

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207154Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 27, 2016
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	207154
Applicant	Allergan, Inc.
Date of Submission	Letter date: April 28, 2015 CDER stamp date: April 28, 2015
PDUFA Goal Date	February 28, 2016
Proprietary Name / Established (USAN) names	ACZONE/ (dapsone)
Dosage forms / Strength	Gel / 7.5%
Proposed Indication(s)	Topical treatment of acne vulgaris in patients 12 years of age and older
Recommended:	<i>Approval</i>

1. Introduction

ACZONE (dapsone) Gel, 7.5% is a topical drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the treatment of acne vulgaris in patients 12 years of age and older. This application is for a new strength and dosing regimen of dapsone. The proposed dosing regimen is once daily.

The active ingredient, dapsone, is synthetic sulfone which is currently marketed in the United States (US) in various topical dosage forms (tablets, gel) and is available since 1955. Dapsone Tablets for oral use (25 mg and 100 mg) is indicated for the treatment of dermatitis herpetiformis and leprosy. The topical dosage form of dapsone, ACZONE (dapsone) Gel, 5% was approved on July 7, 2005, for the treatment of acne vulgaris in patients 12 years of age and older (NDA 021794; Allergan, Inc.). The approved dosing regimen is twice daily.

This NDA, NDA 207154, and NDA 21794 were developed under IND 54,440. NDA 207154 includes letters from Allergan that authorize reference to data associated with NDA 21794 and IND 54,440.

This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

ACZONE (dapsone) Gel, 7.5% was developed under IND 054440. During development program, the applicant interacted with the Agency at two milestone meetings [End of Phase 2 Meeting (August 28, 2013) and Pre-NDA Meeting (November 19, 2014)].

At the EOP2 Meeting, the following key points were discussed:

- The Division did not agree with the applicant's (b) (4). The Division stated that (b) (4) should be assessed because the proposed dapsone gel, 7.5% differs from the approved product, ACZONE Gel, 5%, in both concentration of the active ingredient as well as the excipients in the formulation.
- The applicant's rationale (based on low plasma concentration, historical clinical use and relative bioavailability data to ACZONE Gel, 5%) seemed reasonable to support a waiver to conduct a thorough QT/QTc study for dapsone gel, 7.5%.
- For assessing efficacy for acne indication, the co-primary endpoints regarding the lesion counts recommended by the Division are the absolute change in inflammatory and non-inflammatory lesion counts from baseline. Facial counts should include lesions on the nose.
- The proposed secondary efficacy endpoints of percentage change in inflammatory and noninflammatory lesion counts from baseline to week 12 are acceptable.
- The Agency also provided comments regarding the handling missing data [e.g. recommended a more scientifically sound approach, such as multiple imputation or modeling approach, instead of the last observation carried forward (LOCF) approach].

A Pre-NDA, the following key points of discussion were:

- The applicant proposed to integrate the two pivotal Phase 3 trials for the ISS and ISE. The applicant stated that the four Phase 1 trials (three dermal tolerability studies and one PK study) will not be part of the integrated analysis because the design, treatment exposures, and objectives of those trials were different than the Phase 3 trials. The Agency stated that the proposed approach for the ISS and ISE appeared reasonable.
- In July of 2014, the applicant became aware of a site-specific issue concerning the Phase 3 trial, Clinical Study 225678-006, and Principal Investigator Dr. Ellen Marmur (Site 16078, located at Marmur Medical in New York City, New York). Allergan investigated the issue, which culminated in an on-site assessment 11-12 September 2014, and confirmed the existence of Good Clinical Practice (GCP) compliance issues in the areas of Protocol Adherence and Clinical Study Management. Due to concerns over the overall data integrity for Dr. Marmur's site, Allergan has made the decision to exclude all subjects randomized at the site (51 patients) from the Intent-to-Treat (ITT) analysis. All subjects seen at Dr. Marmur's site will be included in the safety analysis for the NDA.
Given the potential seriousness of the violations described, data from this investigative site should not be included in the primary efficacy analysis. In addition, the Agency

recommended that the statistical analysis should follow the randomization; therefore, as the randomization was stratified by gender and center, the Agency recommended the applicant conduct the analyses stratified by both factors with and without pooling. Line listings should be provided for any safety data collected at this site, but should not be included in analyses.

- The Agency agreed with the applicant proposal of using the gatekeeping approach without the Hochberg's Step-up method when controlling for multiplicity after the applicant clarified that the testing would be done sequentially for total lesion counts followed by inflammatory and non-inflammatory lesion counts before testing the next secondary endpoints.

During the development program, the applicant submitted an Initial Pediatric Study Plan (iPSP) on October 17, 2013 requesting a partial waiver of the requirement to perform pediatric studies in patients from birth to (b) (4) of age for the indication of acne vulgaris. The applicant stated that the reason for waiving pediatric studies is that "necessary studies are impossible or highly impractical (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed) (Section 505B(a)(4)(B)(i) of the Act)". The Division issued an Advice Letter confirming agreement with the initial agreed PSP on March 24, 2014.

3. CMC/Device

Drug substance:

ACZONE (dapsone) Gel, 7.5% contains dapsone as the active ingredient. The drug substance, dapsone is chemically produced. The chemical name of dapsone is: 4-[(4-aminobenzene)sulfonyl]aniline. Dapsone is a white or slightly yellow-white, crystalline powder that has an empirical formula of $C_{12}H_{12}N_2O_2S$ and a molecular weight of 248.30. Dapsone melts in the temperature range of 175 – 181°C and it is very slightly soluble in water, freely soluble in acetone, sparingly soluble in alcohol, and dissolves freely in dilute mineral acids. Detailed CMC information for dapsone is referred to DMF (b) (4). The DMF has been reviewed by CMC reviewer and found adequate in supporting the use of the drug substance in the NDA. (Review by Martin T. Haber, PhD.; Branch II; Division of New Drug API/ONDP; dated December, 18, 2015)

Drug product:

ACZONE (dapsone) Gel, 7.5%, is off-white to yellow gel with suspended dapsone particles. Each gram of ACZONE (dapsone) 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 composition of ACZONE (dapsone) Gel, 7.5% is described in the following table:

Table 1: Composition of ACZONE (dapson) Gel, 7.5%

Component	Function	Quality Standard	Concentration (% w/w)
Dapsone	Drug substance	USP	7.5
DGME	(b) (4)	NF	(b) (4)
(b) (4)		Non-compendial	
MP		NF	
Purified Water		USP	

There are no novel excipients used in the drug product formulation. There is no overage of the API. All excipients are compendial except the (b) (4). The CMC information is provided in DMF (b) (4). The DMF (b) (4) was reviewed on 12/14/2015 and found to be adequate.

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification.

Container Closure System:

ACZONE (dapson) Gel, 7.5%, is packaged in a non-metered airless pump container closure system. The (b) (4) airless pump container system consists of polypropylene bottle with a high density polyethylene piston. (b) (4)

(b) (4). The drug product is supplied in 30 (b) (4), 60 (b) (4) and 90 (b) (4) size bottles containing the same pump (b) (4)

(b) (4) The details on this container closure system are provided in DMF (b) (4). A letter of authorization for this DMF was provided. The product will be available in three different sizes (30 gram, 60 gram, and 90 gram). Additionally, 3 gram professional samples packaged in an (b) (4) are also available.

The extractable and leachable study demonstrated that there is virtually no risk of leachables from the airless pump system. The container closure system is adequate (b) (4). The expiration dating period of 24 months is recommended for the drug product when stored at controlled room temperature based on the 12-month long-term and 6-month accelerated stability data obtained from 3 registration batches of the drug product.

Special Product Quality Labeling Recommendations: Protect from freezing.

The CMC reviewer concluded that the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

The facility review team from the Office of Process and Facility has issued an “Approval” recommendation for the facilities involved in this application.

The reader is referred to the comprehensive reviews by Hitesh Shroff, Ph.D.; Branch V; Division of New Drug Products II/ONDP/OPQ dated December 18, 2015; Yuesheng Ye, Ph.D.; Branch VIII; Division of Process Assessment III/OPF; Sherry (Xiaohui) Shen, CSO; Branch III; Division of Inspection Assessment/OPF, dated January 4, 2016; Vidula Kolhatkar, Ph.D., Branch II, Division of Biopharmaceutics/ONDP dated January 5, 2016; and Elizabeth Berr, PhD. Branch I, Division of Microbiology Assessment/OPF dated January 5, 2016;

Label/Labeling recommendation:

Immediate container labels:

The 30 g, 60 g and 90 g pump labels should be revised to include the following information:

- Display “Lot:” and “Exp:”
- Display a barcode
- Add the following statement in the storage condition description
“[See USP Controlled Room Temperature]”
- List ingredients as shown below:
“Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water.”

The 3 g sample tube labels should be revised to include the following information:

- Display “Lot:” and “Exp:”
- Add the following statement in the storage condition description
“[See USP Controlled Room Temperature]”
- Include “Manufactured for: and by:” same as pump labels.

Carton labels:

The 8 x 3 g sample tubes, 30 g, 60 g and 90 g carton labels should be revised to include the following information:

- Add the following statement in the storage condition description
“[See USP Controlled Room Temperature]”
- List ingredients as shown below:
“Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water.”

The 8 x 3 g sample tube carton labels should be revised to include the following information:

- Display “Lot:” and “Exp:”

Physician Insert

“Highlights” Section

This section should be revised as follows:

- Display the drug product title as shown below:
ACZONE (dapsone) gel, for topical use
- Delete the following statement:
“Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel”

3 “Dosage Forms and Strength” Section

This section should be revised as follows:

- Revise the dosage form description as shown below:
“Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel with suspended particles.”

11 “Description”

This section should be revised as follows:

- Revise the drug product title as shown below:
ACZONE (dapsone) gel, 7.5%
- Replace the chemical name with the following IUPAC name:
4-[(4-aminobenzene)sulfonyl] aniline
- The molecular weight of dapsone should be revised to “248.30”

16 “How supplied/storage and handling”

This section should be revised as follows:

- The following drug product and container closure description should be added.
“ACZONE gel is an off-white to yellow gel with suspended particles It is supplied in airless pumps containing polypropylene bottles with high density polyethylene pistons.”
- The following statement should be added to the storage condition
“[See USP Controlled Room Temperature]”

4. Nonclinical Pharmacology/Toxicology

Dapsone has been evaluated in a battery of nonclinical studies that included evaluation of pharmacology, pharmacokinetics, pharmacodynamics, safety pharmacology, single and repeated-dose general toxicity (involving both oral and topical dermal administration), genetic toxicology, reproductive toxicology (assessment of potential to impact fertility/reproductive success of male and female rodents, developmental toxicity of rats and rabbits, and prenatal and postnatal development, including maternal function, of rodents), carcinogenicity, and special toxicology issues. These studies have been reviewed under NDA 21794 (refer to the

CDER nonclinical reviews of NDA 21794 and IND 54440 for summary and interpretation of the nonclinical data). This application includes letters from Allergan that authorize reference to data associated with NDA 21794 and IND 54440.

