CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 50-819/S-12

Trade Name: Onexton™

Generic Name: Clindamycin phosphate and benzoyl peroxide gel

Sponsor: Dow Pharmaceutical Sciences

Approval Date: November 24, 2014

Indications: For the topical treatment of acne vulgaris in patients 12 years of age and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 050819/S-012

SUPPLEMENT APPROVAL

Dow Pharmaceutical Sciences
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your supplemental New Drug Application (sNDA) dated and received January 30, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Onexton™ (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75%.

We acknowledge receipt of your amendments dated January 31, February 19, March 6, 14, April 24, 28, June 26, July 3, August 14, September 3, October 2, 27, 28, and 30, 2014.

This "Prior Approval" supplemental new drug application provides for introduction of a new strength of clindamycin 1.2% and benzoyl peroxide 3.75%.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 050819/S-012**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf.

Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

TATIANA OUSSOVA
11/24/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ONEXTON Gel safely and effectively. See full prescribing information for ONEXTON Gel.

ONEXTON™ (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% for topical use
Initial U.S. Approval: 2000

----------INDICATIONS AND USAGE----------
ONEXTON Gel is a combination of clindamycin phosphate (a lincosamide antibacterial) and benzoyl peroxide indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Apply a pea-sized amount of ONEXTON Gel to the face once daily. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Gel, 1.2%/3.75%

Each gram of ONEXTON Gel contains 12 mg (1.2%) clindamycin phosphate, equivalent to 10 mg (1%) clindamycin, and 37.5 mg (3.75%) benzoyl peroxide. (3)

----------CONTRAINDICATIONS----------
ONEXTON Gel is contraindicated in:
- Patients who have demonstrated hypersensitivity (e.g., anaphylaxis) to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. (4.1)
- Patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. (4 2)

----------WARNINGS AND PRECAUTIONS----------
- Colitis: Clindamycin can cause severe colitis, which may result in death. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of clindamycin. ONEXTON Gel should be discontinued if significant diarrhea occurs. (5.1)
- Ultraviolet Light and Environmental Exposure: Minimize sun exposure following drug application. (5 2)

----------ADVERSE REACTIONS----------
- The most common adverse reactions are: burning sensation (0.4%); contact dermatitis (0.4%); pruritus (0.4%); and rash (0.4%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- ONEXTON Gel should not be used in combination with erythromycin-containing products because of its clindamycin component. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ONEXTON™ (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

Before applying ONEXTON Gel, wash the face gently with a mild soap, rinse with warm water, and pat the skin dry. Apply a pea-sized amount of ONEXTON Gel to the face once daily. Avoid the eyes, mouth, lips, mucous membranes, or areas of broken skin.

Use of ONEXTON Gel beyond 12 weeks has not been evaluated.

ONEXTON Gel is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Gel, 1.2%/3.75%

Each gram of ONEXTON Gel contains 12 mg (1.2%) clindamycin phosphate, equivalent to 10 mg (1%) clindamycin, and 37.5 mg (3.75%) benzoyl peroxide in a white to off-white, opaque, smooth gel.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

ONEXTON Gel is contraindicated in those individuals who have shown hypersensitivity to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with ONEXTON Gel [see *Adverse Reactions (6.2)*].

4.2 Colitis/Enteritis

ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. If significant diarrhea occurs, ONEXTON Gel should be discontinued.

Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate toxin(s) produced by Clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

5.2 Ultraviolet Light and Environmental Exposure

Minimize sun exposure (including use of tanning beds or sun lamps) following drug application [see *Nonclinical Toxicology (13.1)*].

6 ADVERSE REACTIONS

The following adverse reaction is described in more detail in the *Warnings and Precautions* section of the label:

- Colitis [*See Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates observed in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

These adverse reactions occurred in less than 0.5% of subjects treated with ONEXTON Gel: burning sensation (0.4%); contact dermatitis (0.4%); pruritus (0.4%); and rash (0.4%).

During the clinical trial, subjects were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions either were the same as baseline or increased and peaked around week 4 and were near or improved

from baseline levels by week 12. The percentage of subjects that had symptoms present before treatment (at baseline), during treatment, and the percent with symptoms present at week 12 are shown in Table 1.

Table 1: Local Skin Reactions - Percent of Subjects with Symptoms Present. Results from the Phase 3 Trial of ONEXTON Gel 1.2%/3.75% (N = 243)

	Before Treatment (Baseline)			During Treatment			End of Treatment (Week 12)		
	Mild	**Mod.***	**Severe**	**Mild**	**Mod.***	**Severe**	**Mild**	**Mod.***	**Severe**
Erythema	20	6	0	28	5	<1	15	2	0
Scaling	10	1	0	19	3	0	10	<1	0
Itching	14	3	<1	15	3	0	7	2	0
Burning	5	<1	<1	7	1	<1	3	<1	0
Stinging	5	<1	0	7	0	<1	3	0	<1

*Mod. = Moderate

6.2 Postmarketing Experience

Because postmarketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis, as well as allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin phosphate/benzoyl peroxide.

7 DRUG INTERACTIONS

7.1 Erythromycin

Avoid using ONEXTON Gel in combination with topical or oral erythromycin-containing products due to its clindamycin component. *In vitro* studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this *in vitro* antagonism is not known.

7.2 Concomitant Topical Medications

Concomitant topical acne therapy should be used with caution since a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. If irritancy or dermatitis occurs, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

7.3 Neuromuscular Blocking Agents

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. ONEXTON Gel should be used with caution in patients receiving such agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women treated with ONEXTON Gel. ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ONEXTON Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

8.3 Nursing Mothers

It is not known whether clindamycin is excreted in human milk after topical application of ONEXTON Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of ONEXTON Gel in pediatric patients under the age of 12 years have not been evaluated.

8.5 Geriatric Use

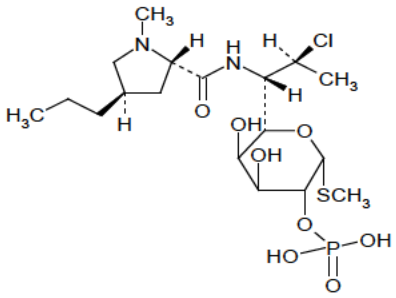
Clinical trials of ONEXTON Gel did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

ONEXTON Gel is a combination product with two active ingredients in a white to off-white, opaque, smooth, aqueous gel formulation intended for topical use. Clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

The chemical name for clindamycin phosphate is *Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2*-(dihydrogen phosphate). The structural formula for clindamycin phosphate is represented below:

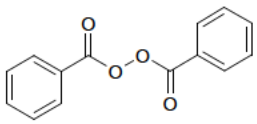
Clindamycin phosphate:



Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$ Molecular Weight: 504.97

Benzoyl peroxide is an antibacterial and keratolytic agent. The structural formula for benzoyl peroxide is represented below:

Benzoyl peroxide:



Molecular Formula: $C_{14}H_{10}O_4$ Molecular Weight: 242.23

ONEXTON Gel contains the following inactive ingredients: carbomer 980, potassium hydroxide, propylene glycol, and purified water. Each gram of ONEXTON Gel contains 12 mg (1.2%) clindamycin phosphate, equivalent to 10 mg (1%) clindamycin, and 37.5 mg (3.75%) benzoyl peroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clindamycin: Clindamycin is a lincosamide antibacterial [see *Clinical Pharmacology (12.4)*].

Benzoyl Peroxide: Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects, but the precise mechanism of action is unknown.

