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dossier created for substance NDA020667-pramipexole dihydrochloride

816ae1ca-1560-48a4-b74c-711535940ae5

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Type at least 3 characters

OECD Exchange of experimental data
NDA020667-pramipexole dihydrochloride

- 1 General information
  1
- 2 Classification and Labelling
- 4 Physical and chemical properties
- 5 Environmental fate and pathways
- 6 Ecotoxicological information
- 7 Toxicological information
  10
  - 7.1 Toxicokinetics, metabolism and distribution
  - 7.2 Acute Toxicity
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    2
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  2
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  5
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1 2 0

Administrative data | Data source | Materials and methods | Results and discussion | Overall remarks, attachments | Applicant's summary and conclusion

Administrative data

Endpoint
carcinogenicity: oral

Type of information
experimental study

Adequacy of study

☐ Robust study summary

☐ Used for classification

☐ Used for SDS

Study period

Reliability

Rationale for reliability incl. deficiencies

Data waiving

Justification for data waiving

Justification for type of information

Attached justification

Attached justification Reason / purpose Actions

Cross-reference

Reason / purpose for cross-reference Related information Remarks Actions

Data source

Reference

Data access

Data protection claimed

Materials and methods

Test guideline

Qualifier Guideline Version / remarks Deviations Actions

Principles of method if other than guideline

GLP compliance

Test material

Test material information

- NDA020667_TM1 | pramipexole dihydrochloride | (6S)-6-N-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine;dihydrochloride | 104632-25-9

Additional test material information

Specific details on test material used for the study
Lot: Batch II

Specific details on test material used for the study (confidential)

Test animals

Species
rat

Strain
Wistar

Details on species / strain selection

Sex
male/female

Details on test animals or test system and environmental conditions
Mean initial weights/age: males: l44.8g 39 days females: 131.6g 39 days

Administration / exposure

Route of administration
oral: feed

Type of inhalation exposure (if applicable)

Vehicle
no data

Mass median aerodynamic diameter (MMAD)

Geometric standard deviation (GSD)

Remarks on MMAD

Details on exposure

Analytical verification of doses or concentrations

Details on analytical verification of doses or concentrations

Duration of treatment / exposure
2 years

Frequency of treatment
not specified

Post exposure period
not specified

Doses / concentrations

Dose / conc. Remarks Actions 1
Dose / conc.
8 mg/kg bw/day (actual dose received)
Remarks
2
Dose / conc.
mg/kg bw/day (actual dose received)
Remarks
3
Dose / conc.
2 mg/kg bw/day (actual dose received)
Remarks
4
Dose / conc.
0.3 mg/kg bw/day (actual dose received)
Remarks

No. of animals per sex per dose
250 males, 250 females for toxicology Three satellite groups (5,.6 and 7) were used for toxicokinetic analyses. Blood was sampled from 5 rats/sex in each group on days 2 and 7 of weeks 2, 50 and 100.

Control animals

Details on study design
Methods: Dosages: 0.3, 2.0, 8.0 mg/kg/day PPX (Lot: Batch II) Low dose is 3-4 fold higher than the ED50 for anti-Parkinsonian effects in monkeys. It is 5-15 times higher than the expected human maintenance dose range of 1.5-4.5 mg/day (70 kg human). The high dose was selected as the highest tolerable dose given the duration of the study and the limitation of excessive CNS stimulation. Route of Administration: Drug-in-diet Species/Strain/Number: Rat/Wistar (Chbb:THOM) 250 males, 250 females for toxicology Three satellite groups (5,.6 and 7) were used for toxicokinetic analyses. Blood was sampled from 5 rats/sex in each group on days 2 and 7 of weeks 2, 50 and 100. Mean initial weights/age: males: l44.8g 39 days females: 131.6g 39 days Parameters monitored/Intervals: Clinical- - - daily . . Body weight - weekly (wks 1-26), monthly (wks 27-104) Food consumption - weekly Water consumption - weekly (weeks 13, 26, 39, 52, 65, 78, 91, 104) Effective dose - calculated weekly (wks 1-26); monthly thereafter Hematology - done only prior to sacrifice Prolactin measurements - by RIA in wks 60 and 69 Plasma Conc - in satellite groups as described above Histopathology - on the following tissues: Tissues were fixed in 7.5% formalin (except eyes and Harderian glands were fixed in Susas solution, and the testes with epididymides in Bouins solution), embedded in Paraplast, and stained with HE.

