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APPLICATION NUMBER:

207154Orig1s000

SUMMARY REVIEW

Decisional Memorandum to the File

Date:	February 17, 2016
From:	Kendall A. Marcus, M.D. Director, Division of Dermatology and Dental Products
Subject:	Summary and Recommendations
NDA/BLA #:	207154 Allergan, Inc.
Submission Date **PDUFA Goal**	April 28, 2015 February 28, 2016
Proprietary / Generic (USAN) names	ACZONE (dapsone) Gel 7.5%
Dosage forms / strength	Topical gel
Proposed Indication(s)	Treatment of acne vulgaris in patients 12 years of age and older

1. Introduction/Background

With this New Drug Application (NDA), the applicant seeks marketing approval for ACZONE (dapsone) Gel, 7.5%, applied once daily, for the treatment of acne vulgaris in patients 12 years of age and older. The active ingredient, dapsone, also known as diaminodiphenyl sulfone, has both anti-inflammatory and antimicrobial properties. Dapsone is currently marketed in the United States (US) in both topical and oral dosage forms. ACZONE Gel, 5%, applied twice daily, was approved in 2005 for the treatment of acne vulgaris in patients 12 years of age and older. Dapsone Tablets (25 mg and 100 mg) were approved in 1992 for the systemic treatment of dermatitis herpetiformis and leprosy. Various professional treatment guidelines also recommend the off-label use of Dapsone Tablets as an alternative for prevention and treatment of pneumocystis pneumonia (PCP) and as an alternative for prevention of toxoplasmosis encephalitis in HIV-infected patients.

Acne vulgaris is a complex skin disorder involving multiple abnormalities of the pilosebaceous gland, including hyperkeratinization, increased sebum production, bacterial proliferation, and inflammation. The face, anterior trunk, and upper back are the most commonly affected areas due to higher concentrations of these glands. Dapsone inhibits growth of certain species of bacteria through inhibition of folic acid synthesis, but the specific mechanism of action of dapsone for the treatment of acne vulgaris is not known. Current topical therapies approved for the treatment of acne include retinoids, antibiotics (including dapsone) and benzoyl peroxide while approved systemic therapies include antibiotics and hormonal therapy.

This application includes letters from Allergan that authorize reference to data associated with NDA 21,794 and IND 54,440, for ACZONE (dapsone) Gel, 5%. The conditions of use of ACZONE Gel, 7.5%, including the volume of product applied per treatment, the

maximum area treated, and the patient population, will be similar to those associated with ACZONE Gel, 5%, with the exception that the 7.5% product will be labeled for once daily application as compared to twice daily application for the 5% product. Clinical use of ACZONE Gel, 7.5%, will generally include application of about 2 g of product containing 150 mg dapsone, while use of ACZONE Gel, 5%, will generally include twice daily application of a total of about 4 g of product containing 200 mg dapsone.

The clinical development program for ACZONE Gel, 7.5% is composed of 2 pivotal Phase 3 trials, 4 Phase 1trials that include a pharmacokinetic (PK) trial in patients with moderate acne vulgaris and 3 dermal tolerability trials in healthy subjects.

2. CMC

For complete details, please refer to Office of Product Quality's (OPQ) Integrated Quality Assessment completed by the Quality Review Team.

Aczone Gel, 7.5% is an off-white to yellow aqueous gel with suspended dapsone particles for topical use. It is packaged in a (b) (4) airless pump container closure system. The (b) (4) airless pump container system consists of a polypropylene bottle with a high density polyethylene piston. Each gram of ACZONE Gel, 7.5%, contains 75 mg of dapsone in a gel of diethylene glycol monoethyl ether, methylparaben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80, and purified water.

The Drug Master File (DMF) (b) (4) was reviewed and found adequate to support the use of the drug substance in this application. The identity, strength, purity (including microbial limits) and quality of the drug product are deemed assured. The facility review team from the Office of Process and Facility has issued an "Approval" recommendation for the facilities submitted in support of this application.

3. Nonclinical Pharmacology/Toxicology

Please refer to the review prepared by Norman See, PhD, the Pharmacology/Toxicology reviewer, for full details. This NDA is considered approvable from a pharm/tox perspective. The NDA was considered to be a 505(b)(1) NDA because the sponsor owns all the necessary nonclinical data for ACZONE (dapsone) Gel, 5% to support the ACZONE (dapsone) Gel, 7.5% application.

Substantial toxicity was not observed in chronic toxicology studies in which dapsone topical gel was dermally applied. No effects were observed in male or female rabbits treated topically for nine months. Dapsone topical gel is not an irritant of skin or eyes, is not phototoxic, and is non-sensitizing.

