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SuperUser EPA/ORD/CCTE/SCDCD

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- Substances
- NDA021016-eletriptan hydrobromide

dossier created for substance NDA021016-eletriptan hydrobromide

6bc166cb-facc-45fd-906d-ebda9bcade83

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Type at least 3 characters

OECD Exchange of experimental data
NDA021016-eletriptan hydrobromide

- 1 General information
  1
- 2 Classification and Labelling
- 4 Physical and chemical properties
- 5 Environmental fate and pathways
- 6 Ecotoxicological information
- 7 Toxicological information
  6
  - 7.1 Toxicokinetics, metabolism and distribution
  - 7.2 Acute Toxicity
  - 7.3 Irritation / corrosion
  - 7.4 Sensitisation
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    3
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- 7.7 Carcinogenicity
  2
  - Rat, 2 year dietary mix_94-912-03
  - Mouse, 2 year dietary mix_94021
- 7.8 Toxicity to reproduction
- 7.9 Specific investigations
- 7.10 Exposure related observations in humans
  1
- 7.11 Toxic effects on livestock and pets
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- 8 Analytical methods
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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

- NDA021016_TM1 | eletriptan hydrobromide | 5-[2-(benzenesulfonyl)ethyl]-3-[[(2R)-1-methylpyrrolidin-2-yl]methyl]-1H-indole;hydrobromide | 177834-92-3

Additional test material information

Specific details on test material used for the study
R107 and R109

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

Test animals

Species
mouse

Strain
CD-1

Details on species / strain selection

Sex
male/female

Details on test animals or test system and environmental conditions

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
2 years

Post exposure period
not specified

Doses / concentrations

Dose / conc. Remarks Actions 1
Dose / conc.
400 mg/kg bw/day (actual dose received)
Remarks
2
Dose / conc.
20 mg/kg bw/day (actual dose received)
Remarks
3
Dose / conc.
mg/kg bw/day (actual dose received)
Remarks
4
Dose / conc.
90 mg/kg bw/day (actual dose received)
Remarks

No. of animals per sex per dose
50/sex

Control animals

Details on study design
Mouse, 2 year dietary mix (94021) GLP, QA This study was reviewed by Barry Rosloff, Ph.D. The tables and figures referred to have not been attached. A) DOSAGE 50/sex at 0, 0, 20, 90, or 400 mg/kg/day, in diet Strain: CD-1 Drug batch numbers: R107 and R109 Lab performing study: Pfizer Centre de Recherche 37401 AmboiseCedcx France Dates of study: 1994-1996

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)

Dermal irritation (if dermal study)

Description (incidence and severity)

Mortality

Description (incidence)

Body weight and weight changes

Description (incidence and severity)
Weight gain was slightly decreased in HD M and HD F starting from the first week of treatment. Weights near the end of the study were approximately 5% and 13% below control in HD M and HD F, resp. Weight gain was slightly decreased in MD F beginning after the 2nd month of treatment, although this only occasionally reached statistical significance; weights near the end of the study were approximately 5% below control. Weight gain in LD M was very slightly increased after 3 months. Sponsor-supplied body weight curves below.

Food consumption and compound intake (if feeding study)

Description (incidence and severity)
Slightly decreased at HD of both sexes throughout the study, with the notable exception that consumption was slightly (arid statistically significantly) increased in HD F during week 1. As with weight gain, food consumption was slightly decreased in MD F, although this did not become apparent until later in the study (approx. 8 months) than did the decrease in weight gain. Food consumption was sporadically slightly increased in LD M. Food consumption curves are attached.

Food efficiency

Description (incidence and severity)

Water consumption and compound intake (if drinking water study)

Description (incidence and severity)
At HD, slight decreases throughout most of study (although slightly increased first week). Slight decreases in MD F during latter part of study.

Ophthalmological findings

Description (incidence and severity)

Haematological findings

Description (incidence and severity)
Slightly decreased RBC, Hb, and Hct, and slightly increased platelets, in HD M. Very slight, non-statistically significant changes rn same directions as above seen in MD M. Other parameters measured: RDW, large unstained cells, WBC, differential, bone marrow smears. (No summary data shown for the latter).

