CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207154 S-004
Priority or Standard	Priority
Submit Date(s)	3/15/2019
Received Date(s)	3/15/2019
PDUFA Goal Date	9/15/2019
Division/Office	DDDP/OND
Reviewer Name(s)	Amy S. Woitach
Review Completion Date	8/30/2019
Established/Proper Name	Dapsone gel, 7.5%
(Proposed) Trade Name	Aczone gel, 7.5%
Applicant	ALMIRALL LLC
Dosage Form(s)	Topical gel
Applicant Proposed Dosing Regimen(s)	Apply to affected areas once a day
Applicant Proposed Indication(s)/Population(s)	Treatment of acne vulgaris in patients 9 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Acne Vulgaris in patients 9 years of age and older

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

ACZONE (dapsone) Gel, 7.5% was approved in 2016 for a treatment of acne vulgaris in patients 12 years of age and older. The original approval action included a postmarketing requirement (PMR 3017-1) to assess the pharmacokinetics (PK), safety and treatment effect of dapsone gel in subjects 9 to 11 years of age. The purpose of this efficacy supplement is to fulfill the PMR and to extend the indication in patients down to 9 years of age. The applicant submitted a Phase 4 pediatric study
report (Study #1679-401-006) to support this change in labeling.

1.2. Conclusions

Substantial evidence of effectiveness for ACZONE Gel, 7.5% in the treatment of acne vulgaris was established under the original approval. Refer to Dr. Patricia C. Brown's original 1/21/2016 clinical review. Efficacy demonstrated in the adult/ adolescent population can be extrapolated to the early adolescent (9-12 years of age) population. No new safety signal was identified in the submitted data from the PK/safety/tolerability study conducted in children 9 to <12 years of age. A favorable overall benefit/risk assessment supports expansion of the indication to patients 9 years of age and older. PMR 3017-1 is considered as fulfilled based on completion and review of study 1679-401-006.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles which primarily affects adolescents and young adults. Onset occurs in puberty, but may persist past the third decade of life, and it affects all races. The disease may be associated with impairment of quality of life. ACZONE Gel, 7.5% has been shown to reduce both comedonal and clinically inflammatory lesions in patients 12 year of age and older with acne vulgaris. Additional information provided in this submission supports safe and effective use of ACZONE Gel, 7.5% in patients 9 years of age and older with acne vulgaris. ACZONE Gel, 7.5% would provide an addition to the armamentarium of acne treatment options for moderate to severe acne vulgaris in this younger population. In view of a favorable overall benefit/risk assessment, approval of this application supplement is recommended.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acne vulgaris is a chronic disease of pilosebaceous follicles that is multi-factorial in etiology and characterized by the formation of two major types of acne lesions: noninflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe cases, nodules/nodulocystic lesions). Acne vulgaris has its onset in puberty, but may persist past the third decade of life, and it affects all races. • In clinical practice, the choice of treatment depends on the type, number, and severity of skin lesions present. Topical agents are common treatments for acne in early adolescents.	Acne is a common condition in children and adults. The choice of treatment is a clinical choice made by the physician and the patients and depends on type, severity, and location of lesions. Aczone has been shown to reduce both comedonal and clinically inflammatory lesions in patients 12 year of age and older with acne vulgaris. Expanding the indication to children age 9 to 11 years would provide an addition to the armamentarium of acne treatment options for moderate to severe acne vulgaris in early

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		early adolescent children.
Current Treatment Options	• Many topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies include oral and topical antibiotics and antimicrobials, systemic hormonal, and topical retinoids.	Aczone Gel, 7.5% represents another available treatment for this condition in children 9 years to 11 years and 11 months of age.
Benefit	• In clinical trials, Aczone Gel, 7.5% was effective in the treatment of moderate to severe inflammatory acne vulgaris in patients 12 years of age and older. • Refer to Dr. Patricia C. Brown's original 1/21/2016 clinical review. • Efficacy demonstrated in the adult/adolescent population can be extrapolated to the early adolescent (9-12 years of age) population as the mechanism of action of acne is similar in the early adolescent age group.	Early adolescent acne is common and may precede other signs of pubertal maturation. Aczone Gel, 7.5% represents another available treatment in this population.
Risk and Risk Management	• No new safety signal was identified in the submitted data from the PK/safety/tolerability study conducted in children 9 to <12 years of age.	The safety profile for Aczone Gel, 7.5% in the early adolescent population appears generally consistent with the population (12 years and older) evaluated in the initial approval.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this supplement application.

