- Dossier preparation manuals
- Q&A
- Create support request
- IUCLID user community
- Additional information
- Video tutorials

SuperUser EPA/ORD/CCTE/SCDCD

- User Settings
- Logout

- Dashboard
- Substances
- NDA208854-naldemedine tosylate

dossier created for substance NDA208854-naldemedine tosylate

1d6c192b-6f21-4c83-b43b-77791292f5d6

View Dossiers | Validate

- Export to i6z
- Extract to dataset
- Create component PDF/RTF
- Create document PDF/RTF
- Compare
- Generate report
- Dissemination preview

Type at least 3 characters

OECD Exchange of experimental data
NDA208854-naldemedine tosylate

- 1 General information
  1
- 2 Classification and Labelling
- 4 Physical and chemical properties
- 5 Environmental fate and pathways
- 6 Ecotoxicological information
- 7 Toxicological information
  11
  - 7.1 Toxicokinetics, metabolism and distribution
  - 7.2 Acute Toxicity
  - 7.3 Irritation / corrosion
  - 7.4 Sensitisation
  - 7.5 Repeated dose toxicity
    11
    - 7.5.1 Repeated dose toxicity: oral

11

- Preliminary Carcinogenicity Study (Gavage) of S-297995 monotosylate in Mice for 2 Weeks_S-297995-TB-218-R
- Three-Month Oral Toxicity Study of RSC-297995 monotosylate in Dogs_S-297995-TF-109-L
- One-Month Oral Toxicity Study of RSC-297995 mono tosylate in Rats (Supplement)_R-297995-TB-091-L
- Two-Week Oral Toxicity Study of S-297995 monotosylate in Non-Pregnant Rabbits, Amendment to Final Report_S-297995-TF-119L
- Thirteen-Week Repeated-Dose Oral Toxicity- Study of S-297995 in Mice_S-297995-TF-226-L
- One-Mouth Oral Toxicity' Study of RSC-297995 monotosylate in Dogs_R-297995-TB-046-L
- One-Month Oral Toxicity Study of RSC-297995 monotosylate in Rats_R-297995-TB-048-L
- Preliminary Two-week Oral Toxicity Study of RSC-297995 monotosylate in Dogs_R-297995-TBAXJ2-R
- Preliminary Two-Week Oral Toxicity Study of RSC-297995 monotosylate in Rats_R-297995-TB-003-R
- Six-Montlh Oral Toxicity Study of RSC-297995 monotosylate in Rats_R-297995-TF-108-L
- Nine-Month Oral Toxicity Study of S-297995 monotosylate in Dogs_S-297995-TF-219-L

- 7.5.2 Repeated dose toxicity: inhalation
- 7.5.3 Repeated dose toxicity: dermal
- 7.5.4 Repeated dose toxicity: other routes

- 7.6 Genetic toxicity
- 7.7 Carcinogenicity
- 7.8 Toxicity to reproduction
- 7.9 Specific investigations
- 7.10 Exposure related observations in humans
- 7.11 Toxic effects on livestock and pets
- 7.12 Additional toxicological information

- 8 Analytical methods
- 11 Guidance on safe use
- Inherited templates

UUID d8d1a14c-263e-48c8-85ba-95073416495e Hide empty fields

- 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
sub-chronic toxicity: 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

Limit test

Test material

Test material information

- NDA208854_TM1 | naldemedine tosylate | 17-(cyclopropylmethyl)-6,7-didehydro-4,5a-epoxy-3,6,14-trihydroxy-N-[2-(3- phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide 4- methylbenzenesulfonic acid | 1345728-04-2

Additional test material information

Specific details on test material used for the study

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

Test animals

Species
dog

Strain
Beagle

Details on species / strain selection

Sex
male/female

Details on test animals or test system and environmental conditions
Age: 10-12 months Weight: 9.88 to 12.88 kg for males and 9.40 to 12.18 kg for females

Administration / exposure

Route of administration
oral: gavage

Details on route of administration

Vehicle
methylcellulose

[default] : methylcellulose aqueous solution (0.5 w/v% MC)

