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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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- Export to i6z
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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
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  - 7.4 Sensitisation
  - 7.5 Repeated dose toxicity
    3
  - 7.6 Genetic toxicity

- 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
- 7.12 Additional toxicological information

- 8 Analytical methods
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- Inherited templates

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- Compare Document

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

- 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
batch R109 and R203

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

Test animals

Species
rat

Strain
Sprague-Dawley

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
not specified

Post exposure period
not specified

Doses / concentrations

Dose / conc. Remarks Actions 1
Dose / conc.
50 mg/kg bw/day (actual dose received)
Remarks
after month 8
2
Dose / conc.
75 mg/kg bw/day (actual dose received)
Remarks
lowered to 50 mKD after 8 months
3
Dose / conc.
mg/kg bw/day (actual dose received)
Remarks
4
Dose / conc.
3 mg/kg bw/day (actual dose received)
Remarks
5
Dose / conc.
15 mg/kg bw/day (actual dose received)
Remarks

No. of animals per sex per dose
65/s/gr with 2 control groups

Control animals

Details on study design
Rat. 2 year dietary mix (94-912-03) GLP, QA Pfizer Central Research (Groton, CT), conducted in 1994 - 1996 Sprague-Dawley rats - 3, 15, 75 mg/kg (lowered to 50 mg/kg for F after 8 months) 65/s/gr with 2 control groups

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)
Body Weight. BW gain was reduced throughout the study in HD M and F such that BW's at the end of the study were 20 and 33% less than control, respectively (sponsor- supplied BW curves are provided below). Because of the excessive decrease in BW gain, the sponsor decreased the HD for F from 75 to 50 mg/kg after S months of treatment. From 17 months onward BW in MD F was 6 - 12% less than control, with differences being occasionally statistically significant. Effects on BW were generally paralleled by decreased food consumption, although the decreased BW gain in HD F was evident within the first weeks of the study, preceding the effect on food consumption. The decrease in food consumption does not appear to be related to palatability because it was not notable until weeks 6-8.

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)

Clinical biochemistry findings

Description (incidence and severity)
Clinical Chem. Parameters were measured at 6, 12 and 18 months in 10/s/gr. Bilirubin increased 58 - 75% and 23 - 53% in all treated M and F groups, respectively, but only at 6 months. Triglycendes were decreased -60% in HD F at 12 and 18 months. A similar decrease did not reach statistical significance in HD M ar 18 months, but appears to be a drug-related effect based on individual animal data.

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)
Organ Weights. Absolute kidney weight was 20% less than control in HD M and absolute liver weight was 21 % less than control in HD F. Relative brain and testis weights were 24 and 53% greater than control, respectively, in HD M. Relative heart, kidney and brain weights were 17, 25 and 40% greater than control, respectively, in HD F. The effect on organ weights likely reflects the decreased BW gain at the HD.

Gross pathological findings

Description (incidence and severity)

Neuropathological findings

Description (incidence and severity)

Histopathological findings: non-neoplastic

Description (incidence and severity)
Increased non-neoplastic histopathology was limited to HD M and included an increased incidence of liver eosinophilic foci, thyroid follicular cell hyperplasia, and pituitary pars distalis hyperplasia. The incidence of several histopathological findings were decreased in HD M and/or F, likely owing to the deficit in BW gain experienced at the HD.

Histopathological findings: neoplastic

Description (incidence and severity)
Pathology. The sponsor reports no treatment-related gross pathology (no data were provided). Notable histopathology changes are tabulated below and include an increased incidence of testicular interstitial cell adenoma in HD M. The sponsor states that the increased incidence was not significant after Bonferoni correction for multiplicity of testing, but Bonferoni correction in carcinogenicity studies is not accepted by the Agency because of it's tendency to overcorrect given the sheer number of comparisons being made. The sponsor also attributes the increased incidence to the greater longevity of the HD M group (all testicular tumors were identified in animals surviving ≥ 19 months); however, the increase is statistically significant even after adjustment for survival. The 17.2% incidence exceeds the historical control range reported by ---- for studies conducted in 19S4 - 1989 (1.4 - 10.0%, mean 4.7%). The incidence of histiocytic sarcomas was increased in MD M (6.2% v. 1.5%), but did not exceed the historical control range reported by ------- for studies conducted in 1984- 1989 (1.4 - 7.1%, mean 1.6%).