Aorta, heart, kidneys, liver, lungs, and gross lesion were also stained with Masson-Goldners trichrome technique. Sectioning was as follows: Statistics Analyses of routine samples were by Bartletts test, or one-way ANOVA and Newman-Keuls test. Tumor-bearing animals were categorized according to Peto et al. (1980) (1: incidental; 2: probably incidental; 3: probably fatal; 4: fatal), and analyzed using the positive and negative trend tests with respect to dose, and test for heterogeneity. Only p-values <0.05 for rare neoplasms, and <0.01 for common neoplasms were considered statistically significant. The Exact Log Rank test was also used for group comparisons only when the number of tumor-bearing animals in a group was greater than 2, and for between- group comparisons of the number of premature decedents.

Positive control

Examinations

Observations and examinations performed and frequency

Sacrifice and pathology

Other examinations

Statistics

Any other information on materials and methods incl. tables

Results and discussion

Results of examinations

Clinical signs

Description (incidence and severity)
Clinical: increased activity - HDF

Dermal irritation (if dermal study)

Description (incidence and severity)

Mortality

Description (incidence)
Mortality: 40 males and 69 females died over the course of the study. Causes of death are in Table C.5.b.l. No clear time- or dose-relationship was evident to implicate PPX as a causative factor.

Body weight and weight changes

Description (incidence and severity)
Body Weight Gain (Fig. c.5.b.l): LDM - sig. decrease - weeks 1-12, 15, 19, 21-23, 25-82 M & HDM - sig. decrease - all time points except HDM at wks 90-106 LDF - sig. decrease - all time points except wks 14, l5j 90 M & HDF - sig. decrease - all time points Food-Intake (Fig. C.5.b.2): Males - tendency for decrease; no sig. effect at end of study LDF - tendency for decrease; no sig. effect at end of study M & HDF - tendency for increase

Food consumption and compound intake (if feeding study)

Description (incidence and severity)

Food efficiency

Description (incidence and severity)

Water consumption and compound intake (if drinking water study)

Description (incidence and severity)

Ophthalmological findings

Description (incidence and severity)

Haematological findings

Description (incidence and severity)
Hematology: . Group variations (at termination): Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident increased RBC - MDF, HDF increased Hct - MDF, HDF increased MCH - HDM decreased MCH - HDF increased MCHC - HDM decreased MCHC - L, M & HDF decreased eosinophils - L, M & HDF decreased monocytes - M & HDF Individual variations (at termination): increased WBCs - 1 Con M, 1 Con F 1 LDM, 1 LDF 1 MDM 1 HDM anemia, slight - 5 Con M, 7 Con F 2 LDF 2 MDM 2 HDF " , marked - 1 MDF polycythemia - 1 Con M 1 MDM 1 HDM Individual variations (in moribund sacrifices) (Tab, C.5.b.2t Prolactin Measurements (Tab. C.5.b.3): An inverse dose-relationship was observed at both time points in both sexes except for MDM at week 60, which had higher levels than control males.