12.3 Pharmacokinetics

The systemic absorption of ONEXTON Gel has not been evaluated. The systemic absorption of clindamycin was investigated in an open-label, multiple-dose trial in 16 adult subjects with moderate to severe acne vulgaris treated with 1 gram of a marketed gel containing clindamycin 1%/benzoyl peroxide 2.5% applied to the face once daily for 30 days. This product has the same formulation as ONEXTON Gel but with a lower concentration of benzoyl peroxide. Twelve subjects (75%) had at least one quantifiable clindamycin plasma concentration above the lower limit of quantification (LOQ = 0.5 ng/mL) on Day 1 or Day 30. On Day 1, the mean (± standard deviation) peak plasma concentrations (C_{max}) was 0.78 ± 0.22 ng/mL (n=9 with measurable concentrations), and the

mean AUC_{0-t} was 5.29 ± 0.81 h.ng/mL (n=4). On Day 30, the mean C_{max} was 1.22 ± 0.88 ng/mL (n=10), and the mean AUC_{0-t} was 8.42 ± 6.01 h.ng/mL (n=6). Clindamycin plasma concentrations were below LOQ in all subjects at 24 hours post-dose on the three tested days (Day 1, 15, and 30).

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid.

12.4 Microbiology

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis.

Clindamycin and benzoyl peroxide individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris. In an *in vitro* study, the MIC for benzoyl peroxide against *Propionibacterium acnes* is 128 mg/L. The clinical significance of this activity against *P. acnes* is not known.

P. acnes resistance to clindamycin has been documented. Resistance to clindamycin is often associated with resistance to erythromycin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility testing of ONEXTON Gel have not been performed.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times amount of clindamycin and 2.4, 7.2, and 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, respectively) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 1.6, 4.8, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, respectively) for up to 97 weeks did not cause any increase in tumors. In a 52-week dermal photocarcinogenicity study in hairless mice, (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation.

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies have not been performed with ONEXTON Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g ONEXTON Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

14 CLINICAL STUDIES

The safety and efficacy of once daily use of ONEXTON Gel was assessed in a 12-week multi-center, randomized, blinded trial in subjects 12 years and older with moderate to severe acne vulgaris. This trial evaluated ONEXTON Gel compared to vehicle gel.

The co-primary efficacy variables for this trial were:

(1) Mean absolute change from baseline at week 12 in

- Inflammatory lesion counts
- Non-inflammatory lesion counts

(2) Percent of subjects who had a two grade reduction from baseline on an Evaluator's Global Severity (EGS) score.

The EGS scoring scale used in the clinical trial for ONEXTON Gel is as follows:

Table 2: EGS Scoring Scale

Grade	Description
Clear	Normal, clear skin with no evidence of acne
Almost Clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion
Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions
Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and more than 2 nodulocystic lesions

The results of the trial at Week 12 are presented in Table 3:

Table 3: Results of Phase 3 Trial with ONEXTON Gel 1.2%/3.75% at Week 12

	ONEXTON Gel N = 253	**Vehicle Gel N = 245**
EGSS:		
Clear or Almost Clear	29%	15%
2-grade reduction from baseline	35%	17%
Inflammatory Lesions:		
Mean absolute reduction	16.3	8.2
Mean percent (%) reduction	60.4%	31.3%
Non-Inflammatory Lesions:		
Mean absolute reduction	19.2	9.6
Mean percent (%) reduction	51.8%	27.6%

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ONEXTON Gel 1.2%/3.75% is a white to off-white smooth gel supplied as a 50 g pump (NDC 0187-3050-50)

16.2 Dispensing Instructions for the Pharmacist

- Dispense ONEXTON Gel with a 10 week expiration date.
- Specify “Store at room temperature up to 25°C (77°F). Do not freeze.”

16.3 Storage and Handling

- PHARMACIST: Prior to Dispensing: Store in a refrigerator, 2°C to 8°C (36°F to 46°F).
- PATIENT: Store at room temperature at or below 25°C (77°F).
- Protect from freezing.
- Store pump upright.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

- Patients who develop allergic reactions such as severe swelling or shortness of breath should discontinue use and contact their physician immediately.
- ONEXTON Gel may cause irritation such as erythema, scaling, itching, or burning, especially when used in combination with other topical acne therapies.
- Patients should limit excessive or prolonged exposure to sunlight. To minimize exposure to sunlight, a hat or other clothing should be worn. Sunscreen may also be used.
- ONEXTON Gel may bleach hair or colored fabric.

PATIENT INFORMATION
ONEXTON™ (ON-EX-TUN)
(clindamycin phosphate and benzoyl peroxide) Gel, 1.2% / 3.75%

Important information: For use on skin only (topical use). Do not get ONEXTON Gel in your mouth, eyes, vagina, on your lips, or on cuts or open wounds.

What is ONEXTON Gel?

ONEXTON Gel is a prescription medicine used on the skin (topical) to treat acne vulgaris in people 12 years of age and older. ONEXTON Gel contains clindamycin phosphate and benzoyl peroxide.

It is not known if ONEXTON Gel is safe and effective for use longer than 12 weeks.
It is not known if ONEXTON Gel is safe and effective in children under 12 years of age.

Who should not use ONEXTON Gel?

Do not use ONEXTON Gel if you have:

- had an allergic reaction to clindamycin, benzoyl peroxide, lincomycin or any of the ingredients in ONEXTON Gel. See the end of this leaflet for a complete list of ingredients in ONEXTON Gel.
- Crohn's disease or ulcerative colitis
- had inflammation of the colon (colitis), or severe diarrhea with past antibiotic use

What should I tell my doctor before using ONEXTON Gel?

Before using ONEXTON Gel, tell your doctor about all of your medical conditions, including if you:

- plan to have surgery with general anesthesia
- are pregnant or plan to become pregnant. It is not known if ONEXTON Gel will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ONEXTON Gel passes into your breast milk. ONEXTON Gel contains the medicine clindamycin. Clindamycin when taken by mouth or by injection has been reported to appear in breast milk. You and your doctor should decide if you will use ONEXTON Gel while breastfeeding.

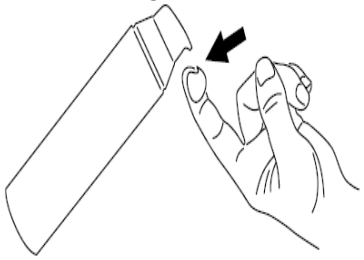
Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements, and skin products you use. Using other topical acne products may increase the irritation of your skin when used with ONEXTON Gel.

- Especially tell your doctor if you take a medicine that contains erythromycin. ONEXTON Gel should not be used with products that contain erythromycin.

How should I use ONEXTON Gel?

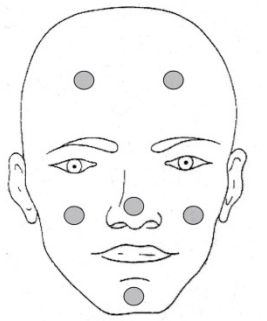
- Use ONEXTON Gel exactly as your doctor tells you to use it.
- Apply ONEXTON Gel to your face 1 time each day.
- Before you apply ONEXTON Gel, wash your face gently with a mild soap, rinse with warm water, and pat your skin dry.
- To apply ONEXTON Gel to your face, use the pump to dispense 1 pea-sized amount of ONEXTON Gel onto your fingertip (See Figure 1). One pea-sized amount of ONEXTON Gel should be enough to cover your entire face.

Figure 1



- Dot the 1 pea-sized amount of ONEXTON Gel onto six areas of your face (chin, left cheek, right cheek, nose, left forehead, right forehead). See Figure 2.

Figure 2



- After applying the ONEXTON Gel this way, spread the gel over your face and gently rub it in. It is important to spread the gel over your whole face.
- Wash your hands with soap and water after applying ONEXTON Gel.
- If your doctor tells you to put ONEXTON Gel on other areas of your skin with acne, be sure to ask how much you should use.
- Do not use more ONEXTON Gel than prescribed.

What should I avoid while using ONEXTON Gel?