2. Therapeutic Context

2.1. Analysis of Condition

Acne vulgaris is a chronic disease of pilosebaceous follicles that is multi-factorial in etiology and characterized by the formation of two major types of acne lesions: noninflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe cases, nodules/nodulo-cystic lesions). Acne vulgaris has its onset in puberty but may persist past the third decade of life, and it affects all races.

2.2. Analysis of Current Treatment Options

A number of topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies for acne vulgaris include oral and topical antibiotics and antimicrobials [e.g. erythromycin, clindamycin, benzoyl peroxide (BPO)] systemic hormonal therapies (e.g. ethinyl estradiol/norgestimate) and topical retinoids (e.g. tretinoin, tazarotene). The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne. Other treatment options which are used less frequently include: physical modalities (e.g., chemical peels, intralesional corticosteroids and laser therapy), complementary/alternative therapies (e.g., tea tree oil, herbal supplements and biofeedback) and dietary management (e.g., low glycemic index diets and low calcium diets.) Factors which influence the choice of treatment are lesion type(s), disease severity, personal preference, and individual patient characteristics (e.g., age, sex, skin sensitivity, predisposition for hyperpigmentation/scarring.)

The algorithm for acne management of the early adolescent is essentially the same as for the adolescent, though these recommendations are based more strongly on expert opinion. Topical therapy alone or in combination is recommended as initial treatment of mild acne. BPO as a single agent, topical retinoids, or combinations of topical retinoids, antibiotics, and BPO as individual agents or fixed-dose combinations may be used. Moderate acne may be initially treated with topical combinations including a retinoid and BPO and/ or antibiotics, or with oral antibiotics in addition to a topical retinoid and BPO and/or topical antibiotics. Because acne routinely presents in patients younger than 12 years of age, topical retinoids are widely used off-label in this age group.

Table 1: Approved Treatment for Acne Vulgaris by Drug Category

Categories	Drug Products
Topical	
Benzoyl peroxide	Multiple products
Sulfa products	Sulfacetamide, Sulfacetamide/Sulfur
Azelaic acid	Azelaic acid cream
Antibiotics	Clindamycin, Erythromycin, Dapsone
Retinoids	Tretinoin, Adapalene, Tazarotene
Salicylic acid	Multiple products
Systemic	
Antibiotics	Tetracycline, Doxycycline, Minocycline
Retinoids Isotretinoin	Isotretinoin
Hormonal therapies[2]	Various oral contraceptives

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ACZONE (dapsone) Gel, 7.5% was originally approved on 02/25/2016 for once daily (QD) topical treatment of acne vulgaris (AV) in patients 12 years of age and older. The approval of ACZONE 7.5% included a postmarketing requirement (PMR 3017-1) to assess the product in subjects 9 to <12 years of age, including pharmacokinetic (PK) assessment in at least 16 evaluable subjects under maximal use conditions. The Agency waived the pediatric requirement for subjects 8 year 11 months of age and younger.

3.2. Summary of Presubmission/Submission Regulatory Activity

The design of study 1679-401-006 was reviewed under IND 054440.

The applicant conducted Phase 4 study 1679-401-006 and submitted the study report and proposed labeling to comply with the PMR 3017-1.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No inspections were requested for this open-labeled study.