Details on oral exposure
Dose volume: 5 mL/kg

Analytical verification of doses or concentrations
no data

Details on analytical verification of doses or concentrations

Duration of treatment / exposure
3 months

Frequency of treatment
once daily

Doses / concentrations

Dose / conc. Remarks Actions 1
Dose / conc.
5 mg/kg bw/day (actual dose received)
Remarks
tosylate form
2
Dose / conc.
mg/kg bw/day (actual dose received)
Remarks
tosylate form
3
Dose / conc.
1 mg/kg bw/day (actual dose received)
Remarks
tosylate form
4
Dose / conc.
30 mg/kg bw/day (actual dose received)
Remarks
tosylate form

No. of animals per sex per dose
4

Control animals

Details on study design
Doses: S-297995 monotosylate was given at 0 (vehicle control), 1, 5 and 30 mg/kg/day Frequency of dosing: Once daily Route of administration: By gavage Dose volume: 5 mL/kg Formulation/Vehicle: Methylcellulose aqueous solution (0.5 w/v% MC) Species/Strain: Beagle dog Number/Sex/Group: 4 animals sex group (main study) Age: 10-12 months Weight: 9.88 to 12.88 kg for males and 9.40 to 12.18 kg for females Satellite groups: 3 animals sex group (control and 30 mg/kg/day)(recovery) Unique study design: None Deviation from study protocol: 15 minor deviations were reported.

Positive control

Examinations

Observations and examinations performed and frequency

Sacrifice and pathology

Optional endpoint(s)

Other examinations

Statistics

Any other information on materials and methods incl. tables

Results and discussion

Results of examinations

Clinical signs

Description (incidence and severity)
Vomitus was observed for 1 of the 7 females in the control group. 1 of the 4 animals sex in the 1 mg/kg group. 3 of the 4 males and 2 of the 4 females in the 5 mg/kg group and all 7 animals/sex in the 30 mg-kg group during the dosing period as shown in the Table below. The incidence of vomitus was comparable to that commonly noted in beagle dogs in many of these animals, but was slightly higher in 1 male in the 5 mg/kg group

and 4 animals sex in the 30 mg kg group, suggesting effects of the test article. However, the total incidences of vomitus (1♦12) were still of small values as compared to total incidences of observations (273). and in most cases there were no effects on body weights or food consumption in these animals, excluding 1 female (Animal No. 74) in the 30 mg 'kg group. Therefore, this finding was considered to be of no toxicological significance at least at 5 mg kg. Salivation was observed for 4 males and 3 females in the 30 mg kg group immediately prior to or after dosing or at 1 hour post-dosing from Day 37 of dosing. In addition, scant feces were observed in 1 female in this group on Days 48 and 49 of dosing. No marked clinical signs were observed in any animal during the recovery7 period. Vaginal haemorrhage was observed for 14 females during the dosing and recovery7 periods, regardless of the dose levels. This sign was due to estrus commonly observed in female dogs and the incidence or onset times were not dose-related.

Mortality

Description (incidence)
All animals survived during the study.

Body weight and weight changes

Description (incidence and severity)
Initial mean body weights for control males and females were 11.54 kg and 11.29 kg. respectively. On day 91 after dosing, mean body weight for males and females were 10.44 kg and 10.36 kg. respectively. No statistically significant changes were noted in any treated group as compared to the control group during the dosing period or during the recovery7 period as shown in the figure below.

Food consumption and compound intake (if feeding study)

Description (incidence and severity)
Food consumption was decreased in 1 female (Animal No. 74) in the 30 mg/kg group and was below 80 g vs. ♦ 300g food consumption of controls on Days 41-43. 45-47. 52 and 83 of dosing. The sponsor did not explain the observation. No statistically significant differences were noted in any treated group as compared to the control group during the dosing period. No marked food consumption changes were evident in any animal in the 30 mg/kg group during the recovery period.

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)
No treatment-related ophthalmological abnormalities were evident in any animal during Week 13 of dosing or Week 4 of recovery.