In addition, the Study “AGN-225678: 3-Month Dermal Toxicity Study in Rats” (study No. 20053240) was conducted to assess ACZONE® (dapsone) Gel, 7.5% for potential to induce toxicity when topically applied to the skin of rats.

The pharmacology-toxicology reviewer, Norman A See, Ph.D. summarized the pivotal data reviewed under NDA 21794:

General toxicology:

Substantial toxicity was not observed in chronic toxicology studies in which dapsone topical gel was dermally applied. No adverse effects were observed in female rats treated daily for six months, although the mean RBC, HGB, and HCT values of male dapsone-treated animals were slightly, but significantly, reduced, and the mean weight of the spleen was significantly increased, in male rats that received dapsone gel. No effects were observed in male or female rabbits treated topically for nine months.

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; 3 mg/kg/day was an apparent no-adverse-effect-level (NOAEL) in that study.

Genetic toxicology:

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.

Carcinogenicity:

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 exec-CAC to be acceptable. No evidence of carcinogenicity was obtained in either study.

Reproductive toxicology:

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. Statistically significant reductions in percentage of motile sperm were observed at exposures of 3 mg/kg/day and above. The mean numbers of embryo implantations and viable embryos were significantly reduced in untreated females mated with males that had

been dosed at 12 mg/kg/day or greater, presumably due to reduced numbers or effectiveness of sperm, indicating impairment of fertility. 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.

When administered at a dosage of 150 mg/kg/day to rabbits on days 6-18 of gestation, dapsone significantly increased the incidence of early resorptions. Two does at this dosage delivered prematurely and seven does resorbed all fetuses. 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 30 mg/kg/day.

Little toxicity was observed in a two-generation study in which F0 females were administered the test articles daily from gestation day 7 through day 27 postpartum at exposures of 3, 12, and 30 mg/kg/day dapsone. The mean number of stillborn pups per litter was slightly, but statistically significantly, higher in high-dose dapsone litters than in control litters. No effects were observed on pup viability, physical development, behavior, learning ability, or reproduction.

Special toxicology:

Dapsone topical gel is not an irritant of skin or eyes, is not phototoxic, and is nonsensitizing.

Per pharmacology-toxicology reviewer, key findings from the Study AGN-225678 (3-Month Dermal Toxicity Study in Rats) are summarized:

Formulations containing dapsone at concentrations ranging from 3.75% to 15% w/w were topically applied to rats once daily for approximately 92 days (1 or 2 mL/kg per application). In addition, a group of rats received a formulation that contained both dapsone and (b) (4). No treatment-related deaths occurred, and no dermal irritation at the treatment site was observed. Exposure to dapsone trended to correlate with reduced mean body weights in both genders. Erythrocytic parameters (e.g., RBC, HGB, HCT) tended to be reduced in animals exposed to dapsone, particularly males. Reticulocyte counts were increased in these animals. Methemoglobinemia was observed in treatment groups. Treatment-related effects on mean organ weight included trends (which achieved statistical significance in some instances) toward increased mean thyroid weight in males and females, increased mean splenic weight in males, and decreased mean thymus weight in females. The primary microscopic

lesions appeared to be related to increased erythrocyte turnover, which was presumably secondary to dapsone-induced oxidative damage to erythrocytes. Those changes included increased hematopoiesis/erythropoiesis in the bone marrow, spleen, and liver, increased iron in the liver, spleen and kidney, pigmentation in the kidneys, and congestion in the spleen.

Impurities/Excipients

The proposed specifications for organic impurities of the drug product are acceptable; no specified or individual unspecified dapsone-related impurities of the drug product exceed the qualification limit under the ICH Q3B document (the qualification threshold for degradation products that are associated with dapsone under NDA 207154 is 0.2% of the label strength of the API). The product contains no novel excipients.

The reader is referred to the comprehensive review by Norman A See, Ph.D. dated November 12, 2015.

There are no outstanding pharmacology-toxicology issues.

The pharmacology-toxicology reviewer, Norman A See, Ph.D., recommended *Approval* of this application (review dated November 12, 2015).

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted one pharmacokinetic (PK) trial, Study 225678-004, to compare the PK of ACZONE (dapsone) Gel, 7.5% (formulation 11080X, to-be-marketed formulation) applied once-daily (QD) for 28 days with ACZONE (dapsone) Gel, 5% applied twice-daily (BID) for 28 days in subjects (≥ 16 years of age) with moderate acne vulgaris (score of 3 on GAAS). For each application, study product (2 grams) was topically applied (by study staff) to the face, upper chest, upper back, and shoulders corresponding to a treatment area of approximately 1000 cm².

Plasma concentrations of dapsone, its metabolites N-acetyl dapsone (NAD) and dapsone hydroxylamine (DHA), and N-formyl dapsone (NFD) were collected prior to administration of the morning dose on days 1, 7, 14, 18, 21, 26, 27, on day 28 (pre-dose, 1, 2, 4, 6, 8, 10, and 12 hours post-dose), on days 29 to 32 (24, 30, 36, 48, 72, and 96 hours after the last dose), on day 35 (168 hours after the last dose), and early exit (if applicable), and were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Mean C_{troughs} 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 2.

Table 2: Summary of plasma dapsone PK parameters following dosing on Day 28

PK parameter	Dapsone Gel, 7.5% QD (TBM formulation 11080X) N=19	ACZONE Gel, 5% BID N=18
C _{max} (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

Source_Clinical Pharmacology Review (p.7, Table 3)

The Clinical Pharmacology reviewer concluded the following:

“Relative to Aczone Gel, 5%, daily systemic exposure of dapsone, defined by the geometric mean ratio for maximum plasma concentration (C_{max}) 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 C_{max} and AUC0-24, these differences were statistically significant; however, the upper limit of 90% CI were close to 100% (93% for C_{max} and 92% for AUC0-24) and therefore the statistically significantly lower systemic exposure may not be clinically meaningful.”

Trial 225678-004 included pediatric subjects ≥16 years of age (7/19 in ACZONE Gel, 7.5% group and 6 /18 in ACZONE Gel, 5% group). The data showed similar systemic exposure to dapsone and its metabolites DHA and NAD between subjects 16 to <18 years of age and those ≥18 years of age. In addition, because systemic exposure of dapsone in patients 12 – 15 years of age is similar to those 16 years and older (per ACZONE Gel, 5% labeling), additional PK trial in subjects ages 12 -15 years was not requested for ACZONE Gel, 7.5%.

Long-term safety study was not conducted with ACZONE Gel, 7.5%. However, in a long-term safety study of ACZONE Gel, 5%, periodic blood samples were collected up to 12 months to determine systemic exposure of dapsone and its metabolites. Based on the measurable dapsone concentrations from 408 subjects, neither gender nor race appeared to affect the pharmacokinetics of dapsone. Exposure to dapsone were approximately the same between the 12-15 years (N=155) and >16 years (N=253) age groups. Additionally, there was no evidence of increasing systemic exposure to dapsone over the time.

Clinical Pharmacology Team Labeling Recommendations:

The following changes are recommended for sections 5, 7 and 12 of the label. Deletions are noted as ~~strike through~~ and additions are noted as double underline.

5 WARNINGS AND PRECAUTIONS

5.1 Hema (b) (4)

Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia.

Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to

hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.

In clinical studies, there was no evidence of clinically relevant hemolysis or hemolytic anemia in patients treated with topical dapson. Some patients with G6PD deficiency using twice daily dapson gel, 5%, developed laboratory changes suggestive of mild hemolysis.

(b) (4)

Combination of topical dapson with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

(b) (4)

If signs and symptoms suggestive of hemolytic anemia (b) (4) occur,

(b) (4)

ACZONE[®] Gel, 7.5% (b) (4) in patients who are taking oral dapson or antimalarial medications because of the potential for (b) (4) hemolytic reactions.

7 DRUG INTERACTIONS

(b) (4)

No formal drug-drug interaction studies were conducted with **ACZONE**[®] Gel, 7.5%.

7.1 Trimethoprim-Sulfamethoxazole

A drug-drug interaction study evaluated the effect of the use of dapson gel, 5% 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 dapson and its metabolites increased in the presence of TMP/SMX. The systemic exposure from **ACZONE**[®] Gel, 7.5% is expected to be about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

7.2 Topical Benzoyl Peroxide

Topical application of dapson gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discoloration of the skin and facial hair.

7.3 Drug Interactions with Oral Dapson

Certain concomitant medications (such as rifampin, anticonvulsants, St. John's wort) may increase the formation of dapsone hydroxylamine, a metabolite of dapsone associated with hemolysis. With oral dapsone treatment, folic acid antagonists such as pyrimethamine have been noted to possibly increase the likelihood of hematologic reactions.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

(b) (4) The mechanism of action of dapsone gel in treating acne vulgaris is not known.

12.3 Pharmacokinetics

In a pharmacokinetic study, male and female subjects 16 years of age or older with acne vulgaris (N=19) (b) (4) received 2 grams of ACZONE Gel, 7.5%, topically to the (b) (4) face, upper chest, upper back and shoulders once daily for 28 days (b) (4)

(b) (4) Steady state for dapsone was reached within 7 days of dosing (b) (4). On Day 28, the mean dapsone maximum plasma concentration (C_{max}) and area under the concentration-time curve from 0-24 hours post dose (AUC_{0-24h}) were 13.0 ± 6.8 ng/mL and (b) (4) 282 ± 146 ng·h/mL, respectively (b) (4)

(b) (4)

(b) (4) The systemic exposure from ACZONE® Gel, 7.5% is expected to be about 1% of that from a 100 mg oral dose.

The applicant proposed to omit section 7.3 and 7.4 of ACZONE Gel, 5% labeling regarding concomitant use with drugs that induce methemoglobinemia. As per clinical pharmacology reviewer, based on the 90% CIs for C_{max} and AUC₀₋₂₄, these differences were statistically significant; however, the upper limit of 90% CI were close to 100% (93% for C_{max} and 92% for AUC₀₋₂₄). The statistically significantly lower systemic exposure may therefore not be clinically meaningful and a caution regarding concomitant use of drugs that induce methemoglobinemia that is pertinent for ACZONE Gel, 5% is also understood to be pertinent for ACZONE Gel, 7.5%. Therefore, information from Section 7.3 and Section 7.4 for ACZONE Gel, 5% labeling will be included into the labeling for ACZONE Gel, 7.5%.

7.4 Concomitant Use with Drugs that Induce Methemoglobinemia

Concomitant use of ACZONE® Gel, 7.5% with drugs that induce methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine,

para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine may increase the risk for developing methemoglobinemia [see Warnings and Precautions (5.1)].