- Limit your time in sunlight. Avoid using tanning beds or sun lamps. If you have to be in sunlight, wear a wide-brimmed hat or other protective clothing, and a sunscreen with SPF 15 rating or higher.
- Avoid getting ONEXTON Gel in your hair or on colored fabric. ONEXTON Gel may bleach hair or colored fabric.

What are possible side effects with ONEXTON Gel?

ONEXTON Gel may cause serious side effects, including:

- **Inflammation of the colon (colitis).** Stop using ONEXTON Gel and call your doctor right away if you have severe watery diarrhea, or bloody diarrhea.
- **Allergic reactions.** Stop using ONEXTON Gel, call your doctor and get help right away if you get severe itching, swelling of your face, eyes, lips tongue or throat, or trouble breathing.

The most common side effect with ONEXTON Gel is skin irritation. Stop using ONEXTON Gel and call your doctor if you have a skin rash or burning, or your skin becomes very red, itchy or swollen.

Talk to your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects with ONEXTON Gel.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Valeant Pharmaceuticals North America LLC at 1-800-321-4576.

How should I store ONEXTON Gel?

- Store ONEXTON Gel at room temperature at or below 77°F (25°C). Do not freeze.
- Store pump upright.
- Keep the container tightly closed.
- The expiration date of ONEXTON Gel is 10 weeks from the date you fill your prescription. Safely throw away expired ONEXTON Gel.

Keep ONEXTON Gel and all medicines out of the reach of children.

General information about the safe and effective use of ONEXTON Gel

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ONEXTON Gel for a condition for which it was not prescribed. Do not give ONEXTON Gel to other people, even if they have the same symptoms you have. It may harm them. You can also ask your doctor or pharmacist for information about ONEXTON Gel that is written for health professionals.

What are the ingredients in ONEXTON Gel?

Active ingredients: clindamycin phosphate 1.2% and benzoyl peroxide 3.75%

Inactive ingredients: carbomer 980, potassium hydroxide, propylene glycol, and purified water

Manufactured for: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA
By: Contract Pharmaceuticals Limited, Mississauga, Ontario, Canada L5N 6L6
U.S. Patents 5,733,886 and 8,288,434 For more information about ONEXTON Gel, call 1-800-321-4576.

This Patient Information has been approved by the U.S. Food and Drug Administration.

9389300 Rev. 11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 21, 2014
From	Tatiana Oussova, M.D., M.P.H.
Subject	Deputy for Safety Summary Review
NDA/BLA # **Supplement #**	NDA 050819 S-012
Applicant Name	Dow Pharmaceutical Sciences
Date of Submission	January 27, 2014
PDUFA Goal Date	November 30, 2014
Proprietary Name / Established (USAN) Name	Onexton Gel/clindamycin phosphate 1.2% and benzoyl peroxide 3.75%
Dosage Forms / Strength	Gel
Proposed Indication(s)	Topical treatment of acne vulgaris in patients ages 12 years and older
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Gary Chiang, MD, MPH
Statistical Review	Matthew Guerra, Ph.D.
Pharmacology Toxicology Review	Jiaqin Yao, Ph.D.
CMC Review/OBP Review	Yubing Tang, Ph.D.
Clinical Pharmacology Review	An-Chi Lu, M.S., Pharm.D.
DDMAC	
DSI	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation

Signatory Authority Review

1. Introduction

This is a 505 (b)(2) supplemental application to NDA 50819 for Acanya Gel ((clindamycin phosphate 1.2% and benzoyl peroxide 2.5%). The applicant, Dow Pharmaceutical Sciences is seeking an approval of a new product formulation with a higher, than in Acanya, strength of benzoyl peroxide (clindamycin phosphate 1.2% and benzoyl peroxide 3.75%). The original Acanya application approved under NDA 50819 in October, 2008 was a 505 (b)(2) application. The indication remains unchanged- the topical treatment of acne vulgaris in patients 12 years of age and older.
There are no outstanding clinical or regulatory concerns. The review team has completed the review of this application and recommended an approval. This review will briefly summarize the review team conclusions and my concurrence with the approval recommendation.

2. Background

The drug product is a fixed-dose combination of a lincosamide antimicrobial (clindamycin phosphate 1.2%) and bacteriocidal/keratolytic (benzoyl peroxide 3.75%) in a dosage form of gel.
Both active ingredients have been approved individually in various formulations for marketing in the United States. Additionally, this combination is currently marketed in the United States as Acanya® Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%), Duac® Topical Gel (clindamycin 1% - benzoyl peroxide 5%), and BenzaClin® Gel (clindamycin 1% - benzoyl peroxide 5%), in addition to several generic versions of this combination. Benzoyl peroxide is a monographed product and is available OTC in concentrations up to 10%. The applicant owns the rights to the data of the marketed formulations in Acanya® Gel and BenzaClin® Gel.

The applicant submitted data from a single, randomized, multicenter, vehicle-controlled, Phase 3 trial. The applicant relied on the Agency findings of safety for the marketed NDA products, including non-clinical data and long-term safety data from the clinical experience of the marketed products.

There are no outstanding issues that preclude approval of this application.

3. CMC/Device

(b) (4) for the higher concentration of benzoyl peroxide. The manufacturers and (b) (4) are identical to those already approved for Acanya Gel.

(b) (4)

Manufacturing site inspections were acceptable. There are no outstanding issues.
I concur with the conclusion reached by CMC reviewer on approvability of this application.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/ toxicology data were submitted with this application.

5. Clinical Pharmacology/Biopharmaceutics

The applicant requested a waiver for a conduct of PK trial with Onexton Gel. No new clinical pharmacology/biopharmaceutics data were submitted with this application.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The applicant submitted data from a single, randomized, multicenter, vehicle-controlled, parallel group, Phase 3 trial. A total of 498 subjects 12 years of age and above with acne vulgaris were enrolled from 28 centers in the U.S. and randomized to either ONEXTON gel or vehicle gel. Co-primary endpoints were the proportion of subjects who achieve at least a 2-grade reduction from baseline to Week 12 in the Evaluator's Global Severity Score (EGSS), absolute change in inflammatory lesion counts from baseline to Week 12, and absolute change in non-inflammatory lesion counts from baseline to Week 12.
Co-secondary endpoints were the proportion of subjects who achieve an EGSS of 0 (clear) or 1 (almost clear) at Week 12, percent change in inflammatory lesion counts from baseline to Week 12, and percent change in non-inflammatory lesion counts from baseline to Week 12.
The co-primary and co-secondary efficacy endpoints were all statistically significant.

ONEXTON (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75% was superior to vehicle gel in the treatment of acne vulgaris. Statistical reviewer found that efficacy results were comparable to those seen with Acanya. No direct comparison of those two formulations was performed by the applicant.

8. Safety

Clincial trial enrolled 498 subjects. Of those, 243 were exposed to Onexton Gel applied once daily and 236 were exposed to vehicle placebo. The planned duration of exposure was 12 weeks. Approximately 22% of ONEXTON subjects and 24% of vehicle subjects reported at least one adverse event.
The most common treatment-emergent adverse event were nasopharyngitis and sinusitis (7.4% and 2.9%, respectively). Specific treatment-related adverse events include: burning sensation, contact dermatitis, pruritus, and rash. All occurred with the frequency of less than 1%.
No new safety concerns were identified in the clinical trials conducted with ONEXTON Gel, and expected adverse events would primarily be limited to local irritation adverse reactions.

9. Advisory Committee Meeting

No Advisory Committee discussion was necessary for this application.

10. Pediatrics

This supplemental application did not trigger PREA.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

Labeling discussions with the applicant have concluded, with submission of agreed upon physician's labeling, patient labeling, and carton/container labeling.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action - This application will be approved.