4.2. Product Quality

Not applicable. The approved Aczone product was used in the study. Refer to Dr. Patricia C. Brown's original 1/21/2016 clinical review for the clinical perspective on product quality.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable. There was no nonclinical review of this submission. Refer to Dr. Patricia C. Brown's original 1/21/2016 clinical review for the clinical perspective on pharmacology/toxicology.

4.5. Clinical Pharmacology

The Applicant assessed PK of dapsone and its metabolites [dapsone hydroxylamine (DHA) and N-acetyl dapsone (NAD)] in 16 subjects 9 to 11 years old with acne vulgaris under maximal use conditions. Subjects in a PK-cohort received topical application of the drug on the entire face, neck, upper chest, upper back and shoulders once daily for 8 days. Plasma concentrations were assessed at pre-dose and at 10-hour post-dose on Day 8 (Week 1 visit).

The Mean ± SD of plasma dapsone concentration at the 10-hour post dose-time point at Week 1 visit was 20.0 ± 12.5 ng/mL and for DHA and NAD metabolites the mean ± SD plasma concentrations the Week 1 visit were 1.40 ± 1.10 ng/mL and 9.01 ± 7.37 ng/mL, respectively.

Plasma concentrations of dapsone and its metabolites in subjects 9 to 11 years of age following QD application under maximal use conditions were low and appeared to reach steady state at the Week 1 visit following 8 days of treatment. The PK cohort had 6/17 subjects at age of 9 years, which is a reasonable number of pediatric subjects for the study.

From Clinical Pharmacology perspective, the applicant's pediatric study results support the proposed labeling change to include intended treatment patient age down to 9 years of age. For a summary of Clinical Pharmacology and Biopharmaceutics findings refer to Dr. Luke Oh's 08/08/2019 clinical pharmacology review. Dr. Oh concluded:

> NDA 207154/S-004 is acceptable from a Clinical Pharmacology perspective pending agreement on recommended labeling changes. PMR 3017-1 is considered as fulfilled from a Clinical Pharmacology perspective.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Clinical Studies Submitted

One open-labelled study was submitted to support extending the indicated age for ACZONE Gel, 7.5% in the treatment of acne vulgaris down to 9 years old.

Study 1679-401-006
Title: An open-label Phase 4 safety and efficacy trial of ACZONE (Dapsone) Gel, 7.5% in 9 to 11

Overview and Objective

- To evaluate the safety and tolerability of ACZONE 7.5% administered topically once daily (QD) for 12 weeks in 9 to 11-year-olds with acne vulgaris
- To evaluate the peak and trough plasma drug concentrations in 9 to 11-year-olds with acne vulgaris following QD dosing of ACZONE 7.5% under maximal use conditions for the first 8 days
- To explore the efficacy of ACZONE 7.5% administered topically QD in 9 to 11-year-olds with acne vulgaris

Trial Design

This study was a multi-center, non-comparative study in 9 to 11-year-old subjects with

mild, moderate, or severe acne vulgaris. The study assessed the safety, tolerability, PK, and efficacy of Aczone 7.5% applied QD for up to 12 weeks. The study included 2 cohorts receiving different exposures:

- PK Cohort: ACZONE 7.5% applied once-daily to the entire face, neck, upper chest, upper back and shoulders starting on Day 1 under maximal use conditions (i.e., ~2 grams/day) for 8 consecutive days. After the Week 1 Visit, study treatment was to be applied in a thin layer to the subject's face once-daily for 11 weeks. Additionally, acne-affected areas on the upper chest, upper back, and shoulders were also to be treated with a thin layer of study treatment during the final 11 weeks.

- Non-PK Cohort: ACZONE 7.5% applied once-daily in a thin layer to the subject's face for 12 weeks. Acne-affected areas on the upper chest, upper back, and shoulders should have also been treated with a thin layer of study treatment.

Subjects returned to the study center at Weeks 1, 2, 4, 8, and 12/early exit) for a total of up to 7 visits.

