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
April 28, 2015
PDUFA Goal
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 dianminodiphenyl sulphone, 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 benzyol 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 1 trials 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 an airless pump container closure system. The 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) 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.
Of note, for the assessment of GAAS, the interpretation of a “few” or “no” lesions seemed to vary from investigator to investigator. Some subjects counted as successes under the GAAS seemed to have relatively high lesion counts for the definition of “none” (no evidence of facial acne vulgaris) or “minimal” (a few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present). Subjects scored as 0 (none) had as many as 10 inflammatory lesions or 45 non-inflammatory lesions. Subjects scored as 1 (minimal) had as many as 57 inflammatory lesions or 102 non-inflammatory lesions.

7. Clinical/Safety

Please refer to the review completed by Patricia Brown, M.D., the clinical reviewer, for full details of the safety review. This NDA is considered approvable from a safety perspective.

The applicant submitted data from the Phase 3 Trials 006 and 007 to establish the safety of their product applied once daily for 12 weeks in the topical treatment of acne vulgaris. Additional safety data are available from PK Trial 004 and dermal safety studies. All of the trials were conducted with the final-to-be-marketed formulation.

The pooled safety database includes 4336 subjects exposed to study drugs; 2161 to ACZONE Gel, 7.5% and 2175 to Vehicle. Safety was assessed by adverse events, local tolerability (at baseline and at Weeks 1, 2, 4, 8, and 12) and vital signs (at screening and at the Week 12/early exit visit). The local dermal tolerability assessment for the face was performed by the investigators or appropriately trained designee and by the patient. Assessments included dryness, scaling, and erythema (assessed by the investigator) and stinging/burning (assessed by the patient). Each assessment used 4-point scales: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

A few subjects in either treatment arm discontinued from the trials due to adverse events considered related to treatment. Three subjects in the ACZONE Gel arm discontinued for the events of application site acne and dermatitis; application site vesicles, swelling and
pruritus; and application site discomfort. In the Vehicle arm 2 subjects discontinued for mild application site pain and 1 subject discontinued for application site acne.

The frequency of application site treatment-emergent adverse events (TEAEs) was similar between ACZONE Gel-treated and Vehicle-treated subjects. The most common application site TEAEs occurring in ≥1% of subjects in any treatment group were: application site dryness (1.2% in the ACZONE Gel group versus 1.0% in the Vehicle group), application site pruritus (1.1% versus 0.6%), and application site pain (0.5% versus 1.5%). The proportion of subjects experiencing TEAEs was similar among those aged 12 to 17 years of age as compared with those subjects > 18 years of age and among males and females.

Treatment-related TEAEs, or adverse drug reactions (ADRs), were reported in 3.5% (75/2161) of subjects in the ACZONE Gel treatment arm and 3.4% (73/2175) of subjects in the Vehicle treatment arm. The most common ADRs occurring at a rate greater than vehicle were application site dryness (1.1% in the ACZONE Gel group versus 1.0% in the Vehicle group) and application site pruritus (0.9% versus 0.5%).

Approved labeling for ACZONE Gel, 5%, includes warnings and precautions for methemoglobinemia, hematologic effects, peripheral neuropathy and serious skin reactions. The Warning and Precautions section of labeling for ACZONE Gel, 7.5% will contain language similar to the current approved labeling for ACZONE Gel, 5%.

Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia, peripheral neuropathy (motor loss and muscle weakness) and serious skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria). These types of skin reactions were not observed in topical ACZONE Gel, 5% clinical trials or in the ACZONE Gel, 7.5% development program.

Labeling for ACZONE Gel, 5% was modified in July 2015 to include the information that cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with the use of ACZONE Gel, 5%. In the ACZONE Gel, 7.5% development program, two events were reported in two subjects (of note, the subjects were a parent and child) in a Phase 1 dermal safety trial that were considered potentially related to methemoglobinemia. Both subjects reported possible cyanosis, which is usually the first presenting symptom of methemoglobinemia, and tremor. The events resolved within one hour of removal of test patches containing the dapsone gel, which is inconsistent with the Tmax and the half-life of dapsone. For this and other reasons, the two cases are not considered definitive regarding an association between the use of ACZONE Gel, 7.5% and the occurrence of methemoglobinemia.

Clinically significant changes in methemoglobin levels over the course of PK Trial 004 were not seen. Mean methemoglobin levels at baseline were 0.76%, and 0.74% in the ACZONE Gel, 7.5%, and ACZONE Gel, 5% gel groups, respectively. At Day 28, the mean change from baseline was -0.02, and -0.02 in each group, respectively.
Similarly, clinically significant changes in other hematologic parameters were not seen.

8. Advisory Committee Meeting

No regulatory issues were identified during the review of this application that required input from an advisory committee.

9. Pediatrics

Because necessary studies are impossible or highly impractical, a partial waiver for the study of acne in pediatric patients ages 0 to 9 years will be granted. Prior to this NDA submission, the Agency agreed with the proposed iPSP and study of pediatric patients down to an age of 12 years; however, review of the literature indicates that acne vulgaris is increasing in prevalence in younger children. As a result, a deferral of pediatric study of patients 9 years to 11 years 11 months will be granted and the applicant will be required to conduct an open-label study to assess safety, pharmacokinetics, and treatment effect of ACZONE Gel, 7.5% applied once daily in 100 pediatric subjects age 9 to 11 years 11 months with acne vulgaris.

10. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application. GMP inspections received an “Acceptable” determination from the Office of Process and Facilities.

11. Labeling

The ACZONE Gel, 7.5% product will have a separate label from the existing ACZONE Gel, 5% product at the applicant’s request. Review of the proposed label was based on evaluation of clinical trial data and DMEPA, DRISK, and OPDP reviews.

Because this product is not a new molecular entity, changes to the label consistent with the Pregnancy and Lactation Labeling Rule (PLLR) will be deferred to a later time. Proposed labeling will mirror that of the currently approved ACZONE Gel, 5% product.

Product labeling appears adequate to communicate safety information to prescribers.

12. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

I concur with the recommendations of the multi-disciplinary review team to approve NDA 207154 ACZONE (dapsone) Gel, 7.5% for the treatment of acne vulgaris in patients 12 years of age and older.
Risk-benefit assessment: Efficacy of ACZONE (dapsone) Gel, 7.5% was established in two adequate and well-controlled clinical trials. Safety of the product is demonstrated through data from the clinical development program as well as extensive postmarketing experience with the 5% gel formulation.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Postmarketing requirements (PMR): 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 postmarketing trial to assess PK in subjects 9 years to 11 years 11 months will be required.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
02/17/2016