- Risk Benefit Assessment

The benefits and risks of this product used for the treatment of acne in a population 12 years of age and older are consistent with the benefits and risk observed with similar products. This applicant has provided sufficient data to support the approval of this new formulation.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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

/s/

TATIANA OUSSOVA
11/21/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b)(2)
Application Number(s)	050819
Priority or Standard	Standard
Submit Date(s)	27-JAN-2014
Received Date(s)	30-JAN-2014
PDUFA Goal Date	20-NOV-2014
Division / Office	DDDP/ODE3/OND
Reviewer Name(s)	Gary Chiang, MD, MPH
Review Completion Date	10-OCT-2014
Established Name	Clindamycin Phosphate and Benzoyl Peroxide
(Proposed) Trade Name	ONEXTON GEL
Therapeutic Class	Lincosamide antimicrobial and bacteriocidal/keratolytic
Applicant	Dow Pharmaceutical Sciences
Formulation(s)	Gel
Dosing Regimen	Once Daily
Indication(s)	Moderate to severe acne vulgaris
Intended Population(s)	Patients 12 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals North America, LLC, has submitted a supplement to the NDA 50819 for topical drug product Acanya® (clindamycin phosphate 1.2% - benzoyl peroxide 2.5%) Gel, proposing a new formulation with clindamycin phosphate 1.2% and benzoyl peroxide 3.75% (ONEXTON Gel). The combination product is indicated for the once daily topical treatment of acne vulgaris in patients 12 years and older.

Both active ingredients have been approved individually in various formulations for marketing in the United States. Additionally, this combination is currently marketed in the United States as Acanya® Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%), Duac® Topical Gel (clindamycin 1% - benzoyl peroxide 5%),and BenzaClin® Gel (clindamycin 1% - benzoyl peroxide 5%), in addition to several generic versions of this combination. The regulatory pathway for the supplement is a 505(b)(2).

The applicant has demonstrated that ONEXTON Gel is safe and effective for the treatment of acne vulgaris in subjects 12 years and older when used once daily for 12 weeks in one single pivotal clinical study. The applicant owns the rights to the data from the upper and lower bracketed strengths of the marketed formulations in Acanya® Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%) and BenzaClin® Gel (clindamycin 1% - benzoyl peroxide 5%). The applicant will depend on the Agencies findings of safety and efficacy for the marketed NDA products, including non-clinical data and long-term safety from the clinical experience of the marketed products. From a clinical perspective, it is recommended that the application be approved.

1.2 Risk Benefit Assessment

Safety assessments for this application are based on clinical trial results as well as marketing experience for other combination products with clindamycin and benzoyl peroxide. Several combinations product with the same active ingredients are currently marketed in the United States. This includes Duac® Topical Gel (clindamycin 1% - benzoyl peroxide 5%), BenzaClin® Gel (clindamycin 1% - benzoyl peroxide 5%), and Acanya® Gel (clindamycin 1% - benzoyl peroxide 2.5%). In addition, there is extensive safety experience with each active ingredient marketed as individual formulations or over-the-counter preparations (benzoyl peroxide 2.5% – 10%).

There were no deaths or serious adverse events which were considered related to the proposed product. The most common adverse event associated with the use of ONEXTON Gel is application site irritation.

No new safety concerns were identified in the clinical trials conducted with ONEXTON Gel, and expected adverse events would primarily be limited to local irritation adverse reactions. The benefit of this topical product outweighs its risk. This product does not enhance clinician options for the treatment of this disease as there are other similar products with minor formulation differences for the treatment of acne vulgaris.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for REMS or additional risk management steps beyond product labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

The combination product clindamycin phosphate 1.2% -benzoyl peroxide 3.75% gel has been referred to by the following names in the applicant's submission:

- 1.2% clindamycin phosphate/3.375% BPO product
- Acanya 3.75% Gel
- ONEXTON Gel
- ACYA Gel

The proposed topical combination drug product, ONEXTON Gel, consists of clindamycin phosphate 1.2% (lincosamide antimicrobial) and benzoyl peroxide 3.75% (bacteriocidal/keratolytic) in an aqueous gel-based formulation, developed for the treatment of moderate to severe acne vulgaris.

Acanya® Gel (clindamycin 1% - benzoyl peroxide 2.5%) consisted of a 505(b)(2) application referencing DUAC® Topical Gel (clindamycin 1% - benzoyl peroxide 5%) and BenzaClin® Gel (clindamycin 1% - benzoyl peroxide 5%) during its approval. This application was correctly identified as a 505 (b)(2) and the applicant does not need a bridge to the original products.

Reviewer's comment: *A 505 (b)(2) applicant may amend or supplement a 505 (b)(2) application to seek approval of a different strength without breaching the Medicare Modernization Act of 2003 (MMA)*.

The original Acanya application approved under NDA 50819 in October, 2008 was a 505 (b)(2) application. There was a review concern regarding the bridge for systemic safety, as not clinical bridging study with Benzaclin was conducted to support the application.

The supervisory review for Acanya by Dr, Stanka Kukich summarizes the review of the bridge for the original application:

"This application was submitted under 505(b)(2) section of the Federal Food, Drug, and Cosmetic Act and it relies on the published literature to provide necessary nonclinical information regarding benzoyl peroxide and clindamycin.

The applicant intended to reference genotoxicity data for clindamycin in the BenzaClin Gel label through establishing a clinical bridge that included clinical bioavailability study of (b) (4) *(clindamycin phosphate* (b) (4) *and benzoyl peroxide* (b) (4) *) Gel and BenzaClin Gel, an approved listed drug. The applicant did not include to-be-marketed formulation of clindamycin/benzoyl peroxide in the clinical bioavailability study and, therefore, cannot reference data in the BenzaClin Gel label. However, the applicant has conducted carcinogenicity studies with the product, therefore, a clinical bridge or information from the literature regarding genotoxicity of clindamycin is not necessary for the approvability of this product.*

During the development program for clindamycin phosphate 1.2% and benzoyl peroxide 2.5%, it was discussed that the in vivo bioavailability study under maximum use conditions would be needed and that an in vitro percutaneous absorption study alone would not be sufficient because non-viable normal skin has different permeation properties than diseased skin. The recommendation from clinical pharmacology is that the data from an in vivo bioavailability study under maximum use conditions for 1% clindamycin/2.5% benzoyl peroxide have to be provided preapproval or as a post-marketing commitment depending on the safety of this product.

The applicant has agreed to conduct, as a post-marketing commitment, a maximum use systemic exposure bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients in Acanya Gel.

Long-term safety studies are not recommended since the safety profile of clindamycin and benzoyl peroxide has been well described and well known. No safety signal was identified in the clinical trials."

The PMC was successfully completed. Adequate nonclinical information for this ONEXTON Gel application is available to determine that additional nonclinical information is not necessary, and the nonclinical review team recommends approval of the current application.

2.1 Product Information

Acanya (clindamycin phosphate and BPO) Gel, 1.2%/2.5% for the topical treatment of acne vulgaris was approved on October 23, 2008 under NDA 50819. Each of the active ingredients is described below and has significant clinical use experience.

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic derived from the parent compound lincomycin. Its mechanism of action is the inhibition of bacterial protein synthesis at the bacterial ribosome. Clindamycin binds preferentially to the 50S ribosomal subunit and affects the process of peptide chain initiation. Clindamycin phosphate is inactive *in vitro* – rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin. Clindamycin phosphate has not been shown to be keratolytic, does not change the sebum excretion rate, but has been shown to inhibit the chemotactic activity of human leukocytes *in vitro*, which may be a mechanism by which certain antimicrobial agents suppress inflammatory disease.