Study Endpoints

The objective of the study was to evaluate the safety (including PK) and tolerability of ACZONE 7.5% administered topically once daily for 12 weeks in 9 to 11-year-olds with acne vulgaris. Plasma samples were collected to evaluate plasma concentrations of dapsone and its metabolites at pre-dose and 10 hours post-dose (i.e., peak) at the Week 1 visit.

Exploratory efficacy measurements included the following:

- Investigator's Global Assessment (IGA): Acne severity on the face was evaluated by the investigator using a 5-point scale provided in of the protocol (Appendix 16.1.1).
- Lesions: Inflammatory, noninflammatory, and total lesions on the face were counted by
the investigator or trained designee.

Neither measurement was designated as primary or secondary.

Compliance with Good Clinical Practices

The applicant states that this study was conducted in conformance with the ICH E6 guideline for Good Clinical Practices and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual.

Financial Disclosure

Table 2 includes a list of investigators and subinvestigators who indicated the presence of financial interests or proprietary interest in this product, or a significant equity in the sponsor as defined in 21 CFR 54.2 (b). They have disclosed the receipt of significant payments of other sorts as defined in 21 CFR 54.2 (f). Steps taken to minimize the potential bias of clinical study results are included in the table.

Table 2: Investigator Financial Interests for Study 1679-401-006

Principal Investigator	Reason for Disclosure	Steps Taken to Minimize Bias
(b) (6)	(b) (6) MD (principal investigator) held Allergan stock exceeding $50,000 which was sold on (b) (6) (b) (6)	None indicated; No potential conflict noted as this site contributed (b) (6) who participated in the study after the potential conflict date of (b) (6)
	(b) (6) MD (principal investigator) has a presence of consultation and honoraria that have a monetary value exceeding $25,000.	• Disclose in Informed Consent Form • Informed consent obtained by staff with no potential conflict
	(b) (6) MD (principal investigator) has a financial arrangement with Allergan plc whereby the value of the compensation could be influenced by the outcome of the trial.	• Disclose in Informed Consent Form • Informed consent obtained by staff with no potential conflict
	(b) (6) MD (principal investigator) has stock in Allergan plc (4,000 shares disclosed).	• Disclose in Informed Consent Form • Use sub-investigators with no potential conflict if there are questions or difficult calls

Subject Disposition

The mean age was 10.4 years. The majority of subjects were female (74.0%, 74/100) and white (62.0%, 62/100) and had a baseline Investigator Global Assessment (IGA) of moderate severity (53.1%, 52/98). Assessment of baseline IGA and inflammation was conducted on the face only.

Protocol Violations/Deviations

- 3 subjects used prohibited concomitant medication (tacrolimus 0.03%, cortisone injection, doxycycline).

Because this is a safety and tolerability study, concomitant medication use will not impact study outcome.

- 2 subjects (11yo and 9yo female) pregnancy testing was not performed as specified in the protocol.

No subject had a positive urine pregnancy test result or reported a pregnancy during the study. The 2 subjects who had missed pregnancy testing are unlikely to contribute significant

information to safe use of the product during pregnancy.

Efficacy Results

This was an open label trial and efficacy assessment is considered as exploratory and supportive. The applicant reported that at Week 12, 46.7% of subjects achieved success (none or minimal disease at the end of 12-week treatment) based on the IGA. Mean ± SD reductions from baseline in inflammatory and noninflammatory lesion counts were -6.2 ± 9.3 (-56.38% change from baseline) and -17.8 ± 17.0 (-46.45%) change from baseline), respectively.

The reported efficacy appears to support the pediatric indication; efficacy will be extrapolated from studies in conducted in subjects 12 years of age and older.

5.1. Review Strategy

This was a multicenter, open label, noncomparative study in 9 to 11-year-old subjects with mild, moderate, or severe acne vulgaris. The study assessed the safety, tolerability, and PK of ACZONE 7.5% applied once daily for up to 12 weeks. Efficacy was explored in the study.

