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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	207154
Supporting document/s:	DSN 1
Applicant's letter date:	28-APR-2015
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Product:	ACZONE® (dapsone) Gel, 7.5%
Indication:	Topical treatment of acne vulgaris in patients 12 years of age or older.
Applicant:	Allergan, Inc.
Review Division:	DDDP
Reviewer:	Norman A. See, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Kendall Marcus, MD
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1 Executive Summary

1.1 Introduction

Topical use of dapsone in the treatment of acne vulgaris, involving twice daily application of ACZONE® (dapsone topical gel), 5%, has been found to be safe under NDA 21-794 (approved 07-JUL-2005). Under NDA 207154 the sponsor has proposed to market a 7.5% dapsone topical product (ACZONE® (dapsone topical gel), 7.5%). The conditions of use of the 7.5% product, including the volume of product applied per treatment, the maximum area treated, and the patient population, will be similar to those associated with 5% dapsone gel, with the exception that the 7.5% product will be labeled for once daily application (in comparison to two daily applications of the 5% product). The approved label of NDA 21-794, and the proposed label of 207154, discuss application of a "pea-sized" amount; a typical individual dose is estimated to approximate 2 g per application. Therefore, clinical use of ACZONE® Gel, 7.5%, typically involves application of approximately (b) (4) dapsone, while use of ACZONE® Gel, 5%, typically involves application of approximately (b) (4) dapsone.

NDA 21-794 and NDA 207154 were developed under IND 54,440. NDA 207154 includes letters from Allergan that authorize reference to data associated with NDA 21-794 and IND 54,440. I will refer to the CDER nonclinical reviews of NDA 21-794, as well as IND 54,440, for summary and interpretation of the nonclinical data.

1.2 Brief Discussion of Nonclinical Findings

Dapsone has been evaluated in a battery of nonclinical studies that included evaluation of pharmacology, pharmacokinetics, general (repeated-dose) toxicology, genetic toxicology, carcinogenicity, reproductive toxicology, and special toxicity studies. Please see reviews of NDA 21-794 for detailed analysis of those data. For convenience, the pivotal data will be summarized below.

Pharmacology: Dapsone inhibits growth of certain species of bacteria through inhibition of folic acid synthesis. The mechanism through which dapsone ameliorates acne is unclear, although reducing the bacterial count may reduce the size and quantity of lesions by reducing inflammation.

ADME: Approximately 10% to 25% of a topically applied dose of dapsone was systemically absorbed by rats and rabbits. In humans, less than 1% of a topically applied dose of dapsone is systemically absorbed. Dapsone is rapidly metabolized to N-acetyl dapsone and hydroxylamine dapsone. Dapsone is primarily excreted in the urine.

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

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