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APPLICATION NUMBER:

207154Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 207154	Submission Date(s): 4/28/2015
Brand Name	Aczone Gel, 7.5%
Generic Name	Dapsone
Primary Reviewer	Doanh Tran, Ph.D.
Secondary Reviewer	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Allergan
Submission Type; Code	Original NDA
Formulation; Strength(s)	Gel, 7.5%
Indication	Topical treatment of acne vulgaris in patients 12 years of age and older

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1 Executive Summary

The applicant submitted an application for a new gel formulation of Aczone (dapsone) Gel, 7.5%, for topical treatment of acne vulgaris in patients 12 years of age and older. Dapsone is a synthetic sulfone with antimicrobial and anti-inflammatory properties. Dapsone is the same drug substance contained in Aczone (dapsone) Gel, 5% (NDA 21794), which is currently approved for twice daily application for the topical treatment of acne vulgaris. The recommended dosage and administration of Aczone Gel, 7.5% will be to apply a thin layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily.

The clinical development program comprised 2 pivotal phase 3 studies, and 4 phase 1 studies including a pharmacokinetic (PK) study in patients with moderate acne vulgaris (Study 225678-004) and 3 dermal tolerability studies in healthy subjects. The development program was based on the target population of patients 12 years of age and older. The Division of Dermatology and Dental Products recommends that for the acne indication, the target age be 9 years of age and older. Therefore, a post marketing requirement to assess PK in subjects 9 years to 11 years 11 months is included in section 1.2 of this review.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 207154 acceptable pending agreement on recommended labeling changes.

1.2 Phase IV Requirements and Commitments

The following post marketing requirement is recommended:

An open-label study to assess safety, pharmacokinetics, and treatment effect of Aczone Gel, 7.5% in 100 pediatric subjects age 9 years to 11 years 11 months with acne vulgaris. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Bioavailability:

Study 225678-004 compared the PK of dapsone gel, 7.5% (formulation 11080X, to-be-marketed formulation) applied once-daily (QD) for 28 days with Aczone Gel, 5% applied twice-daily (BID) for 28 days in subjects (≥16 years of age) with acne vulgaris. Study medication was applied for 28 days to the skin of male and female patients with moderate acne vulgaris by the clinical site staff. For each application, study treatment (2 grams) was topically applied to the face, upper chest, upper back, and shoulders corresponding to a treatment area of approximately 1000 cm^2.

Mean Ctroughs for plasma dapsone were similar for days 7 - 28 suggesting steady state PK was achieved by Day 7 and maintained until Day 28. PK parameters for plasma dapsone following 28 days of dosing are shown in Table 1.

Relative to Aczone Gel, 5%, daily systemic exposure of dapsone, defined by the geometric mean ratio for maximum plasma concentration (Cmax) and area under the concentration-time curve from time 0 to 24 hours postdose (AUC0-24), was approximately 28.6% and 28.7% lower for formulation 11080X, respectively. Based on the 90% CIs for Cmax and AUC0-24, these differences were statistically significant; however, the upper limit of 90% CI were close to 100% (93% for Cmax and 92% for AUC0-24) and therefore the statistically significantly lower systemic exposure may not be clinically meaningful.

Table 1: Summary of plasma dapsone PK parameters

PK parameter	Dapsone Gel, 7.5% QD (TBM formulation 11080X) N=19	Aczone Gel, 5% BID N=18
Cmax (ng/mL)	13.0 ± 6.8	17.6 ± 6.7
AUC0-12 (ng*h/mL)	NA	186 ± 71
AUC0-24 (ng*h/mL)	282 ± 146	379 ± 142

Drug-drug interactions:
The sponsor proposed to omit information contained in section 7.3 of Aczone Gel, 5% label regarding potential interaction with oral dapsone and enzyme inducers such as rifampin, anticonvulsants, St. Johns' wort or folic antagonist such as pyrimethamine that may lead to increased risk of hemolysis. Compared to oral dapsone, the risk of drug interactions is anticipated to be low due to much lower systemic concentration observed following topical dosing of Aczone Gel, 5% and 7.5%. However, because risk of methemoglobinemia has been reported following treatment with Aczone gel, 5% (Aczone Gel, 5% product label), such risk cannot be ruled out for dapsone gel, 7.5%. In addition, risk of hemolysis due to dapsone or its metabolites cannot be ruled out. Therefore, this reviewer concurs with the clinical team's recommendation that the interactions potential as noted in section 7.3 of the Aczone Gel, 5% label should be included in the label for dapsone gel, 7.5%.

Pediatrics:
Pharmacokinetic trial 225678-004 included pediatrics ≥16 years of age (7 of 19 in dapsone gel, 7.5% group and 6 of 18 in Aczone Gel, 5% group). Aczone Gel, 5% label indicates that systemic exposure is pediatrics 12 – 15 years of age is similar to those 16 years and older. Therefore, additional PK trial in subjects ages 12 -15 was not requested for dapsone gel, 7.5%.

Because acne vulgaris do occur in children younger than 12 years of age, the Division of Dermatology and Dental Products recommends evaluation of subjects down to 9 years of age. As part of a post marketing requirement, the Applicant should evaluate the

pharmacokinetic properties of dapsone gel, 7.5% in subjects 9 years to 11 years 11 months of age with acne vulgaris under maximal use conditions. The plan was discussed with the pediatric review committee (PeRC) on 12/2/2015 and the PeRC agreed.

Clinical vs. to-be-marketed formulation:
The to-be-marketed dapsone gel, 7.5% formulation (11080X) was used in all clinical studies, including the 2 phase 3 trials and the 4 phase 1 studies.

Method validation:
Human plasma concentrations of dapsone, N-formyl dapsone (NFD), N-acetyl dapsone (NAD), and dapsone hydroxylamine (DHA) were measured using validated liquid chromatography tandem mass spectrometry methods (LC-MS/MS).

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