Efficacy for the pediatric population ages 9 to <11 is extrapolated from the 12 and older populated evaluated in the original clinical trials. Refer to Dr. Patricia C. Brown's original 1/21/2016 clinical review. Safety was evaluated based on adverse event reporting at each evaluation. The safety evaluation also included an assessment of tolerability and PK.

6. Review of Safety

6.1. Safety Review Approach

In an open label safety and pharmacokinetic study in pediatric subjects 9 to 11 years of age with acne vulgaris, a subset of subjects was assessed for maximal use. These subjects (N = 16) received once daily topical application of approximately 2 grams of ACZONE Gel, 7.5%, to

the entire face, shoulders, upper chest and upper back for 8 days. For a summary of Clinical Pharmacology and Biopharmaceutics findings refer to Dr. Luke Oh's 08/08/2019 clinical pharmacology review. Dr. Oh concluded:

> NDA 207154/S-004 is acceptable from a Clinical Pharmacology perspective pending agreement on recommended labeling changes. PMR 3017-1 is considered as fulfilled from a Clinical Pharmacology perspective.

The subject of this safety review is the assessment of 100 pediatric subjects (17 in the PK Cohort and 83 in the Non-PK Cohort) who were treated with ACZONE Gel, 7.5% and followed for up to 12 weeks. Subjects were assessed for safety based on adverse event reporting and dermal tolerability at each evaluation. Physical exam and vital sign assessments were performed at baseline and end of treatmetent. No clinical laboratory assessments were conducted.

6.2. Review of the Safety Database

6.2.1. Overall Exposure

A total of 100 subjects (17 in the PK Cohort and 83 in the Non-PK Cohort) were treated and followed for up to 12 weeks. The mean number of days subjects were treated was 81.1 (median, 85.0) for the PK Cohort and 81.8 (median, 84.0) for the Non-PK Cohort.

In both cohorts, the majority of subjects (17 in the PK Cohort and 76 in the Non-PK Cohort) were exposed to study treatment for at least 8 weeks. The mean daily dose was highest during Week 1 for the PK Cohort (mean 1.81 g/day), after which, the mean daily dose decreased to levels approaching that in the Non-PK Cohort (< 1 g/day). Mean treatment compliance ranged from 97.89% to 100.0%.

The exposure appears to be representative of likely real-world usage and is consistent with the pivotal clinical trials.

6.2.2. Relevant characteristics of the safety population:

The mean age was 10.4 years (range: 9 to 11 years). The majority of subjects were female (74.0%, 74/100), non-Hispanic or Latino (74.0%), and White (62.0%). The mean numbers of inflammatory, noninflammatory, and total facial lesions were 12.3, 37.2, and 49.5, respectively. The majority of subjects had a baseline IGA of moderate severity (53.1%). Skin phototypes I-VI were evaluated with the majority of subjects characterizes as Type III (40%).

Because of the study design and demographic imbalances, conclusions on subgroup safety analyses could not be determined.

6.2.3. Adequacy of the safety database:

The safety database appears adequate for this supplement.

6.3. Adequacy of Applicant's Clinical Safety Assessments

6.3.1. Issues Regarding Data Integrity and Submission Quality

There does not appear to be issues with data integrity. No inspections were conducted for this pediatric supplement.

6.3.2. Categorization of Adverse Events

All safety data were summarized for both cohorts combined (Total) and by cohort (PK and Non-PK). Adverse events were coded from the verbatim text into preferred term and primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.1). This approach is acceptable.

6.3.3. Routine Clinical Tests

Routine clinical evaluations were designed to assess the safety use of daily application for up to 12 weeks. Safety measurements were adverse events, physical examination, height, weight, vital signs and urine pregnancy test for females of childbearing potential. Tolerability measurements included the assessment of dryness, scaling, and erythema by the investigator and the subject's assessment of stinging/burning on the face. No clinical laboratory assessments were conducted.

6.3.4. Deaths

No deaths occurred in the study

6.3.5. Serious Adverse Events

No serious treatment-emergent adverse events occurred in the study.

