

# Health & Safety Information

## Toxicological Studies

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### 1.1 Primary ocular irritation evaluation in rabbits

**Summary and methodology:** The test article, at a dosage of 0.1 ml, was instilled into the conjunctival sac of the left eye of each of six New Zealand White rabbits. The right eye of the rabbits served as a control. Pre-selection ocular examinations were conducted approximately 24 hours prior to instillation of the test article. Following instillation, ocular examinations were conducted at 1, 24, 48 and 72 hours.

No visual signs of ocular irritation were observed in any of the rabbits at the 1, 24, 48 and 72 hour observation periods. No ocular changes were noted from pre-test in the control eye.

Body weights were taken at the initiation of the study.

These results suggest that the test article, in the activated form, is not a primary ocular irritant when instilled into the eye of albino rabbits.

Data source: T.P.S. Inc.  
Virginia, USA  
November 1997

### 2.1 Acute dermal toxicity study in rabbits

**Summary and methodology:** The test article was activated and applied at 2,000 mg/kg body weight to the closely clipped skin of adult New Zealand White rabbits (5/sex) under an occlusive wrap for 24 hours. Upon removal of the occlusive wrap, applications sites were gently wiped with a damp clean disposable towel to remove any residual test article.

The rabbits were observed closely after dosing and at least twice daily for 14 days for mortality and other toxic effects, then sacrificed and subjected to gross necropsy. Body weights were recorded at study initiation, weekly thereafter and at termination of the study.

All 10 Group BGU1 rabbits gained weight and no sign of systemic toxicity or mortality was observed during the evaluation. There were no gross necropsy findings attributable to treatment with the test article.

Since no deaths occurred, the acute LD50 value from dermal exposure to activated test article under occlusion is greater than 2,000 mg/kg body weight in albino rabbits.

Data source: T.P.S. Inc.  
Virginia, USA  
November 1997

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### 3.1 Primary dermal irritation evaluation in rabbits

**Summary and methodology:** One-half ml aliquots of the test article were applied to intact closely clipped skin on the back of each of six New Zealand White rabbits. The application sites were occluded for four hours, then unwrapped and gently cleaned.

Application sites were evaluated for erythema/eschar and oedema for all animals according to the method of Draize within 30-60 minutes after unwrapping and again at 24, 48, and 72 hours after unwrapping. Body weights were recorded at initiation and termination of the animal phase.

No visual indications of erythema or oedema were present on any of the six rabbits within 30-60 minutes after the occlusive wrap was removed. There were no visible signs of skin irritation at the 24, 48 and 72 hour observation periods following unwrapping.

All of the rabbits gained weight during the 72 hour observation period.

These results suggest that the test article, when applied in activated form, is not a primary irritant to the skin of albino rabbits.

Data source: T.P.S., Inc  
Virginia, USA  
November 1997

### 4.1 Acute oral toxicity evaluation with rats

**Summary and methodology:** Ten albino Sprague Dawley derived rats (5/sex) were dosed by oral gavage with activated test article at a dosage of 5,000 mg/kg body weight. Observations were made up to six hours after dosing and twice daily for 14 days for signs of toxicity, behavioural changes or mortality. All surviving rats were subjected to a complete gross necropsy following the 14 day observation period.

There were no deaths or remarkable clinical signs observed following dosing or at any time during the 14 day observation period.

No remarkable gross necropsy findings were noted in any of the rats at study termination. Nine of the 10 rats gained weight during the study.

The LD<sub>50</sub> for the activated test article is greater than 5,000 mg/kg in the Sprague Dawley rat.

Data source: T.P.S., Inc  
Virginia, USA  
October 1997

## 5.1 Dermal sensitisation evaluation in the guinea pig

**Summary and methodology:** The activated test article was evaluated for dermal sensitisation potential in young adult female guinea pigs. Animals in Groups BGV3 (activated test article) and BFU5 (DNCB positive control) were dosed dermally with 0.4 mL applied to the same close-clipped (24 hours prior to dosing) site on the left shoulder area once a week for 3 weeks. Two weeks following the last induction dose, a single challenge dose was administered dermally to the close-clipped left rear side of each of the group BGV3 and BFU5 animals. Animals in Group BFU2 (DNCB control) were dosed dermally once with 0.4 mL applied to the close-clipped left rear side.

All challenge application sites were read and scored at 24 and 48 hours following dosing. Comparisons were made of the scores of the challenge applications from guinea pigs which received the inductive applications to those which received only the challenge application.