Clinical biochemistry findings

Description (incidence and severity)

Endocrine findings

Description (incidence and severity)

Urinalysis findings

Description (incidence and severity)

Behaviour (functional findings)

Description (incidence and severity)

Immunological findings

Description (incidence and severity)

Organ weight findings including organ / body weight ratios

Description (incidence and severity)

Gross pathological findings

Description (incidence and severity)

Neuropathological findings

Description (incidence and severity)

Histopathological findings: non-neoplastic

Description (incidence and severity)
Non-neoplastic lesions Aside from the retinal degeneration findings which are discussed in other portions of this review, the most significant findings were primarily in reproductive tissuesi putatively due to the prolactin-inhibiting effects of PPX. Macroscopic lesions in treated females included enlarged or discolored ovaries, and uterine dilatation with hemorrhagic or watery contents. Microscopic alterations in these tissues were enlarged corpora lutea, and chronic suppurative lesions in the uterus. These lesions are suggested to result from a estrogen:progesterone imbalance in the absence of prolactin, which normally stimulates progesterone secretion. In addition, the glandular pattern of mammary gland tissue changes from a female-type tubuloalveolar pattern to a more male-like lobuloalveolar pattern in the absence of prolactin. The Leydig cell hyperplasia is also suggested to be linked to prolactin inhibition. In the absence of prolactin, LH receptors will down-regulate leading to compensatory increases in serum LH, and supposedly hypertrophy of Leydig cells (this is a speculative mechanism; a question that arises is how the Leydig cells respond to LH if the receptors are reduced in density). The reduced incidence of adrenal medullary hyperplasia is suggested to result from PPX-inhibition of catecholamine release from adrenal chromaffin cells. Changes in the incidences of microscopic lesions were summarized as follows:

Histopathological findings: neoplastic

Description (incidence and severity)
Neoplastic Lesions: According to the sponsors analysis, the only tumor that occurred with a higher frequency in PPX-treated animals than in controls was the Leydig cell adenoma. However, this tumor occurred with a high background incidence. The mechanism for increased incidence in PPX-treated animals is similar to that described for the Leydig cell hyperplasia. The incidence of squamous papillomas in the cervix approached statistical significance by the Heterogeneity test ($p = 0.0548$), but the highest incidence of these tumors occurred at the lowest dose.

Other effects

Description (incidence and severity)