Benzoyl peroxide is a lipophilic oxidizing agent that kills the anaerobic bacterium *Propionibacterium acnes*, one of the primary causes of acne by depriving the bacteria of the anaerobic environment necessary for growth. Benzoyl peroxide is recognized as GRASE, (generally recognized as safe and effective) for treatment of acne vulgaris in concentrations of 2.5%-10%. It is present in many acne treatment products, including over-the-counter soaps and lotions. The final monograph citation for benzoyl peroxide is published in the Federal Register 2010; 75(42):9767-77.

In addition, other combination products containing 1.2% clindamycin phosphate and BPO (at either 2.5% or 5%) have received Agency approval for the treatment of acne. These include:

1. BenzaClin ((b) (4) clindamycin phosphate, 5% benzoyl peroxide) Topical gel on December 21, 2000 (NDA 50756);
2. Duac (1/2% clindamycin phosphate, 5% benzoyl peroxide) Topical Gel on August 26, 2002 (NDA 50741);
3. Acanya (1.2% clindamycin phosphate, 5% benzoyl peroxide) Gel on October 23, 2008 (NDA 50819)

Although GRASE, BPO is an inherently irritating active ingredient associated with dose dependent irritation (erythema, stinging, burning) and dryness, including flaking.[1] Benzoyl peroxide gel is available as an over-the-counter (OTC) monotherapy for the topical treatment of acne in concentrations from 2.5% - 10%. The Advisory Review Panel on OTC Antimicrobial (II) Drug Products also recognized BPO "is a dose-dependent skin irritant that can also lead to sensitization" and prompted the OTC monograph to specifically require information regarding potential skin irritation to appear on the label (47 FR 12430; 75 FR 9767). Given its irritating effects, varying strengths of BPO allows patients and physicians to increase flexibility in optimizing topical acne therapy.

1 Ceilley RI. Advances in topical delivery systems in acne: new solutions to address concentration dependent irritation and dryness. *Skinmed* 2011 Jan-Feb;9(1):15-21.

2.2 Tables of Currently Available Treatments for Proposed Indications

Clindamycin and benzoyl peroxide are approved topical agents in the treatment of acne vulgaris, alone or in combination. Depending on the severity, there are a number of other topical and systemic drugs available for the treatment of acne vulgaris. These include topical as well as oral antibiotics, retinoids of various strengths, and benzoyl peroxide in monotherapy or in combination drug products. The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne.

Table 1: Topical Antimicrobials

Medications	Dose	List of Preparations
Benzoyl peroxide†	Twice daily	Multiple 2.5% to 10% gels, lotion, creams, pads, masks, cleansers
Clindamycin	Twice daily	1% gel, lotion, solution, foam
Erythromycin	Twice daily	2% gel, solution
Dapsone	Twice daily	5% gel
Sodium sulfacetamide (KLARON®)	Twice daily	10% lotion, wash, suspension, pad plus 10% urea

Source: Adapted from a previous clinical review Gary Chiang MD, MPH
† Benzoyl peroxide is non-prescription

Table 2: Topical Combination Products

Medications	Dose	List of Preparations
Benzoyl peroxide 5% - Clindamycin 1% (BENZACLIN® and DUAC®)	Twice daily	Gel
Benzoyl peroxide 5% - Erythromycin 3% (BENZAMYCIN®)	Twice daily	Gel
Benzoyl peroxide 2.5% - Clindamycin 1.2% (ACANYA®)	Once daily	Gel
Clindamycin 1.2% - Tretinoin 0.025% (ZIANA®)	Once daily, at bedtime	Gel
Benzoyl peroxide 2.5% - Adapalene 0.1% (EPIDUO®)	Once daily	Gel
Azelaic acid (FINACEA® and AZELEX®)	Twice daily	20% cream, 15% gel

Source: Adapted from a previous clinical review Gary Chiang MD, MPH

Table 3: Retinoids (Topical and Oral)

Medications	Dose	List of Preparations
Topical Retinoids		
Tretinoin	Once daily, at bedtime	**Creams:** 0.025%, 0.05%, 0.1% **Gels:** 0.01%, 0.025%, 0.05% **Microsphere gels:** 0.04%, 0.1% **Prepolyolprepolymer gel:** 0.025%
Adapalene	Once daily, at bedtime	**Cream:** 0.1% **Gels:** 0.1%, 0.3%
Tazarotene	Once daily, at bedtime	**Creams:** 0.05%, 0.1% **Gels:** 0.05%, 0.1%
Oral Retinoid		
Oral isotretinoin	0.5mg/kg/day, increasing to 1mg/kg/day; total dose 120 to 150mg/kg over 20 weeks	**oral**

Source: Adapted from a previous clinical review Gary Chiang MD, MPH

Table 4: Oral Antibiotics

Medications	Dose
Tetracycline	500mg twice daily
Doxycycline	50 to 100mg twice daily or 150mg once daily
Minocycline	50 to 100mg twice daily or 1mg/kg.day or the extended release formulation
Erythromycin	500mg twice daily
Trimethoprim-sulfamethoxazole	160mg/800mg once to twice daily
Azithromycin [a]	Intermittent dosing due to long drug half-life; optimum regimen unknown

Source: Adapted from a previous clinical review Gary Chiang MD, MPH
Note: Antibiotics are frequently used in clinical practice, but may not be approved for the indication.
[a] Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. Dermatol Ther. 2008;21(2):86-95.

Table 5: Hormonal Agents

Medications	Dose
Combination oral contraceptives (estrogen/progestin)	Once daily
Spironolactone	25 to 200mg/day; doses of 50 to 100mg/day may be as effective as higher doses and reduce side effects

Source: Adapted from a previous clinical review Gary Chiang MD, MPH

2.3 Availability of Proposed Active Ingredient in the United States

Topical clindamycin phosphate 1% was first approved in 1980. In 1987, Cleocin® T topical gel at a strength of 1% (base equivalent) was approved for the treatment of acne vulgaris. Clindamycin is available systemically as oral and intravenous formulation for the treatment of serious infections caused by anaerobic bacteria and for susceptible strains of streptococci, staphylococci, and pneumococci, while topical clindamycin is indicated only for acne vulgaris.

Benzoyl peroxide is widely available over-the-counter in concentrations of 2.5% to 10% and is recognized as GRASE for the treatment of acne vulgaris.

2.4 Important Safety Issues With Consideration to Related Drugs

The adverse event profile of each of the active ingredients is well-established through extensive clinical experience. Antibiotic associated colitis is a potentially serious concern with the use of clindamycin. Orally and parenterally administered clindamycin has been associated with severe colitis. The use of the topical formulation may result in the absorption of the antibiotic from the skin surface, and cases of antibiotic associated colitis have been reported with topical use. [2,3] Studies indicate that the toxin produced by *Clostridium difficile* is the primary cause of antibiotic associated colitis.

Benzoyl peroxide is rapidly metabolized in the skin to benzoic acid. The systemic absorption is minimal but elevated plasma levels of benzoic acid have been demonstrated after topical application. Systemically absorbed benzoic acid undergoes rapid renal clearance that precludes passage through the liver; no overt systemic toxicity due to drug accumulation is expected. Benzoyl peroxide can cause skin irritation and desquamation when applied topically.

2 Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol 1986; 122 (5): 583-4.
3 Milstone EB, McDonald AJ, Scholhamer Jr CF. Pseudomembranous colitis after topical application of clindamycin. Arch Dermatol 1981; 117 (3): 154-5.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Two meetings were held with the Agency regarding the ACYC 3.75% product. A Pre-NDA teleconference was held on May 2, 2012 to discuss the proposed higher strength BPO product. The sponsor proposed a single Phase 3 clinical trial with the ACYC 3.75% product arm and a vehicle arm in in patients with acne vulgaris. The Agency suggested that two adequate and well controlled studies are generally recommended but also provided that a single study may be acceptable provided the design and statistical findings are sufficiently robust. The Agency also gave advice on relying on the findings of safety and effectiveness of Benzaclin with an established clinical bridge to the approved product or having the right of reference. Without owning the original data, or the right of reference to the Benzaclin product, the sponsor could not rely on that data.