Haematological findings

Description (incidence and severity)
Hematological examinations during Week 4 of dosing revealed the following statistically significant differences (Approx. 10%-15%) from the control means in the 30 mg/kg group: decreases in the red blood cell count (6.6.2♦0.37 xlO6 ♦L vs. 7.33=0.40 xlO6 ♦L of controls in males: 6.42=0:5 xlC6 ♦L vs. 7.34=0.51 iI0fi nL of controls in females) hemoglobin concentration (15.4=0.8 vs. 16.6=0.7 g dL of controls in males: 15.3=1.0 vs. 17.4=1.1 g'dL of controls in females) and hematocrit value (44.9=2.3% vs. 49.3=2.4% of controls in males; 43.4=3.5% vs. 50.8=3.7% of controls in females) in males and females and decreases in the reticulocyte count (21.2=8.9 K10? L VS. 52.3=18.8 10s L of control).-' reticulocyte ratio (0.3♦0.2% vs. 0.9=0.3% of controls) in males. During Week 13 of dosing, the following statistically significant findings were noted in the 30 mg/kg group: decreases in the reticulocyte count, ratio in males (18.5=6.4x 10♦ L vs. 50.0=23.5 xl09/L of control): ratio (0.3=0.1% vs. 0.7=0.3% of controls) and females [count (17.S♦9.4 xlO^tnL vs. 45.9=30.4 xlO L of control)] and decreases in the red blood cell count (6.41=0.36x10 ♦L vs. 7.46=0.55 xl0e ♦L of controls), haemoglobin concentration (14.9=0.7 vs. 16.8=1.3 g dL of controls and hematocrit value (41.7=1.9% vs. 47.7=3.7♦ Q of controls) in males. The decreased reticulocyte count ratio may not appear to have significantly toxicological importance since the hematopoietic cell concentration did not decrease in the active hematopoietic tissue, i.e.. marrow of the sternum, and since the myeloid erythroid cell ratio did not decrease in the marrow of the rib. No marked changes were noted in any animal during Week 4 of recovery.

Clinical biochemistry findings

Description (incidence and severity)
Statistically significant increases (2-3 fold) in ALT. GGT, ALP and total cholesterol (30% increase) and statistically significant decreases in amylase (40%) were noted in males and females in the 30 mg kg group during Week 4 of dosing as compared to the control group, but no changes in albumin (ALB) or A G ratio were observed. During Week 13 of dosing, changes similar to but slightly more advanced than those during Week 4 of dosing were noted in the 30 mg- kg group and the differences from the control values tended to be increased as shown in Table 2 and Table 3 below. In addition, an increase in total bilirubin (33%) was noted in 1 female (Animal No. 74) in this group. Tire aforementioned changes

during the dosing period were no longer evident during Week 4 of recover)'.

Endocrine findings

Description (incidence and severity)

Urinalysis findings

Description (incidence and severity)
There were no test substance-related changes in urinalysis data throughout the study.

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)
There were ho test substance-related charges in absolute and relative weights of any organs.

Gross pathological findings

Description (incidence and severity)
No treatment-related gross pathological lesions were observed in any animal at termination of the dosing or recovery period

Neuropathological findings

Description (incidence and severity)

Histopathological findings: non-neoplastic

Description (incidence and severity)
Adequate Battery Yes Peer Review Yes Histological Findings Treatment-related histopathological lesions were observed in the femoral bone marrow, adipose tissue and liver at termination of the dosing period as follows- Atrophy of the adipose tissue and deposition of the gelatinous material in the femora! bone marrow were observed in 1 animal-sex in the 30 mg. kg group to a slight or moderate degree. Slight atrophy of the pericardial and perirenal adipose tissues was observed in these animals, indicating effects of the test article on the adipose tissues. Slight single cell necrosis in the liver was observed in 1 animal of both sexes in the 30 mg/kg group. In addition, slight extramedullary' hematopoiesis was observed in the liver in 3 males and 1 female in the 30. mg kg group. The lesions in the femoral bone marrow, adipose tissue and liver deserved at termination of the dosing period were no longer evident at termination of the recovery-period.

Histopathological findings: neoplastic

Description (incidence and severity)

Other effects

Description (incidence and severity)
Bone Marrow Examinations No treatment-related changes were noted in any animal at termination of the dosing or recovery period.

