CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-794

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Submission:	NDA 21-794
Product Trade Name:	Aczone®
Product:	Dapsone 5% Gel
Indication:	Treatment of Acne vulgaris
Submission Dates:	August 31, 2004; January 14, 2005; January 19, 2005, February 9, 2005, February 24, 2005, February 25, 2005, March 1, 2005, March 4, 2005, March 7, 2005, , April 7, 2005, April 8, 2005, April 27, 2005.
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I. Executive Summary:

Dapsone (DAP) is a sulfone with anti-inflammatory and antimicrobial properties. DAP oral tablets (25 mg and 100 mg) have been approved since 1980s to control the dermatologic symptoms of dermatitis herpetiformis and for the treatment of leprosy. Atrix Laboratories, Inc. (Atrix), submitted NDA 21-794 as a 505(b) (1) application for 5% DAP Topical Gel (DTG) to be administered twice a day for the treatment of *acne vulgaris*. The gel is intended to be applied to affected areas on the face, chest, back, and shoulders twice daily. In 4 clinical pharmacokinetic studies conducted in the intended patient population, which employed a range of doses, application areas and durations, twice-daily application of 5% DTG resulted in minimal (i.e., only about 1% of that from the 100 mg oral dose) systemic exposure to DAP and its principal metabolites. A dose/formulation was selected based on demonstration of maximum skin penetration of DAP and its minimal systemic breakthrough. While selection of the bid dosing of 5% DTG based on the systemic exposure information is acceptable from a pharmacokinetic point of view, the clinical basis of the selection of the dose and dosing regimen is unknown.

DAP absorption after twice daily topical application of 5% DTG in subjects with acne vulgaris results in low systemic exposure to DAP and its metabolites, regardless of acetylator phenotype, G6PD activity, gram usage or body surface area treated. DAP exposure as measured as AUC after topical application of 5% DTG in acne patients treated under maximal usage conditions was 415 ± 224 ng·h/mL. In contrast, DAP exposure after a single oral 100 mg DAP dose was 52,641 ± 36, 224 ng·h/mL. The short-term exposure study indicates that DAP concentrations at steady-state in plasma was about 1% of that observed following a single 100 mg oral dose of DAP. There was no apparent evidence of increased exposure or of any relationship between adverse events and DAP plasma levels. The long-term study (12-month) also demonstrated low systemic

absorption following topical application and absence of systemic accumulation following long-term use. This study also demonstrated no effects of gender, race, glucose-6-phosphate dehydrogenase (G6PD) deficiency or acetylator phenotype on the levels of DAP in plasma during 5% DTG bid treatment for up to a year.

Given the low systemic absorption of DAP following topical administration, it may take a daily application of 140 to 280 grams to achieve a DAP exposure level similar to a single oral DAP dose of 50 and 100 mg, respectively. Since 30 g would typically cover 100% of a 70 kg person, application of 140 to 280g of 5% DTG is not feasible. In the 4 clinical trials described in this document, the average daily gram use ranged from 1.3 to 2.2 grams per day, a dose considerably lower than DAP doses needed for hemolytic effects. Literature suggests that hemolytic effects are typically associated with DAP doses of >100 mg per day in normal patients and >50 mg in G6PD deficient patients. Given the low absorption profile of DAP after 5% DTG application relative to oral DAP, the likelihood of hematologic adverse events is very low, even in patients with G6PD deficiency. In fact, patients with high plasma concentrations did not have a change in hemoglobin levels and patients with a ≥1 or ≥2 g/dL decrease in hemoglobin did not have high plasma DAP levels (Of note, plasma hemoglobin is a very sensitive biomarker for DAP toxicity).

A drug-drug interaction study evaluated the effect of the use of 5%DTG in combination with double strength (160 mg/800 mg) trimethoprim/sulfamethoxazole (TMP/SMX). During co-administration, systemic levels of TMP and SMX were essentially unchanged. However, levels of DAP and its metabolites increased in presence of TMP/SMX. Systemic exposure (AUC_{0-12}) of DAP and N-acetyl-dapsone (NAD) were increased by about 40% and 20% respectively in presence of TMP/SMX. Notably, systemic exposure (AUC_{0-12}) of dapsone hydroxylamine (DHA) was more than doubled in presence of TMP/SMX. Given that exposure from the proposed topical dose is only about 1% of that from the 100 mg oral dose, the increases in the exposure of DAP and its metabolites are not considered to be clinically relevant.