6.3.6. Dropouts and/or Discontinuations Due to Adverse Effects

One subject in the PK Cohort had a TEAE that led to study discontinuation. The investigator considered the event moderate in severity and treatment-related. The case is as follows:

Subject (b) (6), 11-year-old white female, developed contact dermatitis

of the face, 35 days after the first dose of study treatment. The last dose of study treatment was applied on Day 36, and treatment with tacrolimus was initiated. A patch test was initiated on Day 50, was confirmed positive on Day 52, and was indeterminate (equivocal) on Day 54. The event resolved on Day 54, and the subject was discontinued from the study the same day.

6.3.7. Significant Adverse Events

There were no significant AEs reported.

6.3.8. Treatment Emergent Adverse Events and Adverse Reactions

Twenty-nine (29) Treat Emergent Adverse Events (TEAEs) were reported in 21.0% of subjects [29.4%, 5/17 in the PK Cohort, 19.3% (16/83) in the Non-PK Cohort]. There were no serious TEAEs. One subject reported a TEAE (dermatitis contact) that was considered treatment-related by the investigator; this same event was the only AE that led to study discontinuation and is discussed in section 6.3.6. An overall summary of adverse events is presented in Table 3.

Table 3: Summary of Adverse Events

	Number (%) of Patients		
	PK Cohort (N = 17)	Non-PK Cohort (N = 83)	Total (N = 100)
All TEAEs	5 (29.4)	16 (19.3)	21 (21.0)
Treatment-related TEAEs	1 (5.9)	0	1 (1.0)
Serious TEAEs	0	0	0
Deaths	0	0	0
AEs leading to study discontinuation	1 (5.9)	0	1 (1.0)

Source: Applicant's CSR Table 12-2

Most TEAEs by preferred term were reported in a single subject and resolved without sequelae during the study. The most common TEAEs (i.e., those occurring in ≥ 2 subjects) included the following preferred terms: upper respiratory tract infection (3), Nasopharyngitis (2), pharyngitis streptococcal (2) and dermatitis contact (3). All TEAEs were mild or moderate in severity. The AEs reported appear to be common events seen in the pediatric population. Review of the reported AEs did not identify a new safety signal for topical dapsone.

6.3.9. Laboratory Findings

Clinical laboratory evaluations were not planned or performed during the study.

6.3.10. Vital Signs

No clinically relevant changes in vital sign or height/weight measurements were observed.

6.3.11. Electrocardiograms (ECGs)

ECGs were not planned or performed during the study.

6.3.12. QT

With the original approval, the Division granted a waiver to submit data from a thorough QT/QTc on the basis of low systemic exposure, and absence of a safety signal for cardiac events for the moiety dapsone. No additional QT information is needed for this supplement.

6.3.13. Immunogenicity

Not applicable.

6.4. Analysis of Submission-Specific Safety Issues

Dermal tolerability was assessed on the face at baseline, Weeks 1, 2, 4, 8 and 12. Investigators and subjects used a 4-point scale (none, mild, moderate and severe) to assess dryness, scaling, erythema, (investigator reported) and stinging/burning (subject reported).

Across all timepoints during the 12-week treatment period, the majority of subjects had a severity rating of “none” for all 4 tolerability parameters. Dermal tolerability scores at Week 12 were similar to baseline scores for all 4 tolerability parameters.

For subjects with postbaseline increases in dermal tolerability scores, the most frequently reported increase in severity was from none to mild. No subject had a postbaseline increase to severe for any dermal tolerability assessment. At any given post-dose timepoint, for any given parameter, the percentage of subjects reporting a “moderate” score was 4% or less.

6.5. Additional Safety Explorations

6.5.1. Human Carcinogenicity or Tumor Development

Human carcinogenicity was not assessed as part of the clinical development program. The clinical trial was open-labelled and too short to allow for evaluation of carcinogenicity.