The reader is referred to the comprehensive review by Doanh C Tran, PhD. for a full discussion of the clinical pharmacology data (dated January 11, 2016).

The clinical pharmacology reviewer, Doanh C Tran, PhD., Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3, recommended *Approval* of this application pending agreement on recommended labeling changes.

The following post marketing requirement (PMR) 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.

6. Clinical Microbiology

The applicant did not conduct microbiologic studies.

7. Clinical/Statistical- Efficacy

The applicant submitted data from pivotal trials, 225678-006 (Trial 006) and 225678-007 (Trial 007), to establish the effectiveness of their product, ACZONE (dapsone) Gel, 7.5%, applied once daily for 12 weeks in the treatment of acne vulgaris.

The Trial 006 and Trial 007 were identically-designed, double-blind, randomized, multicenter, vehicle- controlled, parallel-group, Phase 3 trials. The population enrolled was subjects 12 years of age or older with moderate acne vulgaris defined as score of 3 (moderate) on a Global Acne Assessment Score (GAAS) scale, 20-50 inflammatory lesions (papules and pustules) and 30-100 non-inflammatory lesions (open comedones and closed comedones) on the face. Each trial was designed to enroll and randomize approximately 2180 subjects. Eligible subjects were randomized to one of the following treatment in a 1:1 ratio: ACZONE Gel, 7.5% or Vehicle Gel. Randomization was stratified by gender and center. Subjects applied study product once daily for 12 weeks. Subjects were evaluated at the following study visits: screening, baseline (Day 1) and Weeks 1, 2, 4, 8, and 12. An overview of the trials is presented in Table 3.

Table 3: Clinical Study Overview

Trial	Location	Study Population	Treatment Arms	Number of Subjects	Dates
006	U.S. (96 centers) & Canada (9 centers)	Aged 12 years and older, GAAS of 3 (moderate), 20 to 50 inflammatory lesions, and 30 to 100 non-inflammatory lesions	ACZONE Gel, 7.5%	1044*	11/27/2013 – 10/28/2014
			Vehicle Gel	1058*	
007	U.S. (93 centers) & Canada (10 centers)	Aged 12 years and older, GAAS of 3 (moderate), 20 to 50 inflammatory lesions, and 30 to 100 non-inflammatory lesions	ACZONE Gel, 7.5%	1118	11/27/2013 – 10/21/2014
			Vehicle Gel	1120	

*Excluding subjects from center 16078 (25 on ACZONE Gel, 7.5% and 26 on Vehicle Gel).

Source: Statistical Review (p.5, Table 2)

Trial 006 enrolled and randomized a total (excluding center 16078) of 2102 subjects (1044 to ACZONE Gel and 1058 to Vehicle) from 105 centers (96 in U.S. and 9 in Canada). Trial 007 enrolled and randomized a total of 2238 subjects (1118 to ACZONE Gel and 1120 to Vehicle) from 103 centers (93 in U.S. and 10 in Canada). The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and similar between each trial. The mean age was 20 years in the both treatment arms. The majority of the subjects were White (> 54%). Slightly more subjects were female (>55%). All subjects had baseline disease severity “moderate” (GAAS 3) with exception of one subject in Trial 006 who had a GAAS of 4 (severe). The mean inflammatory lesion count was ~ 29 and the mean non-inflammatory lesion count was ~ 47 in the both treatment arms and in the both trials.

The rate of discontinuation was slightly higher in the ACZONE Gel treatment arm (9.2%) compared to the Vehicle treatment arm (7.8%). For Trial 007, the rates of discontinuation were almost identical (8.2% v.8.3%).). The most common reason for withdrawal was ‘Lost to Follow-Up’ (ACZONE Gel treatment arm: 3.6% for Trial 006 and 4% for Trial 007; Vehicle treatment arm: 2.7% for Trial 006 and 3.6% for Trial 007).

The primary analysis population specified in the protocol was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol also specified supportive analyses using the per-protocol (PP). The PP population was defined as all randomized subjects with no protocol deviations during the trial that might potentially affect the primary efficacy analyses.

The co-primary efficacy endpoints were the proportion of subjects achieving a GAAS score of 0 (none) or 1 (minimal) at Week 12, the absolute change in inflammatory and the absolute change non-inflammatory lesion counts from baseline to Week 12.

In both trials, ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.004) to Vehicle. The results from the ITT and PP analyses were similar and are presented in Tables 4 and 5, respectively.

Table 4: Results for the Co-Primary Efficacy Endpoints at Week 12 (MI, ITT)

Endpoint	Trial 006 ⁽¹⁾			Trial 007		
	ACZONE (N=1044)	Vehicle (N=1058)	P-value	ACZONE (N=1118)	Vehicle (N=1120)	P-value
GAAS: None or Minimal*	311.9 (30%)	224.2 (21%)	<0.001 ⁽²⁾	333.3 (30%)	234.1 (21%)	<0.001 ⁽²⁾
Absolute Change in Inflammatory Lesion Counts:						
Mean*	16.1	14.3		15.6	14.0	
LS Mean ⁽³⁾	16.1	14.1	<0.001 ⁽³⁾	15.6	13.8	<0.001 ⁽³⁾
Absolute Change in Non-Inflammatory Lesion Counts:						
Mean*	20.7	18.0		20.8	18.7	
LS Mean ⁽³⁾	20.8	17.6	<0.001 ⁽³⁾	20.7	18.5	0.004 ⁽³⁾

Source: Statistical Review (p.10; Table6)

*The values displayed are the averages over the 20 imputed datasets (MI).

(1) Excluding subjects from center 16078 (a total of 51 subjects).

(2) P-value from a CMH test stratified by gender.

(3) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

Table 5: Results for the Co-Primary Efficacy Endpoints at Week 12 (PP)

Endpoint	Trial 006 ⁽¹⁾			Trial 007		
	ACZONE (N=880)	Vehicle (N=887)	P-value	ACZONE (N=950)	Vehicle (N=955)	P-value
GAAS: None or Minimal	272 (31%)	199 (22%)	<0.001 ⁽²⁾	291 (31%)	203 (21%)	<0.001 ⁽²⁾
Absolute Change in Inflammatory Lesion Counts:						
Mean	16.2	14.6		15.8	14.4	
LS Mean	16.1	14.4	<0.001 ⁽³⁾	15.8	14.2	0.001
Absolute Change in Non-Inflammatory Lesion Counts: Mean	21.1	18.2		21.4	18.9	
LS Mean	21.0	17.9	<0.001 ⁽³⁾	21.1	18.7	<0.001 ⁽³⁾

Source: Statistical Review (p.10 Table 7)

(1) Excluding subjects from center 16078 (a total of 51 subjects)

(2) P-value from a CMH test stratified by gender.

(3) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

For the secondary efficacy endpoints based on lesion counts (i.e., absolute change from baseline in total lesion counts and percent change in lesions counts (inflammatory, non-inflammatory, and total), ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.001) to Vehicle in both trials.

Table 6: Results for the Secondary Efficacy Endpoints at Week 12 (MI⁽¹⁾, LOCF⁽²⁾, ITT)

Endpoint	Trial 006 ⁽³⁾			Trial 007		
	ACZONE (N=1044)	Vehicle (N=1058)	P-value	ACZONE (N=1118)	Vehicle (N=1120)	P-value
Absolute Change in Total Lesion Counts: Mean* LS Mean ⁽⁴⁾	36.9 36.9	32.3 31.7	<0.001 ⁽⁴⁾	36.5 36.2	32.7 32.3	<0.001 ⁽⁴⁾
Percent Change in Total Lesion Counts: Mean* LS Mean ⁽⁴⁾	49.4% 48.7%	42.7% 42.4%	<0.001 ⁽⁴⁾	49.2% 48.9%	43.6% 43.2%	<0.001 ⁽⁴⁾
Percent Change in Inflammatory Lesion Counts: Mean* LS Mean ⁽⁴⁾	56.2% 55.5%	49.5% 49.0%	<0.001 ⁽⁴⁾	54.2% 53.8%	47.6% 47.3%	<0.001 ⁽⁴⁾
Percent Change in Non-Inflammatory Lesion Counts: Mean* LS Mean ⁽⁴⁾	45.0% 44.4%	38.9% 38.4%	<0.001 ⁽⁴⁾	46.2% 45.9%	40.8% 40.4%	0.001 ⁽⁴⁾

Source: Statistical Review (p.13; Table 12)

*The values displayed are the averages over the 20 imputed datasets (MI).

(1) Missing data for lesion count endpoints were imputed using multiple imputation (MI).

(2) Missing data for ASIS endpoints were imputed using last observation carried forward (LOCF). (3) Excluding subjects from center 16078 (a total of 51 subjects).

(4) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

Examination of subgroups indicated that gender and age have an impact on efficacy results with females and adults generally having better outcomes than males and adolescents; however, the treatment differences across subgroups did not vary greatly (i.e., females and adults had better results on both the ACZONE Gel and vehicle treatment arms).

Efficacy rates varied among centers. The applicant's investigation of the treatment-by-center interaction focused on the effects after pooling. As the pooling process could mask center effects, statistical reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. The removal of any one center did not affect the overall conclusions in Trial 006 (p-values ≤ 0.001) and Trial 007 (p-values ≤ 0.01). Two centers ((b) (6) and (b) (6)) in Trial 006 and three centers (b) (6)) in Trial 007 had investigators with disclosable financial interests. The results with and without these centers were very similar, and these centers did not affect the overall conclusion (refer to statistical review, Table 23).

In summary, the applicant has established the efficacy of their product, ACZONE (dapsone) Gel, 7.5%, in the treatment of acne vulgaris in patients 12 years of age and older.

The reader is referred to the comprehensive statistical review and evaluation by Matthew W Guerra, Ph.D. (Division of Biostatistics III) for a more complete discussion of the efficacy results (dated January 14, 2016).