2.6 Other Relevant Background Information

Acne vulgaris is a chronic disease of pilosebaceous follicles that is multi-factorial in etiology and is characterized by the formation of two major types of acne lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe cases, nodules/nodulo-cystic lesions).[4] 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.[5] Two of the most commonly used medications for the treatment of acne are clindamycin and benzoyl peroxide. Clindamycin is an antimicrobial agent that is effective in reducing the colonization of *Propionibacterium acnes,* the predominant bacterium associated with lesion inflammation, within sebaceous follicles. Clindamycin also has anti-inflammatory properties and has been postulated to have indirect comedolytic activity. Benzoyl peroxide is a topical antimicrobial agent with potent bactericidal effect, in addition to comedolytic activity. Given the multiple etiologic factors contributing to the development of acne lesions, combination therapies are often recommended.

3 Ethics and Good Clinical Practices

The Division of Scientific Investigators (DSI) was not consulted to review the conduct of the single pivotal trial.

Reviewer's comment: The clinical team, in consultation with the biostatistics review team, concluded that there were no specific concerns about study sites following preliminary review of the data, and no clinical study sites were referred to DSI for inspection.

4 Gollnick HP, Zouboulis CC, Akamatsu H, Kurokawa I, Schulte A. Pathogenesis and pathogenesis related treatment of acne. J Dermatol 1991;18:489-99.
5 Feldman S, Careccia RE, Barham KL, Hancox J. Diagnosis and treatment of acne. Am Fam Physician. 2004;69(9):2123-30.

3.1 Submission Quality and Integrity

Overall, the quality of the application is acceptable.

3.2 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and the compliance with local and FDA regulatory requirements. The protocol and Informed Consent Forms were reviewed by the Investigations Review Board (IRB) associated with the trial sites or by consulting central IRB. Written informed consents were obtained from subjects at the first (baseline) visit.

3.3 Financial Disclosures

The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators. It was also affirmed that none of the clinical investigators disclosed any proprietary interest in the product, or significant equity interest in the sponsor company. Certification was made that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

(b) (4) the corresponding higher concentration of benzoyl peroxide. The manufacturers (b) (4) are identical to those already approved for Acanya Gel, 2.5%. The already approved container closure systems used for the marketed Acanya Gel, 2.5% (3.5 g physician samples packaged in (b) (4) and 50 g commercial product packaged in (b) (4) are proposed for ONEXTON Gel, 3.75%.

(b) (4)

(b) (4)

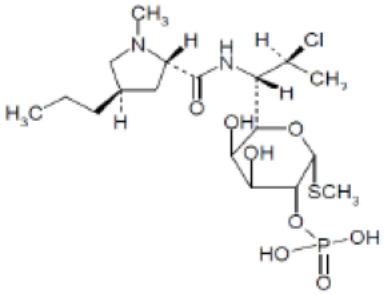
CDER Office of Compliance has issued overall "ACCEPTABLE' recommendation to the manufacturing and testing facilities.

As a result, this supplement is recommended for APPROVAL pending the resolution of the recommended labeling changes.

Figure 1: Chemical name and Structure

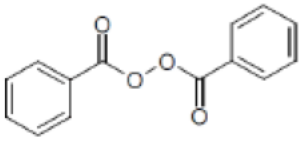
Clindamycin Phosphate, USP

- Methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate)
- $C_{18}H_{34}ClN_2O_8PS$



Benzoyl Peroxide (BPO)

- Peroxide, Dibenzoyl
- $C_{14}H_{10}O_4$



4.2 Clinical Microbiology

Clinical microbiology was not consulted for this supplement. No specific clinical microbiology claims were sought by the applicant.

4.3 Preclinical Pharmacology/Toxicology

Non clinical studies were not conducted for this application. Any information or data necessary for approval of NDA 50,819 that Dow Pharmaceutical Sciences does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 50,819.

The sponsor owns the approved drugs BenzaClin Gel (NDA 50-756) and Acanya Gel (NDA 50-819) for the treatment of acne vulgaris. This product is a combination of Clindamycin, an antibiotic that decreases *Propionibacterium acnes* (*P. acnes*) colonization of skin follicles and reduces the inflammatory aspect of acne and benzoyl peroxide, an antibacterial agent effective against *P. acnes* through oxidation. Additionally, benzoyl peroxide reduces non-inflammatory lesions, possibly through induction of keratolysis and desquamation. Because the sponsor owns both BenzaClin Gel (b) (4) clindamycin phosphate and 5% benzoyl peroxide) and Acanya Gel (1.2% clindamycin phosphate and 2.5% benzoyl peroxide), no new nonclinical studies have been submitted to support this sNDA for Onexton Gel (1.2% clindamycin phosphate and 3.75% benzoyl peroxide) in the (b) (4) as Acanya Gel for the same indication.

The Pharmacology/Toxicology reviewer is recommending for approval. Labeling recommendations are provide in the Pharmacology/Toxicology review by Jiaqin Yao, Ph.D.

4.4 Clinical Pharmacology

This efficacy supplement is for the introduction of ONEXTON Gel (clindamycin phosphate and benzoyl peroxide), 1.2%/3.75%, in addition to the already approved Acanya Gel, 1.2%/2.5%. Acanya® (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/2.5% for the treatment of acne vulgaris was approved on October 23, 2008. The difference between the proposed ONEXTON Gel and the approved Acanya Gel is the concentration of benzoyl peroxide (3.75% vs. 2.5%). The efficacy supplement contains data from one Phase 3 safety and efficacy trial V01-ACYC-301. This trial did not include pharmacokinetic (PK) assessments. The sponsor requests a waiver for conduct of PK trial with ONEXTON Gel.

Reviewer's comment: *The Clinical Pharmacology recommendation is for approval.*

4.4.1 Mechanism of Action

Clindamycin: Clindamycin is a lincosamide antibacterial.

Benzoyl Peroxide: Benzoyl peroxide is an oxidizing agent with bacteriocidal with keratolytic effects, but the precise mechanism of action is unknown.

4.4.2 Pharmacodynamics

In terms of [redacted] ONEXTON Gel [redacted] Acanya Gel [redacted] for the concentration of benzoyl peroxide (3.75% and 2.5%, respectively), but is [redacted] BenzaClin Gel. BenzaClin Gel has an approved generic form, [redacted] ANDA 65443), which was shown to be bioequivalent to BenzaClin Gel in a bioequivalence (BE) trial with clinical endpoint and has a [redacted] to ONEXTON Gel [redacted] for the concentration of benzoyl peroxide (5% vs. 3.75%) and propylene glycol [redacted] **Table 6** is an abbreviated table of select components (active ingredients and propylene glycol) of these formulations. The propylene glycol concentration in [redacted] than ONEXTON Gel [redacted]. Propylene glycol is [redacted]

Table 6: Product Composition between Acanya Gel, ONEXTON Gel, and [redacted] for Benzoyl Peroxide, Clindamycin, and Propylene Glycol

Ingredients	Acanya Gel (%)	Onexton Gel (%)	[redacted] (%)
Benzoyl Peroxide	2.50	3.75	5.00
Clindamycin Phosphate	1.20	1.20	1.20
Propylene Glycol	[redacted]		

4.4.3 Pharmacokinetics

The systemic exposures of clindamycin for Acanya Gel (once daily dosing) and BenzaClin Gel (twice daily dosing) are listed in **Table 7**. At steady state, the Cmax for Acanya Gel ranges from 0.51 to 3.30 ng/mL, and 1.43 to 7.18 ng/mL for BenzaClin Gel. The mean AUC is 8.42±6.007 ng*hr/mL for Acanya Gel, and 30.34±17.39 ng*hr/mL for BenzaClin Gel.