6.5.2. Human Reproduction and Pregnancy

No subject had a positive urine pregnancy test result or reported a pregnancy during the study.

6.5.3. Pediatrics and Assessment of Effects on Growth

At approval, the Agency waived the pediatric study requirement for ages 0 to 8 years 11 months because necessary studies are impossible or highly impracticable. Acne is extremely uncommon in pediatric patients below 9 years of age. The Agency deferred submission of a pediatric study for ages 9 to 11 years 11 months for this application because the product was ready for approval for use in adults and adolescents ages 12 years and above and the pediatric study has not been completed. The deferred pediatric postmarketing study is as follows:

> 3017-1 Conduct an open-label study to assess safety, pharmacokinetics, and treatment effect of ACZONE (dapsone) Gel, 7.5% in 100 pediatric subjects aged 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.

The purpose of this efficacy supplement is to fulfil the PMR and to extend the indication in patients down to 9 years of age. This reviewer finds that the submitted study fulfills PMR 3017-1.

6.5.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose was not reported. Topical dapsone is not known to have drug abuse potential. The occurrence of rebound and relapse of disease after discontinuation of treatment with ACZONE Gel, 7.5% was not examined in this trial.

6.6. Safety in the Postmarket Setting

ACZONE Gel, 7.5% is currently marketed for the treatment of acne vulgaris in patients 12 years of age and older. When used as labeled the product is safe and effective. There is no postmarketing information to suggest that a potential safety risk exists for the 9-11-year-old population.

7. Advisory Committee Meeting and Other External Consultations

Not applicable.

8. Labeling Recommendations

The applicant proposed labeling modifications to sections 1, 5.3, 8.4, and 14. Clinical pharmacology provided labeling recommendations for sections 8.4 and 12.3. See Dr. Luke Oh's clinical pharmacology review for details. Comments below describe the applicant's proposal and the recommended modifications from a clinical perspective.

1 INDICATIONS AND USAGE
The applicant proposed:

> ACZONE® (dapsone) Gel, 7.5%, is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

This is acceptable from a clinical perspective.

5.3 Skin Reactions
The applicant proposed:
Skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria) have been reported with oral dapsone treatment. (b) (4) .

It is recommended to reject the proposed modifications. (b) (4)

8.4 Pediatric Use
The applicant proposed:
Safety and efficacy was evaluated in 1066 subjects aged 12-17 years old treated with ACZONE Gel, 7.5% in the clinical trials. The safety profile for ACZONE Gel, 7.5%, was similar to the vehicle control group. ~~Safety and effectiveness of ACZONE Gel, 7.5%, have not been established in pediatric patients below the age of 12 years.~~

(b) (4)

Safety and effectiveness of ACZONE Gel, 7.5%, have not been established in pediatric patients below the age of 9 years.

The deletion is acceptable. The following revised text is proposed:

> *Use of ACZONE Gel, 7.5% in patients 9 to 11 years of age for this indication is supported by evidence from adequate and well-controlled studies in subjects 12 years of age and older and with additional pharmacokinetic and safety data in pediatric subjects 9 to 11 years of age.* (b) (4) *100 subjects with acne [see Adverse Reactions (6.1), and Clinical Pharmacology (12.3)].*
>
> *Safety and effectiveness of ACZONE Gel, 7.5%, have not been established in pediatric patients below the age of 9 years.*

14 CLINICAL STUDIES

The applicant proposed:

(b) (4)

It is recommended to delete the applicant's proposed labeling (b) (4) *in Section 14.*

9. Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended based on the submitted single, open-labelled pediatric study.

10. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended

11. Appendices

11.1. Financial Disclosure

Investigators with conflicts are listed in section 5.1.Clinical Studies Submitted.

Covered Clinical Study (Name and/or Number): **Study 1679-401-006**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 20		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0		

Significant equity interest held by investigator in Sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Appears this way on original

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMY S WOITACH
09/03/2019 10:00:23 AM

DAVID L KETTL
09/03/2019 10:12:18 AM