Details on results
Mortality All animals survived during the study. Clinical Signs Vomitus was observed for 1 of the 7 females in the control group. 1 of the 4 animals sex in the 1 mg/kg group. 3 of the 4 males and 2 of the 4 females in the 5 mg/kg group and all 7 animals/sex in the 30 mg-kg group during the dosing period as shown in the Table below. The incidence of vomitus was comparable to that commonly noted in beagle dogs in many of these animals, but was slightly higher in 1 male in the 5 mg/kg group and 4 animals sex in the 30 mg kg group, suggesting effects of the test article. However, the total incidences of vomitus (1�12) were still of small values as compared to total incidences of observations (273). and in most cases there were no effects on body weights or food consumption in these animals, excluding 1 female (Animal No. 74) in the 30 mg 'kg group. Therefore, this finding was considered to be of no toxicological significance at least at 5 mg kg. Salivation was observed for 4 males and 3 females in the 30 mg kg group immediately prior to or after dosing or at 1 hour post-dosing from Day 37 of dosing. In addition, scant feces were observed in 1 female in this group on Days 48 and 49 of dosing. No marked clinical signs were observed in any animal during the recovery7 period. Vaginal haemorrhage was observed for 14 females during the dosing and recovery7 periods, regardless of the dose levels. This sign was due to estrus commonly observed in female dogs and the incidence or onset times were not dose-related. Body Weights Initial mean body weights for control males and females were 11.54 kg and 11.29 kg. respectively. On day 91 after dosing, mean body weight for males and females were 10.44 kg and 10.36 kg. respectively. No statistically significant changes were noted in any treated group as compared to the control group during the dosing