Clinical biochemistry findings

Description (incidence and severity)
a) ALT, AST, and AP increased in HD M. Mean values approx. 2x control; highest individual value at HD approx. 2.3x, 3x, and 1.3x highest concurrent control for ALT, AST, and AP, respectively. b) Glucose decreased in MD and HD M (D-R) and HD F; mean value at HD approximately 80% of control. c) Na very slightly increased in HD M. (Mean value approximately 2 mmol/L above control). d) Cl moderately increased at MD and greatly increased at HD, said to be due to interference with the assay by the bromide moiety of the drug. e) Other parameters measured: K, Ca, urea, cholesterol, triglycerides, protein albumin

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)
Absolute and relative liver weights increased in MD and HD M. Relative weights were approximately 1 13 and 1.5x control at MD and HD, resp. Relative liver weight was slightly increased in HD F (1.1x control) with no effect on absolute weight.

Gross pathological findings

Description (incidence and severity)

Neuropathological findings

Description (incidence and severity)

Histopathological findings: non-neoplastic

Description (incidence and severity)
Liver The following showed increased incidence in HD M: hepatocellular adenoma, foci of cellular alteration, single call necrosis, pigmentation (mainly lipofuscin in Kupffer cells), and various “centrilobular changes” (hepatocyte hypertrophy, karyomegaly, heterogeneous cytoplasm). Centrilobular changes also seen m 2/50 MD M and 2/50 HD F. (Incidence values shown in sponsor's summary tables; some also shown in the excerpt below taken from the “Results” section which also contains additional descriptions of some the lesions). Note that eosinophilic, but not basophilic adenomas were increased; also note that according to the sponsor’s descriptions some other drug-related findings were also eosinophilic in nature. Thc incidence of liver carcinomas was not increased. b) Harderian gland The incidence of adenoma was increased in HD M (12% vs 3%, 6% and 6% in controls, LD and MD, resp.). The incidence of hypersecretion in Harderian gland was also increascd in HD M (70 % vs 42 % in control). The incidence of hyperplasia was not increased. Although apparently not considered drug-related by the sponsor, the incidence of harderian gland adenoma in females was 0%, 6%, 4% and 6% in controls, LD, MD, and HD, resp. The incidences of hypersecretion and hyperplasia were not increased in females.

Histopathological findings: neoplastic

Description (incidence and severity)

Other effects

Description (incidence and severity)

Details on results
RESULTS 1) Observed signs. No drug effects. 2) Mortality Results shown in attached figures. The sponsor concludes that mortality was decreased in MD and HD F. Overall survival = 44%. 58% and 68% in control F, MD F, and HD F, resp.) However, as indicated in the attached figure, mortality in all M groups, although similar to controls at the end of the study, was less than that in controls during most of the 2nd year (not dose-related). 3) Body Weight Weight gain was slightly decreased in HD M and HD F starting from the first week of treatment. Weights near the end of the study were approximately 5% and 13% below control in HD M and HD F, resp. Weight gain was slightly decreased in MD F beginning after the 2nd month of treatment, although this only occasionally reached statistical significance; weights near the end of the study were approximately 5% below control. Weight gain in LD M was very slightly increased after 3 months. Sponsor-supplied body weight curves below. 4) Food Consumption Slightly decreased at HD of both sexes throughout the study, with the notable exception that consumption was slightly (arid statistically significantly) increased in HD F during week 1. As with weight gain, food consumption was slightly decreased in MD F, although this did not become apparent until later in the study (approx. 8 months) than did the decrease in weight gain. Food consumption was sporadically slightly increased in LD M. Food consumption curves are attached. 5) Water Consumption At HD, slight decreases throughout most of study (although slightly increased first week). Slight decreases in MD F during latter part of study. 6) Ophthalmoscopic exam (Done in 25/sex in controls and HD pre-study; repeated every 6 months in survivors among these animals) No drug effects. 7) Hematology (Done al termination) Slightly