8. Safety

The applicant submitted data from two pivotal trials, 225678-006 (Trial 006) and 225678-007 (Trial 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 Trial 225678-004 (pharmacokinetic; 4-arm, active controlled) and dermal safety studies [(Trial 225678-009; RIPT sensitization), Trial 225678-010 (phototoxicity), and Trial 225678-011 (photoallergy)]. All of the trials were conducted with the final-to-be-marketed formulation. The trials are summarized in Table below:

Table 7: Overview of clinical trials

Protocol #	Type of trial	Trial Design	Subject Population / # of sites	Test products/dosage regimen	Subjects in group: randomized/completed	Diagnosis / treatment duration
225678-0009	RIPT Sensitization	Phase 1 single-center, evaluator-blinded, within subject comparison	between 18 and 65 1 US	1. Aczone®gel, 7.5% 2. vehicle 3 x weekly, for 21 days	Subset I 40/32 Subset 2 197/170 Total: 237/202	Healthy subjects ~ 6 weeks
225678-10	Phototoxicity	Phase 1 single-center, double-blinded, within subject comparison	between 18 and 65 1 US	1. Aczone®gel, 7.5% 2. vehicle One day	Total: 33/30	Healthy subjects One day
225678-11	Photoallergy	Phase 1 single-center, double-blinded, controlled, randomized, within subject comparison	between 18 and 65 1 US	1. Aczone®gel, 7.5% 2. vehicle 2 x weekly, for 21 days	Total:58/49	Healthy subjects ~ 6 weeks

Cross Discipline Team Leader Review
NDA 207154
ACZONE (dapsone) Gel, 7.5%

Protocol #	Type of trial	Trial Design	Subject Population / # of sites	Test products/dosage regimen	Subjects in group: randomized/completed	Diagnosis / treatment duration
225678-004	PK	Phase 1, multicenter, randomized, investigator-blinded, active-controlled, multiple-dose, parallel-group study	Age 16 to 35 2 US	1. dapsone 7.5% gel (11080X) *ACZONE 2. dapsone 7.5% gel (11078X) 3. dapsone 7.5% gel (11079X) Once daily 4. ACZONE 5% gel Twice daily	Total: 77/72	Moderate acne vulgaris, 3 on GAAS 28 days
225678-006	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 105: 96 US, 9 Canada	1. Aczone 7.5 % gel 2. Vehicle Once daily	1044/948 1058/976 Total: 2102/1924	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks
225678-007	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 103: 93 US, 10 Canada	1. Aczone 7.5 % gel 2. Vehicle Once daily	1118/1026 1120/1027 Total: 2238/2053	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks

Source: Applicant's NDA, from Module 5, adapted from 5.2 Tabular Listing of all Clinical Studies and from 5.3.5.4 Clinical Study Reports 225678-009, 225678-10, 225678-11; 5.3.3.2 225678-004; and 5.3.5.1 225678-006, 225678-007.

Trials 006 and 007 (the pooled safety database) were multicenter, randomized, prospective, vehicle-controlled, and parallel group trials in subjects 12 years of age and older with moderate acne vulgaris on the face (GAAS ≥ 3 , 20-50 inflammatory lesions and 30-100 non-inflammatory lesions). Subjects were to have applied study product to the entire face once daily for 12 weeks. Acne affected areas of the neck, upper chest, upper back, and shoulders could also be treated. The pooled safety database includes 4336 subjects exposed to study drugs; 2161 to ACZONE Gel, 7.5% and 2175 to Vehicle. The mean age for the ACZONE Gel group was 20.3 years and 20.2 years for the Vehicle group. Adolescents (ages 12 to 17 years) comprised 49.3 % of those in the ACZONE Gel group and 49.8 % of those in the Vehicle group. The median total dose used was 41.43 grams in the ACZONE Gel, 7.5% group and 42.27 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 each trial. 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.

There were no deaths reported, and no serious adverse events (SAE) attributable to ACZONE (dapsone) Gel, 7.5%.

Overall, frequencies of treatment emergent adverse events (TEAEs) were similar between ACZONE Gel group (18.3%; 396/2161) and Vehicle group (18.8%; 409/2175). An overview of the TEAEs reported during both trials is presented in the Table 8.

Table 8: Overview of Adverse Events Reported

Subjects With:	Trial 006		Trial 007		Pooled Trials	
	ACZONE (N=1044)	Vehicle (N=1057)	ACZONE (N=1117)	Vehicle (N=1118)	ACZONE (N=2161)	Vehicle (N=2175)
Any Treatment-Emergent AEs	199 (19%)	218 (21%)	197 (18%)	191 (17%)	396 (18%)	409 (19%)
Any Drug-Related ⁽¹⁾ AEs	30 (3%)	35 (3%)	45 (4%)	38 (3%)	75 (3%)	73 (3%)
Any Serious AEs	3 (<1%)	5 (<1%)	4 (<1%)	4 (<1%)	7 (<1%)	9 (<1%)
Any Treatment-Emergent AEs Leading to Discontinuation	4 (<1%)	5 (<1%)	2 (<1%)	2 (<1%)	6 (<1%)	7 (<1%)

Source: pg. 117 of Study Report for Trial 006 and pg. 114 of Study Report for Trial 007.

(1) Assessed by investigator as possibly drug-related.

The treatment emergent adverse events (TEAEs) resulting in subject discontinuation in the ACZONE Gel treatment arm (0.3%; 6/2161) were acute myeloid leukemia (42 days after treatment), application site papules and application site discoloration (8 days after treatment), (application site acne and application site dermatitis (8 days after treatment), erythematous rash and pruritic rash (26 days after treatment); application site vesicles, application site swelling, application site pruritus, and pruritus (2, 1, 2, and 2 days after treatment, respectively), and application site discomfort (1 day after treatment). Seven TEAE that occurred in 3 subjects were considered to be treatment related by the investigator. These events included application site acne and application site dermatitis in 1 subject; application site vesicles, application site swelling, application site pruritus, and pruritus in 1 subject; and application site discomfort (described as mild in severity) in 1 subject.

In the Vehicle treatment arm, seven subjects (0.3%; 7/2175) had TEAEs which led to discontinuation. The events were: application site acne (2 days after treatment); application site pain in two subjects (both 1 day after treatment); urinary tract infection (59 days after treatment); contact dermatitis (38 days after treatment); anxiety (36 days after treatment); and headache (2 days after treatment). Three TEAEs that occurred in 3 subjects were considered to be treatment related by the investigator. These events included application site pain (described as mild in severity) in 2 subjects and application site acne (described as severe) in 1 subject.

The frequency of application site TEAEs was similar between ACZONE 7.5%-treated and vehicle-treated subjects. The most common application site TEAEs (i.e., those occurring in $\geq 1\%$ 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 (ARs), 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 ARs (i.e., those occurring in $\geq 0.9\%$ of subjects and at a rate greater than vehicle) were application site events: 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%).

The applicant conducted 3 dermal safety trials in population of healthy subjects to evaluate the cumulative skin irritation and sensitization (Trial 225678-009), phototoxicity (Trial 225678-010) and photoallergenicity (Trial 225678-011) potential of ACZONE Gel, 7.5%. Under the conditions of those trials, ACZONE (dapsone) Gel, 7.5% and its vehicle did not show potential for sensitization and are unlikely to cause clinically meaningful irritation under normal use conditions. Additionally, ACZONE Gel, 7.5% and its vehicle did not show potential for phototoxicity and photoallergy.

Important safety issues with consideration to related drugs:

Approved labeling for topical dapsone, ACZONE (dapsone) Gel, 5%, includes the following, Section 5 WARNINGS and PRECAUTIONS Section (July 9, 2015):

5.1 Methemoglobinemia

5.2 Hematologic Effects

5.3 Peripheral Neuropathy

5.4 Skin (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria).

The proposed labeling for ACZONE Gel, 7.5% is similar to current approved labeling for ACZONE Gel, 5%.

The reader is referred to the clinical review by Dr. Patricia C. Brown, MD for comprehensive discussion of the safety database (January 21, 2016)

No postmarketing commitments or requirements to address safety concerns (outside of PREA) are warranted. (See Section 10 of this review)

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. Dapsone is not a new molecular entity and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

In the support of current submission, the applicant conducted Phase 3 trials in subjects 12 years of age and older with acne vulgaris. Although, prior to this NDA submission, Division agreed with the proposed iPSP, review of the literature indicates that acne vulgaris is increasing in prevalence in younger children. Its development is strongly linked to the onset of puberty¹. A total of 10% of US girls are menstruating by 11 years of age². The age of pubertal onset has been falling for boys and girls over the past several decades³. According to the National Ambulatory Medical Care Survey, between 1993 and 2009 there were a total of 55 million estimated visits for patients age 18 years and younger with a diagnosis of acne, of these, 4.8% or 2.6 million were for preadolescent acne, ages 7 to 11 years¹. The above information suggests that there are sufficient numbers of patients with acne in the age group less than 12 years and therefore, the applicant should study the safety and treatment effect of their product for the treatment of acne vulgaris in children 9 years to 12 years of age as a postmarketing requirement.

This application was presented to the Pediatric Review Committee (PeRC) on December 2, 2015. The PeRC concurred with the Division's recommendation to grant a partial waiver for ages 0 to 9 years (because necessary studies are impossible or highly impractical) and deferral of pediatric study for patients 9 years to 11 years 11 months. Therefore, to fulfill the requirements of PREA, the applicant will need 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. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions

References:

¹Davis S A, et al. 2013. Treatment of Preadolescent Acne in the United States: An Analysis of Nationally Representative Data. *Pediatric Dermatology*. 30 (6): 680-694.

²Chumlea W C, et al. 2003. Age at Menarche and racial Comparisons in US Girls. *Pediatrics*. 111(1):110-113.

³Goldberg J L, et al. 2011. Changing Age of Acne Vulgaris Visits: Another Sign of Earlier Puberty? *Pediatric Dermatology*. 28 (6):645-648.

11. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk, reviewed the proposed proprietary name, ACZONE, and concluded that it is conditionally acceptable. This was communicated to the applicant in a letter dated July 7, 2015.

A total of four investigator sites were inspected in support of this NDA. No deficiencies were found that would preclude reliance upon the data that was submitted. The reader is referred to the Clinical Inspection Summary by Roy Blay, Ph.D.; Good Clinical Practice Assessment Branch; Division of Clinical Compliance Evaluation; Office of Scientific Investigations; dated January 13, 2016.

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review.

Significant changes incorporated into revised draft labeling, following labeling review, include:

- Revision to the applicant's proposed Section 7 DRUG INTERACTION (Clinical Pharmacology recommendation regarding labeling: see section 5 of this review)
- Revision to the applicant's proposed Section 12 CLINICAL PHARMACOLOGY (Clinical Pharmacology recommendation regarding labeling: see section 5 of this review)
- Revision to the applicant's proposed Section 14 CLINICAL STUDIES

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 207154, ACZONE (dapsone) Gel, 7.5% pending agreement of the applicant with the recommended labeling revisions.

Risk Benefit Assessment

- The risk-benefit assessment supports approval of this product for the treatment of acne vulgaris

Recommendation for Postmarketing Risk Evaluation and Management Strategies

- Postmarketing risk management beyond professional labeling, prescription status and routine pharmacovigilance is not needed.

Recommendation for other Postmarketing Requirements and Commitments

- To fulfill the requirements of PREA, the applicant will need 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. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	<u>06/30/2016</u>
Study/Trial Completion:	<u>03/31/2019</u>
Final Report Submission:	<u>11/30/2019</u>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GORDANA DIGLISIC

03/10/2016

The original review (dated 1/27/16) had error on p 22. This is a corrected version.