period or during the recovery7 period as shown in the figure below. Feed Consumption Food consumption was decreased in 1 female (Animal No. 74) in the 30 mg/kg group and was below 80 g vs. □ 300g food consumption of controls on Days 41-43. 45-47. 52 and 83 of dosing. The sponsor did not explain the observation. No statistically significant differences were noted in any treated group as compared to the control group during the dosing period. No marked food consumption changes were evident in any animal in the 30 mg/kg group during the recovery period. Ophthalmoscopy No treatment-related ophthalmological abnormalities were evident in any animal during Week 13 of dosing or Week 4 of recovery. ECG No treatment-related abnormalities were evident in any ECG parameter in any animal during the dosing or recovery period. Hematology Hematological examinations during Week 4 of dosing revealed the following statistically significant differences (Approx. 10%-l5%) from the control means in the 30 mg/kg group: decreases in the red blood cell count (6.6.2□0.37 xlO6 □L vs. 7.33=0.40 xlO6 □L of controls in males: 6.42=0:5 xlC6 □L vs. 7.34=0.51 il0fi nL of controls in females) hemoglobin concentration (15.4=0.8 vs. 16.6=0.7 g dL of controls in males: 15.3=1.0 vs. 17.4=1.1 g'dL of controls in females) and hematocrit value (44.9=2.3% vs. 49.3=2.4% of controls in males; 43.4=3.5% vs. 50.8=3.7% of controls in females) in males and females and decreases in the reticulocyte count (21.2=8.9 K10? L VS. 52.3=18.8 10s L of control).-' reticulocyte ratio (0.3□0.2% vs. 0.9=0.3% of controls) in males. During Week 13 of dosing, the following statistically significant findings were noted in the 30 mg/kg group: decreases in the reticulocyte count, ratio in males (18.5=6.4x 10□ L vs. 50.0=23.5 xl09/L of control): ratio (0.3=0.1% vs. 0.7=0.3% of controls) and females [count (17.S□9.4 xlO^tnL vs. 45.9=30.4 xlO L of control)] and decreases in the red blood cell count (6.41=0.36x10 □L vs. 7.46=0.55 xl0e □L of controls), haemoglobin concentration (14.9=0.7 vs. 16.8=1.3 g dL of controls and hematocrit value (41.7=1.9% vs. 47.7=3.7□ Q of controls) in males. The decreased reticulocyte count ratio may not appear to have significantly toxicological importance since the hematopoietic cell concentration did not decrease in the active hematopoietic tissue, i.e.. marrow of the sternum, and since the myeloid erythroid cell ratio did not decrease in the marrow of the rib. No marked changes were noted in any animal during Week 4 of recovery. Clinical Chemistry Statistically significant increases (2-3 fold) in ALT. GGT, ALP and total cholesterol (30% increase) and statistically significant decreases in amylase (40%) were noted in males and females in the 30 mg kg group during Week 4 of dosing as compared to the control group, but no changes in albumin (ALB) or A G ratio were observed. During Week 13 of dosing, changes similar to but slightly more advanced than those during Week 4 of dosing were noted in the 30 mg- kg group and the differences from the control values tended to be increased as shown in Table 2 and Table 3 below. In addition, an increase in total bilirubin (33%) was noted in 1 female (Animal No. 74) in this group. Tire aforementioned changes during the dosing period were no longer evident during Week 4 of recover)'. Urinalysis There were no test substance-related changes in urinalysis data throughout the study. Gross Pathology No treatment-related gross pathological lesions were observed in any animal at termination of the dosing or recovery period Organ Weights There were ho test substance-related charges in absolute and relative weights of any organs. Bone Marrow Examinations No treatment-related changes were noted in any animal at termination of the dosing or recovery period. Histopathology Adequate Battery Yes Peer Review Yes Histological Findings Treatment-related histopathological lesions were observed in the femoral bone marrow, adipose tissue and liver at termination of the dosing period as follows- Atrophy of the adipose tissue and deposition of the gelatinous material in the femora! bone marrow were observed in 1 animal-sex in the 30 mg. kg group to a slight or moderate degree. Slight atrophy of the pericardial and perirenal adipose tissues was observed in these animals, indicating effects of the test article on the adipose tissues. Slight single cell necrosis in the liver was observed in 1 animal of both sexes in the 30 mg/kg group. In addition, slight extramedullary' hematopoiesis was observed in the liver in 3 males and 1 female in the 30. mg kg group. The lesions in the femoral bone marrow, adipose tissue and liver deserved at termination of the dosing period were no longer evident at termination of the recovery-period. Special Evaluation None. Toxicokinetics The Tmax values on Days 1.28 and 91 of dosing at 1 to 30 mg/kg/day were 0.4 to 1.4 hours and seemed to be independent of dose levels and the dosing period as shown in the table below. The Cmax values on Days 1. 28 and 91 of dosing increased almost dose-proportionally. The AUC 0-24h values on Days 1. 28 and 91 of dosing increased more than dose-proportionally. Plasma S-297995 concentrations were not affected by repeated dosing except for the 30 mg/kg group, at which the AUC 0-24h tended to increase by repeated dosing. No large difference in the Cmax. AUC 0-24h Tmax was observed between the sexes. S-297995 was not detected in any plasma sample from the control group.

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
<= 30 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- body weight and weight gain

  [default] : no observable effect level

Remarks on result
2

☐ Key result
Dose descriptor
NOEL
Effect level
<= 30 mg/kg bw/day (actual dose received)

Based on
Sex
Basis for effect level

- mortality

  [default] : no observable effect level

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

- clinical signs

  [default] : vomiting

Remarks on result
other: reversible

[default] : reversible

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

- histopathology: non-neoplastic

  [default] : atrophy

Remarks on result
other: slight effect, reversible

[default] : slight effect, reversible

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

- histopathology: non-neoplastic

  [default] : extramedullary hematopoiesis

Remarks on result
other: slight effect, reversible

[default] : slight effect, reversible

6
Key result
Dose descriptor
dose level:
Effect level
30 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- clinical biochemistry

  [default] : increased circulating cholesterol level

Remarks on result
other: reversible

[default] : reversible

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

- clinical biochemistry

  [default] : gamma-glutamyltransferase increased

Remarks on result
other: reversible

[default] : reversible

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

- clinical biochemistry

  [default] : increased circulating alkaline phosphatase level

Remarks on result
other: reversible

[default] : reversible

9
Key result
Dose descriptor
dose level:
Effect level

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

- haematology

  [default] : decreased red blood cell count

Remarks on result
other: reversible

[default] : reversible

10
☐ Key result
Dose descriptor
NOEL
Effect level
<= 30 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- other: bone marrow examinations