decreased RBC, Hb, and Hct, and slightly increased platelets, in HD M. Very slight, non-statistically significant changes rn same directions as above seen in MD M. Other parameters measured: RDW, large unstained cells, WBC, differential, bone marrow smears. (No summary data shown for the latter). 8) Blood chemistry (Done at termination) a) ALT, AST, and AP increased in HD M. Mean values approx. 2x control; highest individual value at HD approx. 2.3x, 3x, and 1.3x highest concurrent control for ALT, AST, and AP, respectively. b) Glucose decreased in MD and HD M (D-R) and HD F; mean value at HD approximately 80% of control. c) Na very slightly increased in HD M. (Mean value approximately 2 mmol/L above control). d) Cl moderately increased at MD and greatly increased at HD, said to be due to interference with the assay by the bromide moiety of the drug. e) Other parameters measured: K, Ca, urea, cholesterol, triglycerides, protein albumin 9) Urinalysis not performed 10) Organ Weight Absolute and relative liver weights increased in MD and HD M. Relative weights were approximately 1 13 and 1.5x control at MD and HD, resp. Relative liver weight was slightly increased in HD F (1.1x control) with no effect on absolute weight. 11) Gross pathology Text states no effect; no summary table presented. 12) Histopathology (Organs shown in the list below, plus organs with macroscopic abnormalities, were examined in al) groups. Summary tables did not break down results by animals which survived to termination and those which did not. These tables arc attached [separate tables for neoplastic and non-neoplastic findings].) a) Liver The following showed increased incidence in HD M: hepatocellular adenoma, foci of cellular alteration, single call necrosis, pigmentation (mainly lipofuscin in Kupffer cells), and various "centrilobular changes" (hepatocyte hypertrophy, karyomegaly, heterogeneous cytoplasm). Centrilobular changes also seen m 2/50 MD M and 2/50 HD F. (Incidence values shown in sponsor's summary tables; some also shown in the excerpt below taken from the "Results" section which also contains additional descriptions of some the lesions). Note that eosinophilic, but not basophilic adenomas were increased; also note that according to the sponsor's descriptions some other drug-related findings were also eosinophilic in nature. Thc incidence of liver carcinomas was not increased. b) Harderian gland The incidence of adenoma was increased in HD M (12% vs 3%, 6% and 6% in controls, LD and MD, resp.). The incidence of hypersecretion in Harderian gland was also increascd in HD M (70 % vs 42 % in control). The incidence of hyperplasia was not increased. Although apparently not considered drug-related by the sponsor, the incidence of harderian gland adenoma in females was 0%, 6%, 4% and 6% in controls, LD, MD, and HD, resp. The incidences of hypersecretion and hyperplasia were not increased in females. C) SUMMARY A 2 year dietary carcinogenicity study was performed in CD-1 mice at daily doses of 20, 90, and 400 mg/kg. There were no drug-related signs or effects on ophthalmoscopic exams. Mortality v. as decreased in MD and HD F. Although there was no drug effect on percent survival in males at termination, mortality was lower than controls in a∏ male groups (not D- R.) during the second year of the study. Body weight gain and food consumption were decreased in MD and HD F and HD M; final weights were 5%, 13%, and 5% below controls, respectively. Hematology and blood chemistry exams showed (1) slightly decreased RBC, Hb, and Hct. and slightly increased platelets, in HD M and equivocally in MD M, (2) increased ALT. AST and AP in HD M, (3) decreased glucose in MD and HD M and HD F, and (4) increased chloride at MD and HD said to be due to assay interference by the drug. Absolute and relative liver weights were increased in MD and HD M; relative (but not absolute) liver weight was slightly increased in HD F. Gross pathology exams were said to show no drug effect although no summary tables were presented. Histopathology exams showed an increase in eosinophilic hepatocellular adenomas in HD M (14% vs 0% in controls; incidence of total [eosinophilic + basophilic] adenomas = 24% vs 9% in controls). Also increased in liver of HD M were foci of cellular alteration, single cell necrosis, pigmentation of Kupffer cells, and centrilobular changes (hepatocyte hypertrophy, karyomegaly. heterogeneous cytoplasm). (Centrilobular changes also secn in 2/50 MD M and 2/50 HD F.) There were no drug effects on the incidence of hepatocellular carcinoma. There was a slight increase in the incidence of harderian gland adenoma in HD M (12% vs 3% in controls). The incidence of hypersecretion in harderian gland was also increased in HD M; the incidence of hyperplasia was not. Although apparently not statistically significant by the sponsor's analysis, it is noted that the incidence of harderian gland adenomas in females was 0%, 6%, 4%, and 6% in controls, LD, MD and HD, respectively. The incidence of hypersecretion and hyperplasia were not increased in females. D) EVALUATION Although the drug did not cause any observed signs, an MTD may be considered to have been reached based on decreased weight gain; final weights at the HD (400 mg/kg) were 5% and 13% below controls in M and F, respectively. (Slight decreases in weight gain were also seen at this dose in a 3 month range-finding study; higher doses were not tested). Since food consumption was decreased in the same groups in which weight gain was decreased, the possibility of poor palatability as an explanation arises. In HD M, both food consumption and body weight were decreased from the first week of treatment, which would support this explanation. However, in HD F, although bodyweights were decreased from the first week, food consumption showed a slight increase during the first week. Furthermore, in MD F, decreases in weight gain did not become apparent until after the second month, and decreased food consumption did not become apparent until 8 months. It thus appears likely that poor palatability is not a necessary cause of the decreased weight gain, although a role for this cannot be ruled out (especially in HD M). Regarding the adequacy of the doses used, the sponsor also states that the AUC for parent drug at a dose of 400 mg/kg (22 ug.hr/ml, obtained in the 3 month range-finding study, results attached is about 33-fold higher than that produced in humans "at the maximal daily clinical dose". However, note that using a maximum human dose of 80 mg b.i.cl., and an estimated daily AUC of 3 ug.hr/ml (per information provided by Biopharm reviewer), a factor of 7 is calculated. It is also noted that no comparative exposure data for metabolites were presented for this highly metabolized drug. Although hepatocellular adenoma is a common tumor type in this strain of mice, the increased incidence in HD M was clearly drug-related, particularly in view of the increase in foci of cellular alteration. The sponsor suggests that the increase in adenomas is related to hepatic enzyme induction; however, it is noted that the enzyme-inducing effect (elevated liver P-450 content) as measured in the 3 month range-finding study was thought to be small. (Also note that aside from a neoplastic effect, other liver toxicity was demonstrated in this study. including elevations of ALT, AST and AP, increased liver weight, and various histopathological changes.) The small increases in harderian gland adenomas are somewhat equivocal. Although statistically significant by the sponsor's analysis, the report states that a drug effect in HD M is "unlikely" since the incidence (12%) was said to be "only slightly above our historical data: however, the only such data cited was an incidence of 5/50 in a control group "of a recent study". In contrast, it is stated in a 1990 book [Faccini, et. a!., Mouse histopathology 1. that the historical incidence at Pfizer/Amboise [where the present study was performed] is under 2%. On the other hand, other published data do show higher values for CD-1 mice, e.g. 13% [range 0-18%] in males and 5% [range 0-7%] in females in a recent Charles River publication). There was no strong evidence for an earlier onset of adenomas in HD M; 3 were found at termination and 1 each on days 684, 709, and 734; all 3 control tumors were found at termination. The fact that survival was greater than controls in most drug groups max have played a role in the increased tumor incidence, although the sponsor's analysis, which presumably took this into account, still showed a statistically significant increase in HD M (when both control groups were combined). In support of an effect in HD M was the finding of increased hypersecretion in this group. Increased hypersecretion was not seen in females. Increased hyperplasia was not seen in males or females.