Cross-Discipline Team Leader Review

Date	January 27, 2016
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	207154
Applicant	Allergan, Inc.
Date of Submission	Letter date: April 28, 2015 CDER stamp date: April 28, 2015
PDUFA Goal Date	February 28, 2016
Proprietary Name / Established (USAN) names	ACZONE/ (dapsone)
Dosage forms / Strength	Gel / 7.5%
Proposed Indication(s)	Topical treatment of acne vulgaris in patients 12 years of age and older
Recommended:	<i>Approval</i>

1. Introduction

ACZONE (dapsone) Gel, 7.5% is a topical drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the treatment of acne vulgaris in patients 12 years of age and older. This application is for a new strength and dosing regimen of dapsone. The proposed dosing regimen is once daily.

The active ingredient, dapsone, is synthetic sulfone which is currently marketed in the United States (US) in various topical dosage forms (tablets, gel) and is available since 1955. Dapsone Tablets for oral use (25 mg and 100 mg) is indicated for the treatment of dermatitis herpetiformis and leprosy. The topical dosage form of dapsone, ACZONE (dapsone) Gel, 5% was approved on July 7, 2005, for the treatment of acne vulgaris in patients 12 years of age and older (NDA 021794; Allergan, Inc.). The approved dosing regimen is twice daily.

This NDA, NDA 207154, and NDA 21794 were developed under IND 54,440. NDA 207154 includes letters from Allergan that authorize reference to data associated with NDA 21794 and IND 54,440.

This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

ACZONE (dapsone) Gel, 7.5% was developed under IND 054440. During development program, the applicant interacted with the Agency at two milestone meetings [End of Phase 2 Meeting (August 28, 2013) and Pre-NDA Meeting (November 19, 2014)].

At the EOP2 Meeting, the following key points were discussed:

- The Division did not agree with the applicant's (b) (4). The Division stated that (b) (4) should be assessed because the proposed dapsone gel, 7.5% differs from the approved product, ACZONE Gel, 5%, in both concentration of the active ingredient as well as the excipients in the formulation.
- The applicant's rationale (based on low plasma concentration, historical clinical use and relative bioavailability data to ACZONE Gel, 5%) seemed reasonable to support a waiver to conduct a thorough QT/QTc study for dapsone gel, 7.5%.
- For assessing efficacy for acne indication, the co-primary endpoints regarding the lesion counts recommended by the Division are the absolute change in inflammatory and non-inflammatory lesion counts from baseline. Facial counts should include lesions on the nose.
- The proposed secondary efficacy endpoints of percentage change in inflammatory and noninflammatory lesion counts from baseline to week 12 are acceptable.
- The Agency also provided comments regarding the handling missing data [e.g. recommended a more scientifically sound approach, such as multiple imputation or modeling approach, instead of the last observation carried forward (LOCF) approach].

A Pre-NDA, the following key points of discussion were:

- The applicant proposed to integrate the two pivotal Phase 3 trials for the ISS and ISE. The applicant stated that the four Phase 1 trials (three dermal tolerability studies and one PK study) will not be part of the integrated analysis because the design, treatment exposures, and objectives of those trials were different than the Phase 3 trials. The Agency stated that the proposed approach for the ISS and ISE appeared reasonable.
- In July of 2014, the applicant became aware of a site-specific issue concerning the Phase 3 trial, Clinical Study 225678-006, and Principal Investigator Dr. Ellen Marmur (Site 16078, located at Marmur Medical in New York City, New York). Allergan investigated the issue, which culminated in an on-site assessment 11-12 September 2014, and confirmed the existence of Good Clinical Practice (GCP) compliance issues in the areas of Protocol Adherence and Clinical Study Management. Due to concerns over the overall data integrity for Dr. Marmur's site, Allergan has made the decision to exclude all subjects randomized at the site (51 patients) from the Intent-to-Treat (ITT) analysis. All subjects seen at Dr. Marmur's site will be included in the safety analysis for the NDA.
Given the potential seriousness of the violations described, data from this investigative site should not be included in the primary efficacy analysis. In addition, the Agency

recommended that the statistical analysis should follow the randomization; therefore, as the randomization was stratified by gender and center, the Agency recommended the applicant conduct the analyses stratified by both factors with and without pooling. Line listings should be provided for any safety data collected at this site, but should not be included in analyses.

- The Agency agreed with the applicant proposal of using the gatekeeping approach without the Hochberg's Step-up method when controlling for multiplicity after the applicant clarified that the testing would be done sequentially for total lesion counts followed by inflammatory and non-inflammatory lesion counts before testing the next secondary endpoints.

During the development program, the applicant submitted an Initial Pediatric Study Plan (iPSP) on October 17, 2013 requesting a partial waiver of the requirement to perform pediatric studies in patients from birth to (b) (4) of age for the indication of acne vulgaris. The applicant stated that the reason for waiving pediatric studies is that "necessary studies are impossible or highly impractical (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed) (Section 505B(a)(4)(B)(i) of the Act)". The Division issued an Advice Letter confirming agreement with the initial agreed PSP on March 24, 2014.

3. CMC/Device

Drug substance:

ACZONE (dapsone) Gel, 7.5% contains dapsone as the active ingredient. The drug substance, dapsone is chemically produced. The chemical name of dapsone is: 4-[(4-aminobenzene)sulfonyl]aniline. Dapsone is a white or slightly yellow-white, crystalline powder that has an empirical formula of $C_{12}H_{12}N_2O_2S$ and a molecular weight of 248.30. Dapsone melts in the temperature range of 175 – 181°C and it is very slightly soluble in water, freely soluble in acetone, sparingly soluble in alcohol, and dissolves freely in dilute mineral acids. Detailed CMC information for dapsone is referred to DMF (b) (4). The DMF has been reviewed by CMC reviewer and found adequate in supporting the use of the drug substance in the NDA. (Review by Martin T. Haber, PhD.; Branch II; Division of New Drug API/ONDP; dated December, 18, 2015)

Drug product:

ACZONE (dapsone) Gel, 7.5%, is off-white to yellow gel with suspended dapsone particles. Each gram of ACZONE (dapsone) 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 composition of ACZONE (dapsone) Gel, 7.5% is described in the following table:

Table 1: Composition of ACZONE (dapson) Gel, 7.5%

Component	Function	Quality Standard	Concentration (% w/w)
Dapsone	Drug substance	USP	7.5
DGME	(b) (4)	NF	(b) (4)
(b) (4)		Non-compendial	
MP		NF	
Purified Water		USP	

There are no novel excipients used in the drug product formulation. There is no overage of the API. All excipients are compendial except the (b) (4). The CMC information is provided in DMF (b) (4). The DMF (b) (4) was reviewed on 12/14/2015 and found to be adequate.

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification.

Container Closure System:

ACZONE (dapson) Gel, 7.5%, is packaged in a non-metered airless pump container closure system. The (b) (4) airless pump container system consists of polypropylene bottle with a high density polyethylene piston. (b) (4)

The drug product is supplied in 30 (b) (4), 60 (b) (4) and 90 (b) (4) size bottles containing the same pump (b) (4)

The details on this container closure system are provided in DMF (b) (4). A letter of authorization for this DMF was provided. The product will be available in three different sizes (30 gram, 60 gram, and 90 gram). Additionally, 3 gram professional samples packaged in an (b) (4) are also available.

The extractable and leachable study demonstrated that there is virtually no risk of leachables from the airless pump system. The container closure system is adequate (b) (4). The expiration dating period of 24 months is recommended for the drug product when stored at controlled room temperature based on the 12-month long-term and 6-month accelerated stability data obtained from 3 registration batches of the drug product.

Special Product Quality Labeling Recommendations: Protect from freezing.

The CMC reviewer concluded that the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

The facility review team from the Office of Process and Facility has issued an “Approval” recommendation for the facilities involved in this application.

The reader is referred to the comprehensive reviews by Hitesh Shroff, Ph.D.; Branch V; Division of New Drug Products II/ONDP/OPQ dated December 18, 2015; Yuesheng Ye, Ph.D.; Branch VIII; Division of Process Assessment III/OPF; Sherry (Xiaohui) Shen, CSO; Branch III; Division of Inspection Assessment/OPF, dated January 4, 2016; Vidula Kolhatkar, Ph.D., Branch II, Division of Biopharmaceutics/ONDP dated January 5, 2016; and Elizabeth Berr, PhD. Branch I, Division of Microbiology Assessment/OPF dated January 5, 2016;

Label/Labeling recommendation:

Immediate container labels:

The 30 g, 60 g and 90 g pump labels should be revised to include the following information:

- Display “Lot:” and “Exp:”
- Display a barcode
- Add the following statement in the storage condition description
“[See USP Controlled Room Temperature]”
- List ingredients as shown below:
“Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water.”

The 3 g sample tube labels should be revised to include the following information:

- Display “Lot:” and “Exp:”
- Add the following statement in the storage condition description
“[See USP Controlled Room Temperature]”
- Include “Manufactured for: and by:” same as pump labels.

Carton labels:

The 8 x 3 g sample tubes, 30 g, 60 g and 90 g carton labels should be revised to include the following information:

- Add the following statement in the storage condition description
“[See USP Controlled Room Temperature]”
- List ingredients as shown below:
“Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water.”

The 8 x 3 g sample tube carton labels should be revised to include the following information:

- Display “Lot:” and “Exp:”

Physician Insert

“Highlights” Section

This section should be revised as follows:

- Display the drug product title as shown below:
ACZONE (dapsone) gel, for topical use
- Delete the following statement:
“Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel”

3 “Dosage Forms and Strength” Section

This section should be revised as follows:

- Revise the dosage form description as shown below:
“Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel with suspended particles.”

11 “Description”

This section should be revised as follows:

- Revise the drug product title as shown below:
ACZONE (dapsone) gel, 7.5%
- Replace the chemical name with the following IUPAC name:
4-[(4-aminobenzene)sulfonyl] aniline
- The molecular weight of dapsone should be revised to “248.30”

16 “How supplied/storage and handling”

This section should be revised as follows:

- The following drug product and container closure description should be added.
“ACZONE gel is an off-white to yellow gel with suspended particles It is supplied in airless pumps containing polypropylene bottles with high density polyethylene pistons.”
- The following statement should be added to the storage condition
“[See USP Controlled Room Temperature]”

4. Nonclinical Pharmacology/Toxicology

Dapsone has been evaluated in a battery of nonclinical studies that included evaluation of pharmacology, pharmacokinetics, pharmacodynamics, safety pharmacology, single and repeated-dose general toxicity (involving both oral and topical dermal administration), genetic toxicology, reproductive toxicology (assessment of potential to impact fertility/reproductive success of male and female rodents, developmental toxicity of rats and rabbits, and prenatal and postnatal development, including maternal function, of rodents), carcinogenicity, and special toxicology issues. These studies have been reviewed under NDA 21794 (refer to the

CDER nonclinical reviews of NDA 21794 and IND 54440 for summary and interpretation of the nonclinical data). This application includes letters from Allergan that authorize reference to data associated with NDA 21794 and IND 54440.