Other effects

Description (incidence and severity)

Details on results
Mortality. There was no detrimental effect of treatment on survival throughout the study. In fact, survival in HD M exceeded that of controls from approximately 17 months onward. Survival at the end of the study is tabulated below. Clinical Signs. There were no notable clinical signs. Body Weight. BW gain was reduced throughout the study in HD M and F such that BW's at the end of the study were 20 and 33% less than control, respectively (sponsor- supplied BW curves are provided below). Because of the excessive decrease in BW gain, the sponsor decreased the HD for F from 75 to 50 mg/kg after S months of treatment. From 17 months onward BW in MD F was 6 - 12% less than control, with differences being occasionally statistically significant. Effects on BW were generally paralleled by decreased food consumption, although the decreased BW gain in HD F was evident within the first weeks of the study, preceding the effect on food consumption. The decrease in food consumption does not appear to be related to palatability because it was not notable until weeks 6-8. Hematology. Parameters were measured at 6, 12 and 18 months in 10⁄s⁄gr. There were no notable findings. Clinical Chem. Parameters were measured at 6, 12 and 18 months in 10/s/gr. Bilirubin increased 58 - 75% and 23 - 53% in all treated M and F groups, respectively, but only at 6 months. Triglycendes were decreased -60% in HD F at 12 and 18 months. A similar decrease did not reach statistical significance in HD M ar 18 months, but appears to be a drug-related effect based on individual animal data. Toxicokinetics Plasma concentrations of eletriptan were determined on Days 91 and 177 in 5⁄s⁄gr. Concentrations in the LD group were generally at or below the 4 ng/ml level of detection. Concentrations in the MD group were 41 and 49 ng/ml on Days 91 and 177,

respectively, and in the HD group were 290 and 430 ng/ml, respectively. Organ Weights. Absolute kidney weight was 20% less than control in HD M and absolute liver weight was 21 % less than control in HD F. Relative brain and testis weights were 24 and 53% greater than control, respectively, in HD M. Relative heart, kidney and brain weights were 17, 25 and 40% greater than control, respectively, in HD F. The effect on organ weights likely reflects the decreased BW gain at the HD. Pathology. The sponsor reports no treatment-related gross pathology (no data were provided). Notable histopathology changes are tabulated below and include an increased incidence of testicular interstitial cell adenoma in HD M. 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Increased non-neoplastic histopathology was limited to HD M and included an increased incidence of liver eosinophilic foci, thyroid follicular cell hyperplasia, and pituitary pars distalis hyperplasia. The incidence of several histopathological findings were decreased in HD M and/or F, likely owing to the deficit in BW gain experienced at the HD. Summary. The incidence of testicular interstitial adenoma was increased in HD M (17.2% v. 6.2%). The sponsor attributed the increase to the greater longevity of HD M compared to control; however, the increase is statistically significant even after adjustment for survival. Furthermore, the 17.2% incidence exceeds the 1.4 - 10.0% historical control range reported by for studies conducted in 1984 - 1989 (data closer to the time frame of this study are not available). The only other tumor incidence that was notably increased was that of histiocytic sarcomas in the Iymphoreticular system of MD M (6.2% v. 1.5%). Although a similar increase did not occur at the HD, the excessive decrease in BW gain at the HD (BW 20% less than control at study termination) may have decreased tumor expression at the HD. The 6.2% incidence of histiocytic sarcoma at thc MD did not occurred the 1.4-7.1% historical control incidence reported by for studies conducted m 1984 - 1989 (data closer to the time frame of this study are not available). Non-Iieoplaslic changes observed in HD M included increased incidences of eosinophilic foci in the liver, follicular cell hyperplasia in the thyroid and pars distalis hyperplasia in the pituitary. There were also a few changes indicative of improved general health in HD M and F, likely related to the decreased BW gain observed at the HD. The incidences of hepatic periportal vacuolation, adrenal cortical vacuolation, chronic nephropathy, testicular periarteritis, testicular tubular atrophy, and mammary gland fibroadenoma were decreased in HD M and/or F. The excessive decrease in BW gain at the HD may have compromised tumor expression, making the 15 mg/kg MD the highest dose from which tumor data can be reliably evaluated. On a mg/m2 basis this dose is approximately equal to the proposed maximum recommended daily dose of 2 x 80 mg. The plasma levels achieved at this dose were approximately 20% of the Cmax achieved in humans given an 80 mg dose. No AUC estimations were made in this study; however, extrapolating linearly from results in the dose range-finding study (100, 200, 300 mg/kg), the AUC achieved in M and F rats at 15 mg/kg is predicted to be approximately equal to the 3000 ng.h/ml exposure achieved in humans at the proposed maximum recommended daily dose. The AUC extrapolated for the 75/50 mg/kg dose is approximately 2 times the exposure achieved in humans at the proposed maximum recommended daily dose It appears that higher doses could have been achieved by gavage rather than dietary administration. In a one month gavage study (97075) in which the HD was 100 mg/kg, there was no effect on BW and toxicity was limited to increased liver weight (~20%) and thyroid follicular hypertrophy in F only. Furthermore, essentially no toxicity was observed in a 6 month gavage study at the HD of 50 mg/kg. Extrapolating toxicokinetic data from the 6 month study, exposure for M and F rats at a 100 mg/kg gavage dose is predicted to be 3 and 6-fold, respectively, the AUC achieved in humans at the proposed maximum recommended daily dose of 2 x 80 mg.