Relevance of carcinogenic effects / potential
Although hepatocellular adenoma is a common tumor type in this strain of mice, the increased incidence in HD M was clearly drug-related, particularly in view of the increase in foci of cellular alteration. The sponsor suggests that the increase in adenomas is related to hepatic enzyme induction; however, it is noted that the enzyme-inducing effect (elevated liver P-450 content) as measured in the 3 month range-finding study was thought to be small. (Also note that aside from a neoplastic effect, other liver toxicity was demonstrated in this study. including elevations of ALT, AST and AP, increased liver weight, and various histopathological changes.) The small increases in harderian gland adenomas are somewhat equivocal. Although statistically significant by the sponsor's analysis, the report states that a drug effect in HD M is “unlikely” since the incidence (12%) was said to be "only slightly above our historical data: however, the only such data cited was an incidence of 5/50 in a control group “of a recent study”. In contrast, it is stated in a 1990 book [Faccini, et. a!., Mouse histopathology 1. that the historical incidence at Pfizer/Amboise [where the present study was performed] is under 2%. On the other hand, other published data do show higher values for CD-1 mice, e.g. 13% [range 0-18%] in males and 5% [range 0-7%] in females in a recent Charles River publication). There was no strong evidence for an earlier onset of adenomas in HD M; 3 were found at termination and 1 each on days 684, 709, and 734; all 3 control tumors were found at termination. The fact that survival was greater than controls in most drug groups max have played a role in the increased tumor incidence, although the sponsor's analysis, which presumably took this into account, still showed a statistically significant increase in HD M (when both control groups were combined). In support of an effect in HD M was the finding of increased hypersecretion in this group. Increased hypersecretion was not seen in females. Increased hyperplasia was not seen in males or females.

