DATA EVALUATION RECORD

MESOTRIONE (ZA1296 (480 g/L SC Formulation))

7/19/2000

Study Type: §81-6, Dermal Sensitization Study

Work Assignment No. 2-01-52N (MRID 44373523)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea pig
OPPTS Number: 870.2600 OPP Guideline Number: §81-6

DP BARCODE: D259369 SUBMISSION CODE: S541375
P.C. CODE: 122990 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): 480 g/L SC Formulation of ZA1296 [40.5% (w:w) ai]

SYNONYMS: None specified

CITATION: Lees, D., and H. Connolly (1995) ZA1296: skin sensitisation to the guinea pig of a 480 g/L SC formulation. Zeneca Central Toxicology Laboratory, Macclesfield, Cheshire, UK. Laboratory Report No. CTL/P/4817, Study No. GG6556. November 29, 1995. MRID 44373523. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, DE.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 44373523) conducted with a 480 g/L SC Formulation of ZA1296 [40.5% (w:w) ai], 30 Hsd/Pos:DH albino male guinea pigs (20 test and 10 control) were tested using methods based on those derived by Buehler. Data were provided from a previously-conducted positive control study (Study No. GG6487) using hexylcinnamaldehyde.

No dermal irritation was observed during the induction phase of the experiment. Forty-eight through 72 hours following a challenge treatment with the undiluted 480 g/L SC Formulation of ZA1296 to previously-induced animals, scattered mild redness was observed at 2/20 (10%) sites. In comparison, challenge with a 30% dilution of the test substance to previously-induced animals elicited no dermal irritation, and no irritation was observed following challenge with undiluted or 30% test substance to naive control animals. Based on the results of this study, **the 480 g/L Formulation of ZA1296 appears to be a mild dermal sensitizer**. In the positive control study, 35% of the previously-induced animals (7/20) exhibited positive dermal sensitization.

This study is classified as **acceptable (§81-6)** and satisfies the guideline requirement for a dermal sensitization study in the guinea pig.

2

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: 480 g/L SC Formulation of ZA1296
   Description: Tannish brown liquid
   Lot/Batch #: WF2381; 14541-25-03
   Purity: 40.5% ZA1296 (w:w)
   CAS #: Not provided

2. Vehicle and positive control: Deionized water

   Positive control data from a previously-conducted study (Study No. GG6487) were provided using hexylcinnamaldehyde (purity not specified) in corn oil.

3. Test animals: Species: Guinea pig
   Strain: CRL:(HA)BR albino
   Age: Young adult
   Weight: 258-350 g (all male; definitive study) and 383-526 g (all female; positive control study)
   Source: Charles River, UK
   Acclimation period: ≥6 Days
   Diet: RGP Diet (Labsure, Lavender Mill, Manea, Cambridgeshire, UK), ad libitum
   Water: Tap water, ad libitum
   Housing: One animal/cage in stainless steel suspended cages
   Environmental conditions:
   Temperature: 17±2 °C
   Humidity: 55±15%
   Air changes: Approximately 25-30 changes/hour
   Photoperiod: 12-hour light/dark cycle

B. STUDY DESIGN and METHODS:

1. In-life dates: August - September 1995 (definitive study)
   June - July 1995 (positive control study)

2. Animal assignment and treatment: The study was conducted using methods based on those derived by Buehler [E. V. Buehler, Arch Derm: 91 p. 171-177 (1965)]. Dose levels for the definitive study were based on the results of a preliminary experiment [refer to page 12 of the study].

3

For the induction treatment (definitive study), fur from the scapular area (approximately 5 x 5 cm) of 20 animals was clipped prior to topical application of 0.4 mL of the undiluted test substance via a lint patch, which was covered with tape and held in place by an adhesive bandage and secured with PVC tape. Following a 6-hour exposure period, the coverings were removed (removal of residual test material was not described). Application of the test material was repeated once weekly at 7-day intervals for 2 consecutive weeks (three total applications). Animals were observed for dermal irritation approximately 1 day following patch removal and just prior to each subsequent induction. Animals in the control group received similar inductions minus the test compound (bandages only). The positive control induction phase was conducted using undiluted hexylcinnamaldehyde and, otherwise, in the same manner as previously described.

Two weeks following the topical induction treatments, a single challenge exposure was conducted using undiluted test substance applied to the top left shorn flank via a lint patch. On the bottom left shorn flank, approximately 0.1-0.2 mL of a 30% (w:v) preparation of the test material (in deionized water) was applied via a lint patch. Similar applications were made to the right side of the animal using only deionized water. The occlusive dressing (lint patch stitched to rubber sheeting) was held in place by adhesive tape and removed after 6 hours. The positive control challenge phase was conducted using 30% (w:v) hexylcinnamaldehyde in corn oil and, otherwise, in the same manner as previously described. Animals were observed for erythematous reactions according to the following scale 24 and 48 hours following patch removal:

0 - No erythema
1 - Scattered mild redness
2 - Moderate diffuse redness
3 - Intense redness and swelling

Body weights were recorded pretest and on study day 25.

II. RESULTS AND DISCUSSION:

A. Induction reactions and duration: No dermal irritation was observed in any animals 48 to 72 hours following induction treatments.

B. Challenge reactions and duration: Scattered mild redness (score of 1) was observed in 2/20 (10%) previously-induced animals 48 and 72 hours following the single challenge treatment with the undiluted 480 g/L SC Formulation of ZA1296. No other dermal irritation was observed to either previously-induced or naive control animals. Based on the results of this study, the 480 g/L Formulation of ZA1296 appears to be a mild dermal sensitizer.

C. Positive control: Following induction with 30% hexylcinnamaldehyde, slight to moderate irritation was observed in all previously-induced animals. Irritation worsened with each

4

subsequent application, and was characterized by erythema, edema, desquamation, and thickening of the skin. In comparison, no irritation was observed in the controls.

Up to 72 hours following challenge with 30% hexylcinnamaldehyde to previously-induced animals, mild redness (score of 1) was observed at 12/20 sites and moderate redness (score of 2) was observed at 7/20 sites. In comparison, 6/10 controls exhibited mild redness (score of 1) up to 72 hours following the challenge treatment. These data indicate that approximately 35% of the previously-induced animals exhibited a positive sensitizing response.

D. Deficiencies: There were no deficiencies that affected the validity of the study results.