Details on results
Results: Mortality: 40 males and 69 females died over the course of the study. Causes of death are in Table C.5.b.l. No clear time- or dose-relationship was evident to implicate PPX as a causative factor. Clinical: increased activity - HDF Body Weight Gain (Fig. c.5.b.l): LDM - sig. decrease - weeks 1-12, 15, 19, 21-23, 25-82 M & HDM - sig. decrease - all time points except HDM at wks 90-106 LDF - sig. decrease - all time points except wks 14, l5j 90 M & HDF - sig. decrease - all time points Food-Intake (Fig. C.5.b.2): Males - tendency for decrease; no sig. effect at end of study LDF - tendency for decrease; no sig. effect at end of study M & HDF - tendency for increase Water Intake: No remarkable trends Effective dose: The large ranges in means, particularly in females, are primarily the result of larger than intended intakes in the latter portion of the study (i.e. after week 74) Hematology: . Group variations (at termination): Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident increased RBC - MDF, HDF increased Hct - MDF, HDF increased MCH - HDM decreased MCH - HDF increased MCHC - HDM decreased MCHC - L, M & HDF decreased eosinophils - L, M & HDF decreased monocytes - M & HDF Individual variations (at termination): increased WBCs - 1 Con M, 1 Con F 1 LDM, 1 LDF 1 MDM 1 HDM anemia, slight - 5 Con M, 7 Con F 2 LDF 2 MDM 2 HDF " , marked - 1 MDF polycythemia - 1 Con M 1 MDM 1 HDM Individual variations (in moribund sacrifices) (Tab, C.5.b.2t Prolactin Measurements (Tab. C.5.b.3): An inverse dose-relationship was observed at both time points in both sexes except for MDM at week 60, which had higher levels than control males. Plasma Concentrations (Tab. C.5.b.4): . Increases in plasma concentrations were approximately dose-proportional. Levels at the 8.00 time-point (time of day) were higher than the 14.00 hr time-point. Measurements taken on different days within the same week did not appear to differ. There was a tendency for drug accumulation in males, but not females; this was particularly evident at week 100. There was no clear sex difference with 1he exception of the HD groups at week 100, where levels in males appeared to be higher. (Note: There appears to be a discrepancy between the graphical and tabular data presentation. This likely occurred because 8 hr was used as a time point reference under two different scenarios - according to time of day (8.00 hr), and according to the number of hours after light onset (14.00 hr) (i.e., blood was collected at 8.00 hr (AM) - two hrs after light onset, and 8 hr after light onset - 14.00 hr). Analysis of the individual data indicates that the tabular presentation on pages 5/24/241-2 is the accurate presentation). Pathology: . Non-neoplastic lesions Aside from the retinal degeneration findings which are discussed in other portions of this review, the most significant findings were primarily in reproductive tissuesi putatively due to the prolactin-inhibiting effects of PPX. Macroscopic lesions in treated females included enlarged or discolored ovaries, and uterine dilatation with hemorrhagic or watery contents. Microscopic alterations in these tissues were enlarged corpora lutea, and chronic suppurative lesions in the uterus. These lesions are suggested to result from a estrogen:progesterone imbalance in the absence of prolactin, which normally stimulates progesterone secretion. In addition, the glandular pattern of mammary gland tissue changes from a female-type tubuloalveolar pattern to a more male-like lobuloalveolar pattern in the absence of prolactin. The Leydig cell hyperplasia is also suggested to be linked to prolactin inhibition. In the absence of prolactin, LH receptors will down-regulate leading to compensatory increases in serum LH, and supposedly hypertrophy of Leydig cells (this is a speculative mechanism; a question that arises is how the Leydig cells respond to LH if the receptors are reduced in density). The reduced incidence of adrenal medullary hyperplasia is suggested to result from PPX-inhibition of catecholamine release from adrenal chromaffin cells. Changes in the incidences of microscopic lesions were summarized as follows: Neoplastic Lesions: According to the sponsors analysis, the only tumor that occurred with a higher frequency in PPX-treated animals than in controls was the Leydig cell adenoma. However, this tumor occurred with a high background incidence. The mechanism for increased incidence in PPX-treated animals is similar to that described for the Leydig cell hyperplasia. The incidence of squamous papillomas in the cervix approached statistical significance by the Heterogeneity test (p = 0.0548), but the highest incidence of these tumors occurred at the lowest dose.

Relevance of carcinogenic effects / potential
Neoplastic Lesions: According to the sponsors analysis, the only tumor that occurred with a higher frequency in PPX-treated animals than in controls was the Leydig cell adenoma. However, this tumor occurred with a high background incidence. The mechanism for increased incidence in PPX-treated animals is similar to that described for the Leydig cell hyperplasia. The incidence of squamous papillomas in the cervix approached statistical significance by the Heterogeneity test (p = 0.0548), but the highest incidence of these tumors occurred at the lowest dose

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Effect levels

Key result Dose descriptor Effect level Based on Sex Basis for effect level Remarks on result Actions 1
☐ Key result
Dose descriptor
NOEL
Effect level
<= 8 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- mortality

Remarks on result
2
☐ Key result
Dose descriptor
dose level:
Effect level

8 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result
3
☐ Key result
Dose descriptor
dose level:
Effect level
8 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
4
☐ Key result
Dose descriptor
dose level:
Effect level
>= 2 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
5
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
other: No effect level reported

[default] : No effect level reported

6
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
male/female
Basis for effect level

- histopathology: neoplastic

Remarks on result
other: No effect level reported

[default] : No effect level reported

7
Key result
Dose descriptor
dose level:
Effect level
>= 2 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
8
Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result
9
Key result
Dose descriptor
dose level:
Effect level
8 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result
10
Key result
Dose descriptor
dose level:
Effect level
8 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result
11
Key result
Dose descriptor
dose level:

Effect level
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
other: No effect level reported

[default] : No effect level reported

12
☐ Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- food consumption and compound intake

Remarks on result
13
☐ Key result
Dose descriptor
dose level:
Effect level
8 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
14
☐ Key result
Dose descriptor
dose level:
Effect level
8 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- clinical signs

