

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 50-746**

**PHARMACOLOGY REVIEW(S)**

**Review and Evaluation of Pharmacology and Toxicology Data  
Division of Anti-Infective Drug Products, HFD-520**

**NDA #:** 50-746 (Amendment to 000)

**SPONSOR:** SmithKline Beecham Pharmaceuticals  
Philadelphia, PA

**AUTHORIZED REPRESENTATIVE:** Debra Hackett  
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**DRUG NAMES:** Bactroban Cream 2%; mupirocin calcium cream

**CATEGORY:** Topical antibacterial

**RELATED SUBMISSIONS:** NDA 50-746 (000)

**NUMBER OF VOLUMES:** 1

**DATE CDER RECEIVED:** 11/4/97

**DATE ASSIGNED:** 11/4/97

**DATE REVIEW STARTED:** 11/12/97

**DATE 1<sup>ST</sup> DRAFT COMPLETED:**

**DATE REVIEW ACCEPTED BY TEAM LEADER:** *December 3, 1997*

**REVIEW OBJECTIVES:** To review the intravenous study in dogs with the degradation products BRL-45294-A and BRL-45295-A (sodium salts of the degradation products).

**TOXICOLOGY:**

**BRL-49294-A and BRL-49295-A: A 14-Day Intravenous Dose Toxicity Study in Dogs; Study #BRL-004910/RSD-100LC1/1.** This study was performed by SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK. A GLP compliance statement is included in the report.

The objective of this study was to qualify the levels of the 2 degradation products that may be present at the end of the shelf-life of the cream formulation.

Animals: 3 beagle dogs/sex/dose, aged 10-12 months at study initiation.

Doses: 0 (sterile saline), 5 or 20 mg/kg/d of a 1:2 mixture of BRL-45294 and 45295 given intravenously daily for 14 or 15 days. The rationale for dose selection was the 3 month intravenous dosing study in dogs with the final product where the NTED (No Toxic Effect Dose) was 20 mg/kg/d. This dose represents a 7x multiple of the maximum possible exposure for a 60 kg person following application of the entire 30 g tube. The low dose (5 mg/kg/d) is approximately 2x the proposed human dose.

Procedure: clinical observations, body weight, feed consumption, EKGs, ophthalmoscopy, hematology, hemostasis, clinical chemistries, urinalyses, organ weights, gross necropsy and histopathology (all appropriate tissues from all animals).

Results: No significant differences from controls were noted in body weight gain, feed consumption, heart rate, EKGs, ophthalmoscopy, gross necropsy or histopathology. Loose feces were noted in the treated animals, but did not affect body weight gain or body condition. Group mean and absolute adrenal weights were significantly decreased (17-26%) in the treated animals when compared to controls, but not in a dose-related fashion. However, the values were within historical control values for the males and within the range of the control females on this study.

The sponsor concluded that administration of the degradation products to dogs at 5 or 20 mg/kg/d for 14 days did not result in any toxicologically significant findings.

**RECOMMENDATION:**

From the results of this dog study, it appears that the degradation products have a similar systemic toxicity profile as the parent compound. However, as the degradants can reach a potential specified limit at the end of the 18-month shelf life of 26% (9%BRL-45294 and 17%BRL-45295, respectively), the genetic toxicity (as per ICH guidelines) and dermal irritation profiles of these degradants should be defined. Therefore, a Phase 4 commitment is requested to define these parameters for the degradants from Bactroban 2% cream. The sponsor should provide the protocols to the Division before initiating these studies.

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VMO, HFD-520

NDA 50-746; Bactroban Cream 2%

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Orig. IND

cc:

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*Dec 12/3/97*

*12/5/97*