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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:	*Approval*

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) (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 (dapsone) 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 (dapsone) 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.

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