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
<= 400 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- ophthalmological examination

Remarks on result
2

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

- clinical biochemistry

Remarks on result
3

☐ Key result
Dose descriptor
NOEL
Effect level
<= 400 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- mortality

Remarks on result
4

☐ Key result
Dose descriptor
dose level:
Effect level

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

- haematology

Remarks on result
other: slight

[default] : slight

5
☐ Key result
Dose descriptor
dose level:
Effect level
400 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
6
☐ 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

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

- histopathology: neoplastic

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

- histopathology: non-neoplastic

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

- organ weights and organ / body weight ratios

Remarks on result
other: slight

[default] : slight

10
Key result
Dose descriptor
NOEL
Effect level
<= 400 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- clinical signs

Remarks on result
11
Key result
Dose descriptor
dose level:
Effect level
400 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
12
Key result
Dose descriptor
dose level:
Effect level
400 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
other: slight

[default] : slight

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

- clinical biochemistry

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

- histopathology: non-neoplastic

Remarks on result
15
Key result
Dose descriptor
dose level:
Effect level
400 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- clinical biochemistry

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

- haematology

Remarks on result
other: slight

[default] : slight

17
Key result
Dose descriptor
dose level:
Effect level

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

- food consumption and compound intake

Remarks on result
other: slight

[default] : slight

18
☐ Key result
Dose descriptor
dose level:
Effect level
>= 20 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- histopathology: neoplastic

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

- histopathology: non-neoplastic

Remarks on result
20
☐ Key result
Dose descriptor
dose level:
Effect level
400 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- clinical biochemistry

Remarks on result
21
☐ Key result
Dose descriptor
NOEL
Effect level
<= 400 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- gross pathology

Remarks on result
22
Key result
Dose descriptor
dose level:
Effect level
>= 90 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- organ weights and organ / body weight ratios

Remarks on result
23
Key result
Dose descriptor
dose level:
Effect level
400 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- clinical biochemistry

Remarks on result
other: slight

[default] : slight

24
Key result
Dose descriptor
dose level:
Effect level
400 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- body weight and weight gain

Remarks on result
25
Key result
Dose descriptor
dose level:
Effect level
>= 90 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- clinical biochemistry

Remarks on result
26
Key result
Dose descriptor
dose level:

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

- food consumption and compound intake

Remarks on result
other: slight

[default] : slight

27
☐ Key result
Dose descriptor
dose level:
Effect level
>= 90 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- organ weights and organ / body weight ratios

Remarks on result
28
☐ Key result
Dose descriptor
dose level:
Effect level
400 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- histopathology: non-neoplastic