  [default] : bone marrow examinations

  [default] : no observable effect level

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

- clinical biochemistry

  [default] : decreased circulating amylase level

Remarks on result
other: reversible

[default] : reversible

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

- clinical biochemistry

  [default] : alanine aminotransferase increased

Remarks on result
other: reversible

[default] : reversible

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

- histopathology: non-neoplastic

  [default] : hepatic necrosis

Remarks on result
other: slight effect, reversible

[default] : slight effect, reversible

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

- haematology

  [default] : decreased hematocrit

Remarks on result
other: reversible

[default] : reversible

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

- histopathology: non-neoplastic

  [default] : abnormal bone mineral content

Remarks on result
other: slight effect, reversible

[default] : slight effect, reversible

16
☐ Key result

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

- other: not specified

  [default] : not specified

Remarks on result
17
☐ Key result
Dose descriptor
NOEL
Effect level
<= 30 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- urinalysis

  [default] : no observable effect level

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

- haematology

  [default] : reticulocyte count decreased

Remarks on result
other: reversible

[default] : reversible

19
☐ Key result
Dose descriptor
NOEL
Effect level
<= 30 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- food consumption and compound intake

  [default] : no observable effect level

Remarks on result
20
☐ Key result
Dose descriptor

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

- haematology

  [default] : reticulocyte count decreased

Remarks on result
other: reversible

[default] : reversible

21
Key result
Dose descriptor
dose level:
Effect level
30 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- clinical signs

  [default] : increased salivation

Remarks on result
other: reversible

[default] : reversible

22
Key result
Dose descriptor
NOEL
Effect level
<= 30 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- ophthalmological examination

  [default] : no observable effect level

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

- histopathology: non-neoplastic

  [default] : renal atrophy

Remarks on result
other: slight effect, reversible

[default] : slight effect, reversible

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

- clinical biochemistry

  [default] : increased circulating bilirubin level

Remarks on result
other: observed in one animal, reversible

[default] : observed in one animal, reversible

25
☐ Key result
Dose descriptor
dose level:
Effect level
30 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- clinical signs

  [default] : decreased defecation amount

Remarks on result
other: observed in one animal, reversible

[default] : observed in one animal, reversible

26
☐ Key result
Dose descriptor
NOEL
Effect level
<= 30 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- organ weights and organ / body weight ratios

  [default] : no observable effect level

Remarks on result
27
☐ Key result
Dose descriptor
dose level:
Effect level
30 mg/kg bw/day (actual dose received)
Based on

Sex
male/female
Basis for effect level

- haematology

  [default] : decreased hemoglobin concentration

Remarks on result
other: reversible

[default] : reversible

28
☐ Key result
Dose descriptor
NOEL
Effect level
<= 30 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- gross pathology

  [default] : no observable effect level

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 1
☐ Key result
Critical effects observed
Lowest effective dose / conc.
System
endocrine system
Organ

- other: adipose tissue

  [default] : adipose tissue

Treatment related
Dose response relationship
Relevant for humans
2
☐ Key result
Critical effects observed
Lowest effective dose / conc.
System
hepatobiliary
Organ

- liver

Treatment related
Dose response relationship
Relevant for humans

Any other information on results incl. tables

Overall remarks, attachments

Overall remarks

Attachments

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

Illustration (picture/graph)

Applicant's summary and conclusion

Conclusions

Executive summary
Slight single cell necrosis in the liver and adipose tissues atrophy were observed at 30 mg/kg/day as target organ toxicities in addition to some in-life observations. Favorable recovery was confirmed after the 1-month drug withdrawal. Therefore, the NOAEL was estimated 5 mg/kg/dav under the condition of the present study.

TOP

- Dashboard
- Substances
- Mixtures / Products
- Articles
- Categories

Toolbox

- Template
- Manage Reports

Inventory manager

- Contact
- Legal entity
- Sites
- Reference substance
- Test material
- Literature reference

User management

- User Settings
- Users
- Roles

About IUCLID

- About
- Help