Skin reactions to DNCB, a known dermal sensitiser, were also evaluated and used to confirm the validity of the test method.

Based on this method, these results suggest that activated test article is not a sensitising agent when administered by dermal application to the close-clipped skin of albino guinea pigs. DNCB was clearly identified as a dermal sensitiser by this method.

All guinea pigs gained weight during the study. No mortality occurred and no signs indicative of systemic toxicity were observed.

Data source: T.P.S., Inc  
Virginia, USA  
June 1998

## 6.1 48 hour human patch test for primary irritation

**Summary and methodology:** The objective of the study was to compare the primary skin irritation potential of Tristel 1100 with that of Nu-Cidex.

In a pilot study, three subjects received occlusive patch applications of both test products on their upper arm for 4 hours. Tristel produced minimal irritation but Nu-Cidex produced severe irritation with erythema, oedema and vesiculation.

The pilot study subjects then received a further 23 hour patch application of Tristel 1100 which produced minimal irritation.

In the main study, 25 subjects received two occluded patch applications of Tristel 1100 on the upper arm which produced minimal irritation.

Due to the severity of the reactions observed with Nu-Cidex it was not included in the main study.

Under the conditions of this test, Tristel 1100 showed negligible irritation potential whereas Nu-Cidex was a strong irritant.

Data source: Consumer Product  
Evaluation Centre  
Ledbury  
Herefordshire  
March 1995

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## 7.1 Comparative skin sensitisation study in the guinea pig – Magnusson-Kligman Maximisation test

**Summary and methodology:** This study was performed to assess the potential of the test article, Tristel 1100, to cause a delayed dermal (Type IV) hypersensitivity response in the guinea pig and to compare this sensitising potential with that of the reference substance, Nu-Cidex, produced by Johnson & Johnson Medical.

The methods were based on those described in the Organisation for Economic Development (OECD) Guideline for the Testing of Chemicals, no. 406, adopted 17 July 1992.

Initially, intradermal and topical irritancy range finding studies were conducted in the test article and the reference substance to determine suitable concentrations of each compound for use in the main study.

The results of the intradermal range finder, using a separate animal for the test article and the reference substance indicated that a 10% v/v aqueous solution of Tristel 1100 or a 5% aqueous solution of Nu-Cidex could be injected intradermally without provoking an unacceptable irritant response.

When undiluted test article and 50, 25 and 12.5% v/v concentration of the test article in water were applied topically to a group of four animals, the minimum irritant concentration was found to be 25%. Topical application of the reference substance to a separate group of four guinea pigs indicated that undiluted Nu-Cidex was non-irritant.

### For the main study, 30 female albino guinea pigs were allocated to groups as indicated below:

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Group	Number of animals
Tristel test group	10
Nu-Cidex test group	10
Tristel control group	5
Nu-Cidex control group	5

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At the sponsor's request, the dose level selected for each phase of the study was the same for both the test article and the reference substance.

### On day one of the main study the intradermal induction was carried out as indicated below:-

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Test animals		Control animals	
Injection between the shoulders of:		Injection between the shoulders of:	
1	A 50% v/v emulsion of Freund's Complete Adjuvant (FCA) and water for injection	1	A 50% v/v emulsion of FCA/water
2	A 50% v/v concentration of the test article or the reference substance in vehicle (water)	2	Water
3	A 5% v/v concentration of the test article or the reference substance in FCA/water	3	Vehicle in FCA/water

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Seven days later undiluted test article was applied over the injection sites on all animals in the Tristel test group. Undiluted reference substance was similarly applied to the injection sites on all animals in the Nu-Cidex test group. The injection sites on all animals in both control groups were treated with water.

On day 22, 14 days after topical induction, a 12.5% v/v aqueous solution of test article was applied to the left flank and water alone to the right flank of all animals in the Tristel group and control groups. Similarly, reference substance at a concentration of 12.5% v/v in water was applied to the left flank and water alone to the right flank of all animals in the Nu-Cidex test and control groups.

Following this challenge, no animal in any test or control group exhibited a positive response 24 or 48 hours after the end of the exposure period.

There is no evidence that the test article, Tristel, or the reference substance, Nu-Cidex, produced a delayed dermal hypersensitivity response in any test animal under the conditions of this study.

Data source: Toxicol Laboratories Limited  
Ledbury  
Herefordshire  
March 1995