In addition, the Study “AGN-225678: 3-Month Dermal Toxicity Study in Rats” (study No. 20053240) was conducted to assess ACZONE® (dapsone) Gel, 7.5% for potential to induce toxicity when topically applied to the skin of rats.

The pharmacology-toxicology reviewer, Norman A See, Ph.D. summarized the pivotal data reviewed under NDA 21794:

General toxicology:

Substantial toxicity was not observed in chronic toxicology studies in which dapsone topical gel was dermally applied. No adverse effects were observed in female rats treated daily for six months, although the mean RBC, HGB, and HCT values of male dapsone-treated animals were slightly, but significantly, reduced, and the mean weight of the spleen was significantly increased, in male rats that received dapsone gel. No effects were observed in male or female rabbits treated topically for nine months.

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; 3 mg/kg/day was an apparent no-adverse-effect-level (NOAEL) in that study.

Genetic toxicology:

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.

Carcinogenicity:

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 exec-CAC to be acceptable. No evidence of carcinogenicity was obtained in either study.

Reproductive toxicology:

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. Statistically significant reductions in percentage of motile sperm were observed at exposures of 3 mg/kg/day and above. The mean numbers of embryo implantations and viable embryos were significantly reduced in untreated females mated with males that had

been dosed at 12 mg/kg/day or greater, presumably due to reduced numbers or effectiveness of sperm, indicating impairment of fertility. 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.

When administered at a dosage of 150 mg/kg/day to rabbits on days 6-18 of gestation, dapsone significantly increased the incidence of early resorptions. Two does at this dosage delivered prematurely and seven does resorbed all fetuses. 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 30 mg/kg/day.

Little toxicity was observed in a two-generation study in which F0 females were administered the test articles daily from gestation day 7 through day 27 postpartum at exposures of 3, 12, and 30 mg/kg/day dapsone. The mean number of stillborn pups per litter was slightly, but statistically significantly, higher in high-dose dapsone litters than in control litters. No effects were observed on pup viability, physical development, behavior, learning ability, or reproduction.

Special toxicology:

Dapsone topical gel is not an irritant of skin or eyes, is not phototoxic, and is nonsensitizing.

Per pharmacology-toxicology reviewer, key findings from the Study AGN-225678 (3-Month Dermal Toxicity Study in Rats) are summarized:

Formulations containing dapsone at concentrations ranging from 3.75% to 15% w/w were topically applied to rats once daily for approximately 92 days (1 or 2 mL/kg per application). In addition, a group of rats received a formulation that contained both dapsone and (b) (4). No treatment-related deaths occurred, and no dermal irritation at the treatment site was observed. Exposure to dapsone trended to correlate with reduced mean body weights in both genders. Erythrocytic parameters (e.g., RBC, HGB, HCT) tended to be reduced in animals exposed to dapsone, particularly males. Reticulocyte counts were increased in these animals. Methemoglobinemia was observed in treatment groups. Treatment-related effects on mean organ weight included trends (which achieved statistical significance in some instances) toward increased mean thyroid weight in males and females, increased mean splenic weight in males, and decreased mean thymus weight in females. The primary microscopic

lesions appeared to be related to increased erythrocyte turnover, which was presumably secondary to dapsone-induced oxidative damage to erythrocytes. Those changes included increased hematopoiesis/erythropoiesis in the bone marrow, spleen, and liver, increased iron in the liver, spleen and kidney, pigmentation in the kidneys, and congestion in the spleen.

Impurities/Excipients

The proposed specifications for organic impurities of the drug product are acceptable; no specified or individual unspecified dapsone-related impurities of the drug product exceed the qualification limit under the ICH Q3B document (the qualification threshold for degradation products that are associated with dapsone under NDA 207154 is 0.2% of the label strength of the API). The product contains no novel excipients.

The reader is referred to the comprehensive review by Norman A See, Ph.D. dated November 12, 2015.

There are no outstanding pharmacology-toxicology issues.

The pharmacology-toxicology reviewer, Norman A See, Ph.D., recommended *Approval* of this application (review dated November 12, 2015).

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted one pharmacokinetic (PK) trial, Study 225678-004, to compare the PK of ACZONE (dapsone) Gel, 7.5% (formulation 11080X, to-be-marketed formulation) applied once-daily (QD) for 28 days with ACZONE (dapsone) Gel, 5% applied twice-daily (BID) for 28 days in subjects (≥ 16 years of age) with moderate acne vulgaris (score of 3 on GAAS). For each application, study product (2 grams) was topically applied (by study staff) to the face, upper chest, upper back, and shoulders corresponding to a treatment area of approximately 1000 cm².

Plasma concentrations of dapsone, its metabolites N-acetyl dapsone (NAD) and dapsone hydroxylamine (DHA), and N-formyl dapsone (NFD) were collected prior to administration of the morning dose on days 1, 7, 14, 18, 21, 26, 27, on day 28 (pre-dose, 1, 2, 4, 6, 8, 10, and 12 hours post-dose), on days 29 to 32 (24, 30, 36, 48, 72, and 96 hours after the last dose), on day 35 (168 hours after the last dose), and early exit (if applicable), and were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Mean C_{troughs} 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 2.

Table 2: Summary of plasma dapsone PK parameters following dosing on Day 28

PK parameter	Dapsone Gel, 7.5% QD (TBM formulation 11080X) N=19	ACZONE Gel, 5% BID N=18
C _{max} (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

Source_Clinical Pharmacology Review (p.7, Table 3)

The Clinical Pharmacology reviewer concluded the following:

“Relative to Aczone Gel, 5%, daily systemic exposure of dapsone, defined by the geometric mean ratio for maximum plasma concentration (C_{max}) 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 C_{max} and AUC0-24, these differences were statistically significant; however, the upper limit of 90% CI were close to 100% (93% for C_{max} and 92% for AUC0-24) and therefore the statistically significantly lower systemic exposure may not be clinically meaningful.”

Trial 225678-004 included pediatric subjects ≥16 years of age (7/19 in ACZONE Gel, 7.5% group and 6 /18 in ACZONE Gel, 5% group). The data showed similar systemic exposure to dapsone and its metabolites DHA and NAD between subjects 16 to <18 years of age and those ≥18 years of age. In addition, because systemic exposure of dapsone in patients 12 – 15 years of age is similar to those 16 years and older (per ACZONE Gel, 5% labeling), additional PK trial in subjects ages 12 -15 years was not requested for ACZONE Gel, 7.5%.

Long-term safety study was not conducted with ACZONE Gel, 7.5%. However, in a long-term safety study of ACZONE Gel, 5%, periodic blood samples were collected up to 12 months to determine systemic exposure of dapsone and its metabolites. Based on the measurable dapsone concentrations from 408 subjects, neither gender nor race appeared to affect the pharmacokinetics of dapsone. Exposure to dapsone were approximately the same between the 12-15 years (N=155) and >16 years (N=253) age groups. Additionally, there was no evidence of increasing systemic exposure to dapsone over the time.

Clinical Pharmacology Team Labeling Recommendations:

The following changes are recommended for sections 5, 7 and 12 of the label. Deletions are noted as ~~strike through~~ and additions are noted as double underline.

5 WARNINGS AND PRECAUTIONS

5.1 Hema (b) (4)

Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia.

Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to

hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.

In clinical studies, there was no evidence of clinically relevant hemolysis or hemolytic anemia in patients treated with topical dapson. Some patients with G6PD deficiency using twice daily dapson gel, 5%, developed laboratory changes suggestive of mild hemolysis.

(b) (4)

Combination of topical dapson with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

(b) (4)

If signs and symptoms suggestive of hemolytic anemia (b) (4) occur,

(b) (4)

ACZONE[®] Gel, 7.5% (b) (4) in patients who are taking oral dapson or antimalarial medications because of the potential for (b) (4) hemolytic reactions.

7 DRUG INTERACTIONS

(b) (4)

No formal drug-drug interaction studies were conducted with **ACZONE**[®] Gel, 7.5%.

7.1 Trimethoprim-Sulfamethoxazole

A drug-drug interaction study evaluated the effect of the use of dapson gel, 5% 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 dapson and its metabolites increased in the presence of TMP/SMX. The systemic exposure from **ACZONE**[®] Gel, 7.5% is expected to be about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

7.2 Topical Benzoyl Peroxide

Topical application of dapson gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discoloration of the skin and facial hair.

7.3 Drug Interactions with Oral Dapson

Certain concomitant medications (such as rifampin, anticonvulsants, St. John's wort) may increase the formation of dapsone hydroxylamine, a metabolite of dapsone associated with hemolysis. With oral dapsone treatment, folic acid antagonists such as pyrimethamine have been noted to possibly increase the likelihood of hematologic reactions.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)
The mechanism of action of dapsone gel in treating acne vulgaris is not known.

12.3 Pharmacokinetics

In a pharmacokinetic study, male and female subjects 16 years of age or older with acne vulgaris (N=19) (b) (4) received 2 grams of ACZONE Gel, 7.5%, topically to the (b) (4) face, upper chest, upper back and shoulders once daily for 28 day (b) (4)

steady state for dapsone was reached within 7 days of dosing (b) (4). On Day 28, the mean dapsone maximum plasma concentration (C_{max}) and area under the concentration-time curve from 0-24 hours post dose (AUC_{0-24h}) were 13.0 ± 6.8 ng/mL and (b) (4) 282 ± 146 ng·h/mL, respectively (b) (4)

(b) (4) The systemic exposure from ACZONE® Gel, 7.5% is expected to be about 1% of that from a 100 mg oral dose.

The applicant proposed to omit section 7.3 and 7.4 of ACZONE Gel, 5% labeling regarding concomitant use with drugs that induce methemoglobinemia. As per clinical pharmacology reviewer, based on the 90% CIs for C_{max} and AUC₀₋₂₄, these differences were statistically significant; however, the upper limit of 90% CI were close to 100% (93% for C_{max} and 92% for AUC₀₋₂₄). The statistically significantly lower systemic exposure may therefore not be clinically meaningful and a caution regarding concomitant use of drugs that induce methemoglobinemia that is pertinent for ACZONE Gel, 5% is also understood to be pertinent for ACZONE Gel, 7.5%. Therefore, information from Section 7.3 and Section 7.4 for ACZONE Gel, 5% labeling will be included into the labeling for ACZONE Gel, 7.5%.

7.4 Concomitant Use with Drugs that Induce Methemoglobinemia

Concomitant use of ACZONE® Gel, 7.5% with drugs that induce methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine,

para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine may increase the risk for developing methemoglobinemia [see Warnings and Precautions (5.1)].