Remarks on result
15
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
female
Basis for effect level

- gross pathology

Remarks on result
other: No effect level reported

[default] : No effect level reported

16
☐ Key result
Dose descriptor
dose level:
Effect level
>= 2 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
17
☐ Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result
18
☐ Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- body weight and weight gain

Remarks on result
19
☐ Key result
Dose descriptor
dose level:
Effect level
>= 2 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
20
☐ Key result
Dose descriptor
dose level:

Effect level
8 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- haematology

Remarks on result
21
☐ Key result
Dose descriptor
NOEL
Effect level
<= 8 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- water consumption and compound intake

Remarks on result
22
☐ Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result
23
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
female
Basis for effect level

- gross pathology

Remarks on result
other: No effect level reported

[default] : No effect level reported

24
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
other: No effect level reported

[default] : No effect level reported

25
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
female
Basis for effect level

- gross pathology

Remarks on result
other: No effect level reported

[default] : No effect level reported

26
☐ Key result
Dose descriptor
NOAEL
Effect level
Based on
Sex
male/female
Basis for effect level

Remarks on result
other: Not reported by medical writer

[default] : Not reported by medical writer

Target system / organ toxicity

Key result Critical effects observed Lowest effective dose / conc. System Organ Treatment related Dose response relationship Relevant for humans Actions

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Any other information on results incl. tables

Overall remarks, attachments

Overall remarks

Attachments

Type Attached (confidential) document Attached (sanitised) documents for publication Remarks Actions

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Illustration (picture/graph)

Applicant's summary and conclusion

Conclusions

Executive summary
Summary: Pramipexole was administered in the diet at doses of 0.3, 2.0, and 8.0 mg/kg/day to Wistar rats (50/sex/dose group, 100sexcontrol) for two years. Toxicokinetic analyses were conducted in satellite groups at weeks 2, 50, and 100. Mortality occurred in all treatment groups at various times during the study; there were no clear drug-related effects. The highest percentage of mortality was 40% in LDF. Body weight gain

