- b. The sponsor modified the standard statement in FDA Draft labeling regarding the

benefit:risk assessment for fetal exposure. The original FDA statement has been reincorporated.

7. Page 19... ANIMAL TOXICOLOGY

Retinotoxicity in Albino Rats

Retinotoxicity (loss of photoreceptor cells, degeneration of the retinal pigment epithelium) was observed in albino rats in the 2-year carcinogenicity study with pramipexole. Retinal lesions were first observed during week 76 and was dose dependent in animals receiving 2 or 8 mg/kg/day (5 and 20 times the highest clinical dose on a mg/m² basis). Lesions were not observed in that study at 0.3 mg/kg/day (0.8 times the highest clinical dose on a mg/m² basis). In rats dosed at 0.3, 2, or 8 mg/kg/day, the plasma AUC was 0.3, 2.5, and 12.5 times the AUC in humans dosed at 1.5 mg tid.

"Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, retinal degeneration occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (62 times the highest clinical dose on a mg/m² basis) and constant light (100 lux), but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats may be uniquely sensitive to the damaging effects of pramipexole and light. Retinotoxicity did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.5, 3.4, and 17.2 times the highest clinical dose on a mg/m² basis). Limited evaluation of the retinas in other long-term animal studies did not reveal signs of retinotoxicity in of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.5, 2.6, and 10.4 times the highest clinical dose on a mg/m² basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks

"The potential significance of this effect in humans has not been established, but cannot be disregarded since disk shedding is a universal mechanism of the vertebrate retina, and

Comments:

- a. The rationale for using "Retinotoxicity" rather than "Retinal degeneration" was described in a preceding section.
- b. According to the FDA consultant, Dr. Tim O'Neill, the evaluations of the retinas in other long-term animal studies were limited, and the labeling should reflect that position.
- c. The original FDA Draft Labeling, which emphasizes that the disk-shedding