The reader is referred to the comprehensive review by Doanh C Tran, PhD. for a full discussion of the clinical pharmacology data (dated January 11, 2016).

The clinical pharmacology reviewer, Doanh C Tran, PhD., Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3, recommended *Approval* of this application pending agreement on recommended labeling changes.

The following post marketing requirement (PMR) 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.

6. Clinical Microbiology

The applicant did not conduct microbiologic studies.

7. Clinical/Statistical- Efficacy

The applicant submitted data from pivotal trials, 225678-006 (Trial 006) and 225678-007 (Trial 007), to establish the effectiveness of their product, ACZONE (dapsone) Gel, 7.5%, applied once daily for 12 weeks in the treatment of acne vulgaris.

The Trial 006 and Trial 007 were identically-designed, double-blind, randomized, multicenter, vehicle- controlled, parallel-group, Phase 3 trials. The population enrolled was subjects 12 years of age or older with moderate acne vulgaris defined as score of 3 (moderate) on a Global Acne Assessment Score (GAAS) scale, 20-50 inflammatory lesions (papules and pustules) and 30-100 non-inflammatory lesions (open comedones and closed comedones) on the face. Each trial was designed to enroll and randomize approximately 2180 subjects. Eligible subjects were randomized to one of the following treatment in a 1:1 ratio: ACZONE Gel, 7.5% or Vehicle Gel. Randomization was stratified by gender and center. Subjects applied study product once daily for 12 weeks. Subjects were evaluated at the following study visits: screening, baseline (Day 1) and Weeks 1, 2, 4, 8, and 12. An overview of the trials is presented in Table 3.

Table 3: Clinical Study Overview

Trial	Location	Study Population	Treatment Arms	Number of Subjects	Dates
006	U.S. (96 centers) & Canada (9 centers)	Aged 12 years and older, GAAS of 3 (moderate), 20 to 50 inflammatory lesions, and 30 to 100 non-inflammatory lesions	ACZONE Gel, 7.5%	1044*	11/27/2013 – 10/28/2014
			Vehicle Gel	1058*	
007	U.S. (93 centers) & Canada (10 centers)	Aged 12 years and older, GAAS of 3 (moderate), 20 to 50 inflammatory lesions, and 30 to 100 non-inflammatory lesions	ACZONE Gel, 7.5%	1118	11/27/2013 – 10/21/2014
			Vehicle Gel	1120	

*Excluding subjects from center 16078 (25 on ACZONE Gel, 7.5% and 26 on Vehicle Gel).

Source: Statistical Review (p.5, Table 2)

Trial 006 enrolled and randomized a total (excluding center 16078) of 2102 subjects (1044 to ACZONE Gel and 1058 to Vehicle) from 105 centers (96 in U.S. and 9 in Canada). Trial 007 enrolled and randomized a total of 2238 subjects (1118 to ACZONE Gel and 1120 to Vehicle) from 103 centers (93 in U.S. and 10 in Canada). The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and similar between each trial. The mean age was 20 years in the both treatment arms. The majority of the subjects were White (> 54%). Slightly more subjects were female (>55%). All subjects had baseline disease severity “moderate” (GAAS 3) with exception of one subject in Trial 006 who had a GAAS of 4 (severe). The mean inflammatory lesion count was ~ 29 and the mean non-inflammatory lesion count was ~ 47 in the both treatment arms and in the both trials.

The rate of discontinuation was slightly higher in the ACZONE Gel treatment arm (9.2%) compared to the Vehicle treatment arm (7.8%). For Trial 007, the rates of discontinuation were almost identical (8.2% v.8.3%).). The most common reason for withdrawal was ‘Lost to Follow-Up’ (ACZONE Gel treatment arm: 3.6% for Trial 006 and 4% for Trial 007; Vehicle treatment arm: 2.7% for Trial 006 and 3.6% for Trial 007).

The primary analysis population specified in the protocol was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol also specified supportive analyses using the per-protocol (PP). The PP population was defined as all randomized subjects with no protocol deviations during the trial that might potentially affect the primary efficacy analyses.

The co-primary efficacy endpoints were the proportion of subjects achieving a GAAS score of 0 (none) or 1 (minimal) at Week 12, the absolute change in inflammatory and the absolute change non-inflammatory lesion counts from baseline to Week 12.

In both trials, ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.004) to Vehicle. The results from the ITT and PP analyses were similar and are presented in Tables 4 and 5, respectively.

Table 4: Results for the Co-Primary Efficacy Endpoints at Week 12 (MI, ITT)

Endpoint	Trial 006 ⁽¹⁾			Trial 007		
	ACZONE (N=1044)	Vehicle (N=1058)	P-value	ACZONE (N=1118)	Vehicle (N=1120)	P-value
GAAS: None or Minimal*	311.9 (30%)	224.2 (21%)	<0.001 ⁽²⁾	333.3 (30%)	234.1 (21%)	<0.001 ⁽²⁾
Absolute Change in Inflammatory Lesion Counts:						
Mean*	16.1	14.3		15.6	14.0	
LS Mean ⁽³⁾	16.1	14.1	<0.001 ⁽³⁾	15.6	13.8	<0.001 ⁽³⁾
Absolute Change in Non-Inflammatory Lesion Counts:						
Mean*	20.7	18.0		20.8	18.7	
LS Mean ⁽³⁾	20.8	17.6	<0.001 ⁽³⁾	20.7	18.5	0.004 ⁽³⁾

Source: Statistical Review (p.10; Table6)

*The values displayed are the averages over the 20 imputed datasets (MI).

(1) Excluding subjects from center 16078 (a total of 51 subjects).

(2) P-value from a CMH test stratified by gender.

(3) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

Table 5: Results for the Co-Primary Efficacy Endpoints at Week 12 (PP)

Endpoint	Trial 006 ⁽¹⁾			Trial 007		
	ACZONE (N=880)	Vehicle (N=887)	P-value	ACZONE (N=950)	Vehicle (N=955)	P-value
GAAS: None or Minimal	272 (31%)	199 (22%)	<0.001 ⁽²⁾	291 (31%)	203 (21%)	<0.001 ⁽²⁾
Absolute Change in Inflammatory Lesion Counts:						
Mean	16.2	14.6		15.8	14.4	
LS Mean	16.1	14.4	<0.001 ⁽³⁾	15.8	14.2	0.001
Absolute Change in Non-Inflammatory Lesion Counts: Mean	21.1	18.2		21.4	18.9	
LS Mean	21.0	17.9	<0.001 ⁽³⁾	21.1	18.7	<0.001 ⁽³⁾

Source: Statistical Review (p.10 Table 7)

(1) Excluding subjects from center 16078 (a total of 51 subjects)

(2) P-value from a CMH test stratified by gender.

(3) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

For the secondary efficacy endpoints based on lesion counts (i.e., absolute change from baseline in total lesion counts and percent change in lesions counts (inflammatory, non-inflammatory, and total), ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.001) to Vehicle in both trials.

Table 6: Results for the Secondary Efficacy Endpoints at Week 12 (MI⁽¹⁾, LOCF⁽²⁾, ITT)

Endpoint	Trial 006 ⁽³⁾			Trial 007		
	ACZONE (N=1044)	Vehicle (N=1058)	P-value	ACZONE (N=1118)	Vehicle (N=1120)	P-value
Absolute Change in Total Lesion Counts: Mean* LS Mean ⁽⁴⁾	36.9 36.9	32.3 31.7	<0.001 ⁽⁴⁾	36.5 36.2	32.7 32.3	<0.001 ⁽⁴⁾
Percent Change in Total Lesion Counts: Mean* LS Mean ⁽⁴⁾	49.4% 48.7%	42.7% 42.4%	<0.001 ⁽⁴⁾	49.2% 48.9%	43.6% 43.2%	<0.001 ⁽⁴⁾
Percent Change in Inflammatory Lesion Counts: Mean* LS Mean ⁽⁴⁾	56.2% 55.5%	49.5% 49.0%	<0.001 ⁽⁴⁾	54.2% 53.8%	47.6% 47.3%	<0.001 ⁽⁴⁾
Percent Change in Non-Inflammatory Lesion Counts: Mean* LS Mean ⁽⁴⁾	45.0% 44.4%	38.9% 38.4%	<0.001 ⁽⁴⁾	46.2% 45.9%	40.8% 40.4%	0.001 ⁽⁴⁾

Source: Statistical Review (p.13; Table 12)

*The values displayed are the averages over the 20 imputed datasets (MI).

(1) Missing data for lesion count endpoints were imputed using multiple imputation (MI).

(2) Missing data for ASIS endpoints were imputed using last observation carried forward (LOCF). (3) Excluding subjects from center 16078 (a total of 51 subjects).

(4) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

Examination of subgroups indicated that gender and age have an impact on efficacy results with females and adults generally having better outcomes than males and adolescents; however, the treatment differences across subgroups did not vary greatly (i.e., females and adults had better results on both the ACZONE Gel and vehicle treatment arms).

Efficacy rates varied among centers. The applicant's investigation of the treatment-by-center interaction focused on the effects after pooling. As the pooling process could mask center effects, statistical reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. The removal of any one center did not affect the overall conclusions in Trial 006 (p-values ≤ 0.001) and Trial 007 (p-values ≤ 0.01). Two centers ((b) (6) and (b) (6)) in Trial 006 and three centers ((b) (6)) in Trial 007 had investigators with disclosable financial interests. The results with and without these centers were very similar, and these centers did not affect the overall conclusion (refer to statistical review, Table 23).

In summary, the applicant has established the efficacy of their product, ACZONE (dapsone) Gel, 7.5%, in the treatment of acne vulgaris in patients 12 years of age and older.

The reader is referred to the comprehensive statistical review and evaluation by Matthew W Guerra, Ph.D. (Division of Biostatistics III) for a more complete discussion of the efficacy results (dated January 14, 2016).