Table 7: The Systemic Exposures of Clindamycin for Acanya Gel and BenzaClin Gel

	Measured	Lower Limit of Quantitation	Mean AUC[a] (ng·hr/mL)	C_{max}[b] (ng/mL)
Acanya Gel	Day 30	0.5 ng/mL	8.42 ± 6.007	0.51 to 3.30
BenzaClin Gel	Day 5	1 ng/mL	30.34 ± 17.394	1.43 to 7.18

[a] AUC presented is AUC_{0-t} (n=6) for Acanya Gel and AUC_{SS} (n=12) for BenzaClin Gel. The $AUC_{0-\infty}$ for Acanya Gel is 24.26 (n=1).

[b] C_{max} presented is the range from minimum to maximum. Values BLQ were excluded for Acanya Gel and set to 0 to BenzaClin Gel.

Regarding absorption of benzoyl peroxide, because the metabolism of benzoyl peroxide to benzoic acid in the skin is complete and rapid, its plasma concentration is not assessed. Since benzoic acid is an endogenous compound and it is also widely used as a food additive (that is considered safe in humans), it would be difficult to accurately evaluate treatment-related exposure of benzoic acid. The contribution of benzoic acid from exogenously administered benzoyl peroxide in ONEXTON Gel is also expected to be limited.

Lastly, in the Phase 3 trial of ONEXTON Gel (V01-ACYC-301), the sponsor stated there were no events associated with gastrointestinal disorders which would be expected with high circulating levels of clindamycin. As additional secondary supporting evidence, there are six approved products with 1.2% clindamycin phosphate. These products, including Ziana Gel (clindamycin phosphate 1.2% and tretinoin 0.025%), Veltin Gel (clindamycin phosphate 1.2% and tretinoin 0.025%), Cleocin Solution 1% (clindamycin phosphate (b) (4)), Clindagel 1% (clindamycin phosphate (b) (4)), Evoclin Foam (clindamycin phosphate (b) (4)), and Duac Gel (clindamycin phosphate 1.2% and benzoyl peroxide 5%), appear to have low clindamycin systemic exposure.

In conclusion, based on the available data, the systemic exposure of clindamycin following once daily administration of ONEXTON Gel would likely be low and bracketed by concentration observed for approved products Acanya Gel (NDA 50819) and (b) (4) (ANDA 65443) and not expected to cause systemic safety concerns. (b) (4) was previously bridged to BenzaClin Gel via a BE trial with clinical endpoint. Under the aforementioned circumstances, the PK waiver for this application is acceptable.

5 Sources of Clinical Data

The applicant owns the data for Acanya Gel (clindamycin phosphate 1.2%/benzoyl peroxide 2.5%) and intends to rely on the data from the original Acanya Gel approval to bracket the new

ONEXTON Gel (clindamycin phosphate 1.2%/benzoyl peroxide 3.375%). The applicant has established a clinical bridge to the safety and efficacy of Acanya Gel through bracketing of the BPO concentrations and performance of a single Phase 3 safety and efficacy study comparing ONEXTON Gel to vehicle gel.

5.1 Tables of Studies/Clinical Trials

Table 8: Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Pivotal	V01-ACYC-301	Module 5.3.5.1	Safety and Efficacy	Randomized, Double-Blind, Parallel, Vehicle Controlled	ACYC Gel (clindamycin phosphate 1.2%/benzoyl peroxide 3.75%); Pea size amount applied to entire face once daily; Topical	ACYC Gel -253 ACYC Vehicle Gel – 245	Patients with moderate to severe acne vulgaris	12 weeks	Complete; Final Report

5.2 Review Strategy

The single Phase 3 clinical trial will be the pivotal evaluation of the drug product.

5.3 Discussion of Individual Studies/Clinical Trials

The single Phase 3 clinical trial was titled: A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of ACYC and ACYC Vehicle Gel in the Treatment of Acne Vulgaris.

This was a multicenter, randomized, double-blind, vehicle-controlled study designed to evaluate the efficacy, safety, and tolerability of ACYC Gel relative to its vehicle (ACYC Vehicle Gel) in subjects 12 to 40 years of age (inclusive) with moderate to severe acne. Randomized subjects applied blinded study drug once daily (at about the same time of day) to the face for 12 weeks. Treatment evaluations were performed at regular 4-week intervals. The design for the clinical study was similar to that used to compare Acanya Gel with its vehicle, including the inclusion/exclusion criteria and the criteria for success.

The entry criteria were representative of patients in the US who have moderate to severe acne. The selected treatment duration of 12-weeks for the evaluation of the study endpoints and was consistent with the overall therapeutic standard of care for acne. The use of multiple investigational centers and a double-blind randomization scheme eliminated single-observer bias.

The subjects were assigned to study treatments based on a predetermined randomization schedule.

Subjects were instructed on the use of pre-approved moisturizers, sunscreens, and cleansers during the study and were required to report all such uses. Subjects who wore makeup were instructed not to wear makeup at any of the assessment study visits. Subjects were also instructed to avoid excessive ultraviolet radiation exposure as might be experienced while sunbathing or tanning. Additionally, subjects were instructed not to apply the study drug on the day of each study visit, prior to the visit. Attempts were made to keep the individual use of concomitant therapies consistent; birth control pills used exclusively for acne were prohibited, as were other medications that could have interfered with the efficacy and/or safety assessments.

The determinations of efficacy and the assessments of cutaneous safety were based on evaluator-blinded evaluations. All evaluators were board-certified/board-eligible dermatologists or dermatologists with documentation of appropriate experience and training.

Approximately 500 subjects were planned for randomization across approximately 25 investigational centers in the US.

Efficacy:

The efficacy variables included the EGSS and lesion counts (inflammatory and non-inflammatory) collected at Screening/Baseline and all subsequent study visits. The co-primary endpoints included the absolute change from Baseline to Week 12 in mean inflammatory lesion counts, the absolute change from Baseline to Week 12 in mean non-inflammatory lesion counts, and the proportion of subjects who achieved at least a 2-grade reduction from Baseline at Week 12 in the EGSS.

The efficacy variable collected in this study included the EGSS and lesion counts.

Table 9: V01-ACYC-301: Evaluator's Global Severity Score

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne
1	Almost clear	Rare noninflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Noninflammatory lesions predominate with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions
5	Very severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and more than 2 nodulocystic lesions

All lesion counts (inflammatory and non-inflammatory) reported in this study represented a static assessment and were taken from the subject's face. Inflammatory lesions included papules, pustules, and nodules. Non-inflammatory lesions included open and closed comedones. For the purposes of lesion counting, papules and pustules were counted and recorded together, nodules were counted and recorded separately, and open and closed comedones were counted and recorded together. For analysis purposes, nodules were included in the total inflammatory lesion count.

Inflammatory lesion count included the total number of facial papules, pustules, and nodules, and the non-inflammatory lesion count included the total number of open and closed facial comedones.