In rats that were orally dosed for 90 days, treatment-related findings observed at 30 mg/kg/day included cyanosis of the skin, hyperactivity, increased WBC count, decreased RBC count, hemoglobin concentration and hematocrit, increased prothrombin time,

splenomegaly, mild splenic "congestion" and mild pigmentation of the spleen. These effects and more were observed at 100 mg/kg/day. The dose of 3 mg/kg/day was an apparent no-adverse-effect-level (NOAEL) in that study.

Dapsone was negative in an Ames assay (both with and without metabolic activation) and in a micronucleus assay. However, dapsone induced chromosomal aberrations in cultured CHO cells, suggesting that it is a clastogen. Dapsone was evaluated for carcinogenicity in a two-year oral (gavage) rat study at dose levels up to 15 mg/kg/day, and in a Tg.AC mouse study. Both studies were judged by the Executive Carcinogenicity Committee to be acceptable. No evidence of carcinogenicity was observed in either study.

Dapsone impaired fertility of male rats, as evidenced by a reduction in the fertility index (number of rats pregnant/number of rats mated), reduced sperm motility (percentage of observed sperm that were motile), and reduced numbers of implantations and viable embryos in the females that did become pregnant. The dose of 2 mg/kg/day was an apparent NOAEL for effects on male fertility.

When administered to female rats at a dosage of 75 mg/kg/day for 15 days prior to mating and for 17 days thereafter, dapsone reduced the mean number of implantations, increased the mean early resorption rate, and reduced the mean litter size. These effects were probably secondary to maternal toxicity. No effects on the incidence of external, visceral or skeletal malformations or variations were observed. Under the conditions of this study, the NOAEL for dapsone was 12 mg/kg/day. Findings were similar in rabbit reproductive studies, except that the NOAEL for dapsone was 30 mg/kg/day.

4. Clinical Pharmacology

Please refer to the review by Doanh Tran, Ph.D., the clinical pharmacology reviewer from the Office of Clinical Pharmacology/DCP III for full details. The clinical pharmacology review team considers this NDA approvable.

A PK trial compared the PK of ACZONE (dapsone) Gel, 7.5%, the to-be-marketed formulation, applied once-daily (QD) for 28 days to ACZONE Gel, 5% applied twice-daily (BID) for 28 days to subjects at least 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 which corresponded to a treatment area of approximately 1000 cm^2. Mean trough concentrations for plasma dapsone were similar for Days 7 – 28, suggesting steady state PK was achieved by Day 7 and maintained until Day 28.

Relative to ACZONE Gel, 5%, the daily systemic exposure of dapsone achieved by once daily application of the 7.5% gel, defined by the geometric mean ratio for maximum plasma concentration (Cmax) and area under the concentration-time curve from time 0 to 24 hours post-dose (AUC0-24), was about 28.6% and 28.7% lower, respectively. Based on the 90% CIs for Cmax and AUC0-24, these differences were statistically significant;

however, the upper limit of the 90% CIs were close to 100% (93% for Cmax and 92% for AUC0-24); therefore, the statistically significantly lower systemic exposure may not be clinically meaningful.

5. Microbiology

No microbiologic studies were conducted in support of this application.

6. Clinical/Statistical

Please refer to the reviews completed by Patricia Brown, M.D., the clinical reviewer, and Matthew Guerra, Ph.D., the biostatistical reviewer, for full details of the efficacy review. They consider this NDA approvable from an efficacy perspective.

In support of the efficacy of ACZONE Gel, 7.5%, the applicant submitted data from two identically-designed, randomized, multicenter, vehicle-controlled, parallel-group, Phase 3 trials (Trials 006 and 007). For enrollment, the protocol specified the following key inclusion criteria: 12 years of age or older, a Global Acne Assessment Score (GAAS) of 3 (moderate), 20-50 inflammatory lesions (papules and pustules) on the face, and 30-100 non-inflammatory lesions (open comedones and closed comedones) on the face. The protocol-specified co-primary efficacy endpoints were the proportion of subjects achieving a GAAS score of 0 (none) or 1 (minimal) at Week 12 and the absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12. Secondary efficacy endpoints included percent change in inflammatory and non-inflammatory lesion counts from baseline to Week 12.

The mean age was 20.3 years and 20.2 years (range of 12 to 63 years) for the ACZONE Gel and the Vehicle groups, respectively. Adolescents (ages 12 to 17 years) comprised 49.5% and Caucasians comprised 57.4% of trial subjects. The median total dose used was 41.4 grams in the ACZONE Gel group and 42.3 grams in the Vehicle group. The duration of exposure and average daily use of study product were similar between treatment arms within each trial and between the two trials.

Table 1 presents the results of the co-primary efficacy endpoints and the secondary efficacy endpoints of percent change in inflammatory and inflammatory lesion counts from baseline to Week 12. In both trials, ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.004) to vehicle gel for all endpoints presented in Table 1.

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