8. Safety

The applicant submitted data from two pivotal trials, 225678-006 (Trial 006) and 225678-007 (Trial 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 Trial 225678-004 (pharmacokinetic; 4-arm, active controlled) and dermal safety studies [(Trial 225678-009; RIPT sensitization), Trial 225678-010 (phototoxicity), and Trial 225678-011 (photoallergy)]. All of the trials were conducted with the final-to-be-marketed formulation. The trials are summarized in Table below:

Table 7: Overview of clinical trials

Protocol #	Type of trial	Trial Design	Subject Population / # of sites	Test products/dosage regimen	Subjects in group: randomized/completed	Diagnosis / treatment duration
225678-0009	RIPT Sensitization	Phase 1 single-center, evaluator-blinded, within subject comparison	between 18 and 65 1 US	1. Aczone®gel, 7.5% 2. vehicle 3 x weekly, for 21 days	Subset I 40/32 Subset 2 197/170 Total: 237/202	Healthy subjects ~ 6 weeks
225678-10	Phototoxicity	Phase 1 single-center, double-blinded, within subject comparison	between 18 and 65 1 US	1. Aczone®gel, 7.5% 2. vehicle One day	Total: 33/30	Healthy subjects One day
225678-11	Photoallergy	Phase 1 single-center, double-blinded, controlled, randomized, within subject comparison	between 18 and 65 1 US	1. Aczone®gel, 7.5% 2. vehicle 2 x weekly, for 21 days	Total:58/49	Healthy subjects ~ 6 weeks

Cross Discipline Team Leader Review
NDA 207154
ACZONE (dapson) Gel, 7.5%

Protocol #	Type of trial	Trial Design	Subject Population / # of sites	Test products/dosage regimen	Subjects in group: randomized/completed	Diagnosis / treatment duration
225678-004	PK	Phase 1, multicenter, randomized, investigator-blinded, active-controlled, multiple-dose, parallel-group study	Age 16 to 35 2 US	1. dapson 7.5% gel (11080X) *ACZONE 2. dapson 7.5% gel (11078X) 3. dapson 7.5% gel (11079X) Once daily 4. ACZONE 5% gel Twice daily	Total: 77/72	Moderate acne vulgaris, 3 on GAAS 28 days
225678-006	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 105: 96 US, 9 Canada	1. Aczone 7.5 % gel 2. Vehicle Once daily	1044/948 1058/976 Total: 2102/1924	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks
225678-007	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 103: 93 US, 10 Canada	1. Aczone 7.5 % gel 2. Vehicle Once daily	1118/1026 1120/1027 Total: 2238/2053	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks

Source: Applicant's NDA, from Module 5, adapted from 5.2 Tabular Listing of all Clinical Studies and from 5.3.5.4 Clinical Study Reports 225678-009, 225678-10, 225678-11; 5.3.3.2 225678-004; and 5.3.5.1 225678-006, 225678-007.

Trials 006 and 007 (the pooled safety database) were multicenter, randomized, prospective, vehicle-controlled, and parallel group trials in subjects 12 years of age and older with moderate acne vulgaris on the face (GAAS ≥ 3 , 20-50 inflammatory lesions and 30-100 non-inflammatory lesions). Subjects were to have applied study product to the entire face once daily for 12 weeks. Acne affected areas of the neck, upper chest, upper back, and shoulders could also be treated. The pooled safety database includes 4336 subjects exposed to study drugs; 2161 to ACZONE Gel, 7.5% and 2175 to Vehicle. The mean age for the ACZONE Gel group was 20.3 years and 20.2 years for the Vehicle group. Adolescents (ages 12 to 17 years) comprised 49.3 % of those in the ACZONE Gel group and 49.8 % of those in the Vehicle group. The median total dose used was 41.43 grams in the ACZONE Gel, 7.5% group and 42.27 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 each trial. 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.

There were no deaths reported, and no serious adverse events (SAE) attributable to ACZONE (dapsone) Gel, 7.5%.

Overall, frequencies of treatment emergent adverse events (TEAEs) were similar between ACZONE Gel group (18.3%; 396/2161) and Vehicle group (18.8%; 409/2175). An overview of the TEAEs reported during both trials is presented in the Table 8.

Table 8: Overview of Adverse Events Reported

Subjects With:	Trial 006		Trial 007		Pooled Trials	
	ACZONE (N=1044)	Vehicle (N=1057)	ACZONE (N=1117)	Vehicle (N=1118)	ACZONE (N=2161)	Vehicle (N=2175)
Any Treatment-Emergent AEs	199 (19%)	218 (21%)	197 (18%)	191 (17%)	396 (18%)	409 (19%)
Any Drug-Related ⁽¹⁾ AEs	30 (3%)	35 (3%)	45 (4%)	38 (3%)	75 (3%)	73 (3%)
Any Serious AEs	3 (<1%)	5 (<1%)	4 (<1%)	4 (<1%)	7 (<1%)	9 (<1%)
Any Treatment-Emergent AEs Leading to Discontinuation	4 (<1%)	5 (<1%)	2 (<1%)	2 (<1%)	6 (<1%)	7 (<1%)

Source: pg. 117 of Study Report for Trial 006 and pg. 114 of Study Report for Trial 007.

(1) Assessed by investigator as possibly drug-related.

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The treatment emergent adverse events (TEAEs) resulting in subject discontinuation in the ACZONE Gel treatment arm (0.3%; 6/2161) were acute myeloid leukemia (42 days after treatment), application site papules and application site discoloration (8 days after treatment), (application site acne and application site dermatitis (8 days after treatment), erythematous rash and pruritic rash (26 days after treatment); application site vesicles, application site swelling, application site pruritus, and pruritus (2, 1, 2, and 2 days after treatment, respectively), and application site discomfort (1 day after treatment). Seven TEAE that occurred in 3 subjects were considered to be treatment related by the investigator. These events included application site acne and application site dermatitis in 1 subject; application site vesicles, application site swelling, application site pruritus, and pruritus in 1 subject; and application site discomfort (described as mild in severity) in 1 subject.

In the Vehicle treatment arm, seven subjects (0.3%; 7/2175) had TEAEs which led to discontinuation. The events were: application site acne (2 days after treatment); application site pain in two subjects (both 1 day after treatment); urinary tract infection (59 days after treatment); contact dermatitis (38 days after treatment); anxiety (36 days after treatment); and headache (2 days after treatment). Three TEAEs that occurred in 3 subjects were considered to be treatment related by the investigator. These events included application site pain (described as mild in severity) in 2 subjects and application site acne (described as severe) in 1 subject.

The frequency of application site TEAEs was similar between ACZONE 7.5%-treated and vehicle-treated subjects. The most common application site TEAEs (i.e., those occurring in $\geq 1\%$ 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 (ARs), 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 ARs (i.e., those occurring in $\geq 0.9\%$ of subjects and at a rate greater than vehicle) were application site events: 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%).

The applicant conducted 3 dermal safety trials in population of healthy subjects to evaluate the cumulative skin irritation and sensitization (Trial 225678-009), phototoxicity (Trial 225678-010) and photoallergenicity (Trial 225678-011) potential of ACZONE Gel, 7.5%. Under the conditions of those trials, ACZONE (dapsone) Gel, 7.5% and its vehicle did not show potential for sensitization and are unlikely to cause clinically meaningful irritation under normal use conditions. Additionally, ACZONE Gel, 7.5% and its vehicle did not show potential for phototoxicity and photoallergy.

Important safety issues with consideration to related drugs:

Approved labeling for topical dapsone, ACZONE (dapsone) Gel, 5%, includes the following, Section 5 WARNINGS and PRECAUTIONS Section (July 9, 2015):

5.1 Methemoglobinemia

5.2 Hematologic Effects

5.3 Peripheral Neuropathy

5.4 Skin (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria).

The proposed labeling for ACZONE Gel, 7.5% is similar to current approved labeling for ACZONE Gel, 5%.

The reader is referred to the clinical review by Dr. Patricia C. Brown, MD for comprehensive discussion of the safety database (January 21, 2016)

No postmarketing commitments or requirements to address safety concerns (outside of PREA) are warranted. (See Section 10 of this review)

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. Dapsone is not a new molecular entity and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

In the support of current submission, the applicant conducted Phase 3 trials in subjects 12 years of age and older with acne vulgaris. Although, prior to this NDA submission, Division agreed with the proposed iPSP, review of the literature indicates that acne vulgaris is increasing in prevalence in younger children. Its development is strongly linked to the onset of puberty¹. A total of 10% of US girls are menstruating by 11 years of age². The age of pubertal onset has been falling for boys and girls over the past several decades³. According to the National Ambulatory Medical Care Survey, between 1993 and 2009 there were a total of 55 million estimated visits for patients age 18 years and younger with a diagnosis of acne, of these, 4.8% or 2.6 million were for preadolescent acne, ages 7 to 11 years¹. The above information suggests that there are sufficient numbers of patients with acne in the age group less than 12 years and therefore, the applicant should study the safety and treatment effect of their product for the treatment of acne vulgaris in children 9 years to 12 years of age as a postmarketing requirement.

This application was presented to the Pediatric Review Committee (PeRC) on December 2, 2015. The PeRC concurred with the Division's recommendation to grant a partial waiver for ages 0 to 9 years (because necessary studies are impossible or highly impractical) and deferral of pediatric study for patients 9 years to 11 years 11 months. Therefore, to fulfill the requirements of PREA, the applicant will need 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. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions

References:

¹Davis S A, et al. 2013. Treatment of Preadolescent Acne in the United States: An Analysis of Nationally Representative Data. *Pediatric Dermatology*. 30 (6): 680-694.

²Chumlea W C, et al. 2003. Age at Menarche and racial Comparisons in US Girls. *Pediatrics*. 111(1):110-113.

³Goldberg J L, et al. 2011. Changing Age of Acne Vulgaris Visits: Another Sign of Earlier Puberty? *Pediatric Dermatology*. 28 (6):645-648.

11. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk, reviewed the proposed proprietary name, ACZONE, and concluded that it is conditionally acceptable. This was communicated to the applicant in a letter dated July 7, 2015.

A total of four investigator sites were inspected in support of this NDA. No deficiencies were found that would preclude reliance upon the data that was submitted. The reader is referred to the Clinical Inspection Summary by Roy Blay, Ph.D.; Good Clinical Practice Assessment Branch; Division of Clinical Compliance Evaluation; Office of Scientific Investigations; dated January 13, 2016.

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review.

Significant changes incorporated into revised draft labeling, following labeling review, include:

- Revision to the applicant's proposed Section 7 DRUG INTERACTION
(Clinical Pharmacology recommendation regarding labeling: see section 5 of this review)
- Revision to the applicant's proposed Section 12 CLINICAL PHARMACOLOGY (Clinical Pharmacology recommendation regarding labeling: see section 5 of this review)
- Revision to the applicant's proposed Section 14 CLINICAL STUDIES

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 207154, ACZONE (dapsone) Gel, 7.5% pending agreement of the applicant with the recommended labeling revisions.

Risk Benefit Assessment

- The risk-benefit assessment supports approval of this product for the treatment of

(b) (4)

Recommendation for Postmarketing Risk Evaluation and Management Strategies

- Postmarketing risk management beyond professional labeling, prescription status and routine pharmacovigilance is not needed.

Recommendation for other Postmarketing Requirements and Commitments

- To fulfill the requirements of PREA, the applicant will need 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. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	<u>06/30/2016</u>
Study/Trial Completion:	<u>03/31/2019</u>
Final Report Submission:	<u>11/30/2019</u>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GORDANA DIGLISIC
01/27/2016