Remarks on result

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

C) SUMMARY A 2 year dietary carcinogenicity study was performed in CD-1 mice at daily doses of 20, 90, and 400 mg/kg. There were no drug-related signs or effects on ophthalmoscopic exams. Mortality v. as decreased in MD and HD F. Although there was no drug effect on percent survival in males at termination, mortality was lower than controls in a∏ male groups (not D- R.) during the second year of the study. Body weight gain and food consumption were decreased in MD and HD F and HD M; final weights were 5%, 13%, and 5% below controls, respectively. Hematology and blood chemistry exams showed (1) slightly decreased RBC, Hb, and Hct. and slightly increased platelets, in HD M and equivocally in MD M, (2) increased ALT. AST and AP in HD M, (3) decreased glucose in MD and HD M and HD F, and (4) increased chloride at MD and HD said to be due to assay interference by the drug. Absolute and relative liver weights were increased in MD and HD M; relative (but not absolute) liver weight was slightly increased in HD F. Gross pathology exams were said to show no drug effect although no summary tables were presented. Histopathology exams showed an increase in eosinophilic hepatocellular adenomas in HD M (14% vs 0% in controls; incidence of total [eosinophilic + basophilic] adenomas = 24% vs 9% in controls). Also increased in liver of HD M were foci of cellular alteration, single cell necrosis, pigmentation of Kupffer cells, and centrilobular changes (hepatocyte hypertrophy, karyomegaly. heterogeneous cytoplasm). (Centrilobular changes also secn in 2/50 MD M and 2/50 HD F.) There were no drug effects on the incidence of hepatocellular carcinoma. There was a slight increase in the incidence of harderian gland adenoma in HD M (12% vs 3% in controls). The incidence of hypersecretion in harderian gland was also increased in HD M; the incidence of hyperplasia was not. Although apparently not statistically significant by the sponsor's analysis, it is noted that the incidence of harderian gland adenomas in females was 0%, 6%, 4%, and 6% in controls, LD, MD and HD, respectively. The incidence of hypersecretion and hyperplasia were not increased in females. D) EVALUATION Although the drug did not cause any observed signs, an MTD may be considered to have been reached based on decreased weight gain; final weights at the HD (400 mg/kg) were 5% and 13% below controls in M and F, respectively. (Slight decreases in weight gain were also seen at this dose in a 3 month range-finding study; higher doses were not tested). Since food consumption was decreased in the same groups in which weight gain was decreased, the possibility of poor palatability as an explanation arises. In HD M, both food consumption and body weight were decreased from the first week of treatment, which would support this explanation. However, in HD F, although bodyweights were decreased from the first week, food consumption showed a slight increase during the first week. Furthermore, in MD F, decreases in weight gain did not become apparent until after the second month, and decreased food consumption did not become apparent until 8 months. It thus appears likely that poor palatability is not a necessary cause of the decreased weight gain, although a role for this cannot be ruled out (especially in HD M). Regarding the adequacy of the doses used, the sponsor also states that the AUC for parent drug at a dose of 400 mg/kg (22 ug.hr/ml, obtained in the 3 month range-finding study, results attached is about 33-fold higher than that produced in humans "at the maximal daily clinical dose". However, note that using a maximum human dose of 80 mg b.i.cl., and an estimated daily AUC of 3 ug.hr/ml (per information provided by Biopharm reviewer), a factor of 7 is calculated. It is also noted that no comparative exposure data for metabolites were presented for this highly metabolized drug. Although hepatocellular adenoma is a common tumor type in this strain of mice, the increased incidence in HD M was clearly drug-related, particularly in view of the increase in foci of cellular alteration. The sponsor suggests that the increase in adenomas is related to hepatic enzyme induction; however, it is noted that the enzyme-inducing effect (elevated liver P-450 content) as measured in the 3 month range-finding study was thought to be small. (Also note that aside from a neoplastic effect, other liver toxicity was demonstrated in this study. including elevations of ALT, AST and AP, increased liver weight, and various histopathological changes.) The small increases in harderian gland adenomas are somewhat equivocal. Although statistically significant by the sponsor's analysis, the report states that a drug effect in HD M is "unlikely" since the incidence (12%) was said to be "only slightly above our historical data: however, the only such data cited was an incidence of 5/50 in a control group "of a recent study". In contrast, it is stated in a 1990 book [Faccini, et. a!., Mouse histopathology 1. that the historical incidence at Pfizer/Amboise [where the present study was performed] is under 2%. On the other hand, other published data do show higher values for CD-1 mice, e.g. 13% [range 0-18%] in males and 5% [range 0-7%] in females in a recent Charles River publication). There was no strong evidence for an earlier onset of adenomas in HD M; 3 were found at termination and 1 each on days 684, 709, and 734; all 3 control tumors were found at termination. The fact that survival was greater than controls in most drug groups max have played a role in the increased tumor incidence, although the sponsor's analysis, which presumably took this into account, still showed a statistically significant increase in HD M (when both control groups were combined). In support of an effect in HD M was the finding of increased hypersecretion in this group. Increased hypersecretion was not seen in females. Increased hyperplasia was not seen in males or females.

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