Overview of Efficacy: The clinical program included 4,622 healthy subjects and patients. The 2 pivotal studies (DAP0203 and DAP0204) were identically designed with respect to objective, procedures, treatment duration, endpoints, and statistical analyses. The objective of both randomized, double-blind, parallel group, 2-arm, vehicle-controlled, multi-center studies was to evaluate the safety and efficacy of topically applied 5% DTG in patients with *acne vulgaris* compared to a vehicle control (VC). Patients applied a thin film of 5% DTG or vehicle to the face twice daily (approximately 10 to 14 hours apart for 12 weeks). Patients were also allowed to treat other acne affected areas; however, these areas were not assessed for efficacy. Patients included males and females, 12 years of age or older. The patients had a clinical diagnosis of *acne vulgaris* of the face, with 20 to 50 inflammatory lesions and 20 to 100 non-inflammatory lesions above the mandibular line at baseline.

The results of each of the pivotal studies demonstrate that 5% DTG is significantly more effective than vehicle control (VC) in each of the populations analyzed.

In Study DAP0203, for the Global Acne Assessment Score, the Week 12/early termination success rate for the 5% DTG group was significantly higher than the VC group, 44.2% versus 35.9% ($p = 0.0003$), in the ITT population. The mean percent reductions from Baseline to Week 12/early termination were statistically greater in the 5% DTG group compared with the VC group. In Study DAP0204, for the Global Acne Assessment Score, the Week 12/early termination success rate for the 5% DTG group was significantly higher than the VC group, 36.9% versus 29.8% ($p = 0.0017$), in the ITT population. For each of the 3 acne lesion types, the mean percent reductions from Baseline to Week 12/early termination were statistically greater in the 5% DTG group compared with the VC group.

For all analyses of the primary and secondary efficacy variables for the 2 pivotal trials and the other large 12-week, vehicle controlled trial, there are statistically significant differences in favor of DTG.

In summary, two identically designed pivotal clinical studies demonstrated that 5% DTG is significantly more effective than VC in each of the populations analyzed (see clinical review for details).

Overview of Safety: The 5% DTG clinical program included over 4,000 participants and 5% DTG has been evaluated in more than 2,300 acne patients. No adverse events of potential clinical concern were identified in the dermal safety studies and the microbiology study in healthy subjects. Although hematological effects such as methemoglobinemia and decreased hemoglobin are well known side effects of oral DAP, no relationship between these events and 5% DTG treatment was observed. There were no clinically important differences between 5% DTG-treated patients and VC-treated patients. Length of exposure to 5% DTG did not affect the prevalence of non-application site adverse events. No clear trends were identified in the subpopulations. There were no deaths in the program and serious adverse events were rare and unrelated to 5% DTG use. No agranulocytosis was reported.

A. Recommendations:

Based on this review, NDA 21-794 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A review of the PK data in this submission has resulted in certain changes in the appropriate sections of the product label. The suggested changes have been incorporated in the section "Labeling Comments".

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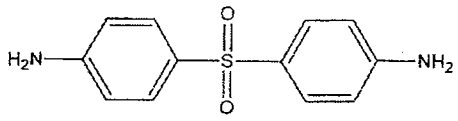
III. Question-Based Review

A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Dapsone (Molecular formula: $C_{12}H_{12}N_2O_2S$; MW: 248.30) is a white to off-white fine crystalline powder with the following structural formula:



It is very slightly soluble in water, freely soluble in acetone, sparingly soluble in alcohol, and dissolves freely in dilute mineral acids. DAP Topical Gel, 5%, is a topical formulation containing DAP, USP (
diethylene glycol monoethyl ether, NF, (DGME) base as shown in the following table:

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