was significantly reduced at most time points in all three treatment groups. In MDF and HDF, body weight gain was reduced by 22 and 28%, respectively, at the end of the study. Other clinical observations included increased spontaneous activity in HDF, decreased food intake in males and LDF, and increased food intake in MDF and HDF. The only neoplastic lesion that occurred at a higher incidence rate in PPX-treated rats were Leydig cell adenomas in MD (2.0 mg/kg/day) and HD (8.0 mg/kg/day) males. Leydig cell hyperplasia also occurred in MD and HD rats. Drug-related decreases in the incidence mammary gland neoplasia (MDF, HDF), benign adrenal medullary neoplasms (LDF, MDF, HDF), and pituitary adenomas (MD, HD of both sexes) were observed. Adrenal medullary hyperplasia was also reduced in MDF and HDF. Non-neoplastic changes in females were enlarged corpora lutea (HD rats), uterine lesions and hemorrhage (MD and HD), alterations in mammary gland patterns from female-like to male/female-like (MD and HD), and diffuse hepatocellular fatty changes (MD and HD). Retinal degeneration occurred in MD and HD groups of both sexes. Toxicokinetic analyses indicated that in the low dose group, plasma exposure levels 2 hrs after light onset were lower the steady-state Cmax in humans receiving the projected maintenance dose of 1.5 mg PPX, t.i.d., 2-5 fold higher than the human Cmaxss after the intermediate dose, and 10-30 fold higher after the highest dose. The proposed mechanism for the neoplastic and non-neoplastie lesions in reproductive and endocrine tissues is PPX-induced inhibition of prolactin secretion as demonstrated at week 60 and 69 (ca. 10-fold decrease in females, 100-fold decrease in males). In males, reductions in serum prolactin purportedly lead to a down-regulation of LH receptors. This triggers a compensatory increase in LH production and release leading to Leydig cell hyperplasia and adenomas. The sponsor cites a study by Rao et al. (1984) which demonstrates that the dopamine agonist bromocriptine elevates LH; however, no evidence for a similar action of PPX on serum LH or LH receptor number was provided. Nonetheless, the finding is suggested to be of questionable relevance to humans given the high background incidence of this tumor in rats (as demonstrated in this experiment), and since several widely- used compounds also produce Leydig cell tumors in rats but are not known to do so in humans (cimetidine, hydralazine, vidarabine, israpidine). Additional evidence that Leydig cell adenomas may be species-specific is that a similar tumor was not observed in the mouse. The reduction in serum prolactin is also suggested to underlie the decreased incidence of pituitary adenomas, since prolactin normally stimulates anterior pituitary cell proliferation.' The decreased incidence of benign adrenal medullary neoplasia is suggested to result from a dopamine receptor-mediated inhibition of chromaffin cell catecholamine release which decreases the proliferative potency of the chromaffin cells. The corpora lutea enlargement, uterine changes, and changes in the glandular pattern of the mammary glands in PPX-treated female rats were also observed in the one year rat study. The sponsor has presented an argument to discount the potential human relevance of this finding based on the divergent effects of prolactin in rats and humans. In the rat, prolactin is luteolytic, and in its absence non-functional corpora lutea persist (and enlarge). In addition, prolactin stimulates progesterone secretion in the rat and a reduction in the prolactin-progesterone stimulus results in unopposed- actions of estrogen. Aging rats are susceptible to a chronic estrogenic state which leads to the uterine changes. However, this does not occur in aging women due to ovarian involution. Once again these proposed pathways in rats should be considered speculative in the case of PPX since studies of PPX- induced hormonal changes were not presented to support these arguments. The role of PPX inhibition of prolactin secretion in the mammary gland tissue pattern change was described in the one-year rat study. Retinal degeneration in both male and female rats from the mid- and high-dose groups was the most notable non-neoplastic finding of this study. Follow-up studies to address this issue have been conducted by the sponsor, submitted to the IND, and reviewed. These studies will be independently reviewed by an FDA consultant (Dr. Tim ONeill). The only noteworthy aspect of the current NDA submission that needs to be addressed as a part of this review is related to dosage level/exposure. The sponsor minimizes the relevance of the retinal degeneration findings in the discussion since the doses at which the effects were observed were "between 20 and 80 times the intended therapeutic dose in man." Based on an expected Cmaxss in humans of ngml, the exposure level in MD rats (ngml) is only times higher than this level. Hepatocellular fatty changes (steatosis) were observed in PPX-treated females. These were characterized as either diffuse or restricted to zones 1 and 2. Increased incidences of diffuse changes were dose-dependent and statistically significant in the MD and HD groups. Fatty changes restricted to zones 1 and 2 occurred at a lower rate (Con=7%; LD=24%, MD=22%, LD=l8%). The potential mechanism or significance of these findings were not discussed. However, in the 52-week rat study, PPX caused a dramatic dose-dependent reduction in serum cholesterol and triglycerides suggesting a possible interference with hepatic transport or mobilization by PPX. Since both the biochemical and histological changes were observed only in females, a hormonal-based mechanism may be responsible. A direct relationship between the biochemical and histological changes could not be established in either study. In the 52-week study, steatosis (peripheral fatty changes) occurred in all treatment groups, but the biochemical changes were more clearly dose-dependent. Clinical chemistry was not analyzed in the two-year study. Finally, there was no clear relationship between steatosis and more severe liver histopathologies; the highest incidence of necrosis (multicellular) was in MD females. In summary, the only potential tumorigenic effect of PPX identified in this study was the induction of Leydig cell adenomas in males, possibly through an indirect hormonal mechanism that is not clinically relevant The marked impairment of body weight development in MDF and LDF interferes with the interpretation of this study, and no conclusions regarding the carcinogenicity of PPX in female rats can be drawn. The "No Effect" dose was considered to be 0.3 mg/kg/day, although a decrease in body weight gain was apparent at this dose.

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