Relevance of carcinogenic effects / potential

Summary. The incidence of testicular interstitial adenoma was increased in HD M (17.2% v. 6.2%). The sponsor attributed the increase to the greater longevity of HD M compared to control; however, the increase is statistically significant even after adjustment for survival. Furthermore, the 17.2% incidence exceeds the 1.4 - 10.0% historical control range reported by for studies conducted in 1984 - 1989 (data closer to the time frame of this study are not available). The only other tumor incidence that was notably increased was that of histiocytic sarcomas in the Iymphoreticular system of MD M (6.2% v. 1.5%). Although a similar increase did not occur at the HD, the excessive decrease in BW gain at the HD (BW 20% less than control at study termination) may have decreased tumor expression at the HD. The 6.2% incidence of histiocytic sarcoma at thc MD did not occurred the 1.4-7.1% historical control incidence reported by for studies conducted m 1984 - 1989 (data closer to the time frame of this study are not available). Non-Iieoplaslic changes observed in HD M included increased incidences of eosinophilic foci in the liver, follicular cell hyperplasia in the thyroid and pars distalis hyperplasia in the pituitary. There were also a few changes indicative of improved general health in HD M and F, likely related to the decreased BW gain observed at the HD. The incidences of hepatic periportal vacuolation, adrenal cortical vacuolation, chronic nephropathy, testicular periarteritis, testicular tubular atrophy, and mammary gland fibroadenoma were decreased in HD M and/or F.

Effect levels

Key result Dose descriptor Effect level Based on Sex Basis for effect level Remarks on result Actions 1

☐ Key result

Dose descriptor

dose level:

Effect level

75 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
2
☐ Key result
Dose descriptor
dose level:
Effect level
75 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
3
☐ Key result
Dose descriptor
dose level:
Effect level
>= 3 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- clinical biochemistry

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

- clinical biochemistry

Remarks on result
5
☐ Key result
Dose descriptor
dose level:
Effect level
75 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
6
☐ Key result
Dose descriptor
dose level:
Effect level
75 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
7
☐ Key result
Dose descriptor
dose level:
Effect level
75 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- histopathology: non-neoplastic

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

- body weight and weight gain

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

- histopathology: non-neoplastic

Remarks on result
10
☐ Key result
Dose descriptor
dose level:
Effect level
75 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
11

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

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

- histopathology: non-neoplastic

Remarks on result
13
Key result
Dose descriptor
dose level:
Effect level
75 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
14
Key result
Dose descriptor
dose level:
Effect level
75 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- histopathology: neoplastic

Remarks on result
15
Key result
Dose descriptor
NOEL
Effect level
<= 75 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- haematology

Remarks on result
16
☐ Key result
Dose descriptor
NOEL
Effect level
<= 75 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- mortality

Remarks on result
17
☐ Key result
Dose descriptor
dose level:
Effect level
75 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

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. The incidence of testicular interstitial adenoma was increased in HD M (17.2% v. 6.2%). The sponsor attributed the increase to the greater longevity of HD M compared to control; however, the increase is statistically significant even after adjustment for survival. Furthermore, the 17.2% incidence exceeds the 1.4 - 10.0% historical control range reported by for studies conducted in 1984 - 1989 (data closer to the time frame of this study are not available). The only other tumor incidence that was notably increased was that of histiocytic sarcomas in the lymphoreticular system of MD M (6.2% v. 1.5%). Although a similar increase did not occur at the HD, the excessive decrease in BW gain at the HD (BW 20% less than control at study termination) may have decreased tumor expression at the HD. The 6.2% incidence of histiocytic sarcoma at thc MD did not occurred the 1.4-7.1% historical control incidence reported by for studies conducted m 1984 - 1989 (data closer to the time frame of this study are not available). Non-lieoplaslic changes observed in HD M included increased incidences of eosinophilic foci in the liver, follicular cell

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