Table 10: V01-ACYC-301: Study Plan

PROCEDURES	Visit 1 [a] Screening	Visit 2 [b] Baseline (Day 0)	Visit 3 [b] Week 4 (Day 28 ± 3 days)	Visit 4 [b] Week 8 (Day 56 ± 3 days)	Visit 5 [c] Week 12 (Day 84 -3/+5 days)
Informed consent/assent	X				
Subject number obtained from IXRS	X				
Demographics and medical history	X				
Inclusion/exclusion criteria	X	X			
Previous Therapies	X				
PSS and Acne-QoL questionnaire		X			X
SSA[d]		X	X	X	X
Urine pregnancy test (all premenarchal females and females of childbearing potential)	X	X	X	X	X
Oily/shiny skin assessment		X			X
Lesion counts	X	X	X	X	X
EGSS	X	X	X	X	X
Abbreviated physical examination		X			X
Photographs (select investigational centers only)		X			X
Cutaneous safety evaluation		X	X	X	X
Cutaneous tolerability evaluation		X	X	X	X
Subject randomized in IXRS and kit number obtained		X			
Subject instructions administered		X			
Study containers weighed		X	X	X	X
Study drug dispensed[e]		X	X	X	
Application of first dose in clinic		X			
Test Materials Collected			X	X	X
Subject compliance reviewed			X	X	X
Concomitant and prohibited therapies reviewed	X	X	X	X	X
Adverse events	X	X	X	X	X
End of study eCRF					X

Abbreviations: Acne-QoL = acne-specific quality of life; eCRF = electronic case report form; EGSS = evaluator's global severity score; IXRS = interactive voice and web response system; PSS = patient satisfaction survey; SSA = subject self-assessment

[a] If no washout was needed, Visits 1 and 2 may have occurred on the same day; otherwise, Visit 2 occurred within 1 month of Visit 1.
[b] All visit dates were in reference to the Baseline visit (eg, Visit 4 occurred 8 weeks ± 3 days after the Baseline visit)
[c] All Week 12 procedures were completed for subjects who discontinued the study.
[d] The Week 2 SSA was sent home with instructions for the subject to complete the assessment 2 weeks later and to return the assessment at the Week 4 visit. The investigational center called the subject at Week 2 to remind them to complete the assessment.
[e] One container of study drug was dispensed at the Baseline, Week 4, and Week 8 visits. Unused study drug kits were maintained in a refrigerated area.

Safety:

Safety was primarily evaluated through a review of AEs (both volunteered and elicited), evaluator assessments of cutaneous safety (scaling and erythema), and subject assessments of cutaneous tolerability (itching, burning, and stinging). Each of the safety variables was collected at Baseline and all subsequent study visits. Separate from these safety assessments, abbreviated physical examinations (including height, weight, and vital signs) were conducted at Baseline and

Week 12, urine pregnancy tests were performed at every study visit on premenarchal females and females of childbearing potential, and concomitant medication uses were documented.

Cutaneous Safety Evaluations

Table 11: Scaling Assessment

Score	Grade	Description
0	None	No scaling
1	Mild	Barely perceptible, fine scales present on limited areas of the face
2	Moderate	Fine scale generalized to all areas of the face
3	Severe	Scaling and peeling of skin over all areas of the face

Table 12: Erythema Assessment

Score	Grade	Description
0	None	No evidence of erythema present
1	Mild	Slight pink coloration
2	Moderate	Definite redness
3	Severe	Marked erythema, bright red to dusky dark red in color

Cutaneous Tolerability Evaluations

Table 13: Itching Assessment

Score	Grade	Description
0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching that is somewhat bothersome
3	Severe	Intense itching that may interrupt daily activities and/or sleep

Table 14: Burning Assessment

Score	Grade	Description
0	None	No burning
1	Mild	Slight burning sensation, not really bothersome
2	Moderate	Definite warm, burning sensation that is somewhat bothersome
3	Severe	Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Table 15: Stinging Assessment

Score	Grade	Description
0	None	No stinging
1	Mild	Slight stinging sensation, not really bothersome
2	Moderate	Definite stinging sensation that is somewhat bothersome
3	Severe	Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Adverse events data was collected using MedDRA version 15.1.

6 Review of Efficacy

Efficacy Summary

A single clinical trial evaluated three co-primary efficacy endpoints at Week 12. The endpoints included absolute changes from Baseline in inflammatory lesion counts, the absolute change from Baseline in non-inflammatory lesion counts, and the percentage of subjects who achieved a 2 grade reduction from Baseline in EGSS.

Table 16: Results of the Co-Primary Efficacy Results at Week 12 for ONEXTON Phase 3 Clinical Trial (ITT).

	ONEXTON Gel N = 253	Vehicle Gel N = 245
EGSS: 2-grade reduction from baseline*	89 (35.2%)	41.6 (17.0%)
Inflammatory Lesions:		
Mean absolute change	16.3	8.2
Mean percent (%) reduction	60.4%	31.3%
Non-Inflammatory Lesions:		
Mean absolute change	19.2	9.6
Mean percent (%) reduction	51.8%	27.6%

Source: Agency Biostatistical Reviewer's analysis
(1) Missing data for the ONEXTON gel trial was imputed using MI-MCMC.
(2) Least squares means and p-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model. *The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

6.1 Indication

The proposed indication for ONEXTON Gel is for the topical treatment of acne vulgaris in patients 12 years of age and older.

6.1.1 Methods

The applicant conducted a single Phase 3 clinical trial in subjects 12 years of age and older with acne vulgaris. As discussed in the background section, the applicant was previously given the advice of conducting two clinical trials as part of the demonstration of safety and efficacy in the proposed drug product. The applicant argued that given the historical clinical use of clindamycin and benzoyl peroxide, both as a single product and in combination acne medications; in addition to the clinical success of Acanya Gel, the single Phase 3 clinical trial was sufficiently robust to provide adequate and well-controlled data for approval.

Reviewer's comment: *The applicant took a risk in their development plans for ONEXTON Gel. The Agency advised two Phase 3 clinical trials for safety and efficacy, but the applicant completed only a single trial. The historical use of clindamycin and benzoyl peroxide in acne is otherwise safe from the extensive clinical experience perspective. Clindamycin is in multiple topical acne products, including generics and over-the-counter products; and benzoyl peroxide is GRASE in a final monograph up to 10%. This reviewer recommends that the study provided by the applicant is sufficient for approval with consideration of the clinical history from the combination of clindamycin and benzoyl peroxide in treatment of acne vulgaris.*

6.1.2 Demographics

The ITT analysis set ranged in age from 12 to 40 years, with a mean (SD) age of 18.7 (5.82) years. The subjects were mostly balanced by sex (256 males and 242 females out of 498 subjects [51.4% and 48.6% respectively]), and were predominately not Hispanic or Latino (362 or 498 subjects [72.7%]) and White (418 of 498 subjects [83.9%]).

Subjects in the ONEXTON Gel group were younger (mean [SD]: 18.2 [5.60] years) than subjects in the Vehicle Gel group (mean [SD]: 19.3 [6.00] years); the differences in ages was statistically significant (p=0.020). There were no significant differences between treatment groups in regard to sex, ethnicity, or race.

Table 17: Subject Demographics for V01-ACYC-301 (ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	Total (N=498)	*p-value*
Age (years)				
Mean	18.2	19.3	18.7	0.020 [a]
Standard deviation	5.6	6.00	5.82	
Median	16.0	17.0	17.0	
Minimum to maximum	12 to 40	12 to 39	12 to 40	
Sex, n (%)				
Male	130 (51.4)	126 (51.4)	256 (51.4)	0.921 [b]
Female	123 (48.6)	119 (48.6)	242 (48.6)	
Ethnicity, n (%)				
Hispanic or Latino	64 (25.3)	72 (29.4)	136 (27.3)	0.241 [b]
Not Hispanic or Latino	189 (74.7)	173 (70.6)	362 (72.7)	
Race, n (%)				
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0.704 [b]
Asian	6 (2.4)	4 (1.6)	10 (2.0)	
Black or African American	33 (13.0)	24 (9.8)	57 (11.4)	
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.4)	2 (0.4)	
White	208 (82.2)	210 (85.7)	418 (83.9)	
Multiple/other	5 (2.0)	6 (2.4)	11 (2.3)	

[a] *P-value* from a 2-way analysis of variance with factors of treatment group and analysis center.
[b] *P-value* from a Cochran-Mantel-Haenszel general association test, stratified by analysis center.

6.1.3 Subject Disposition

A total of 498 subjects were randomized to study drug at 28 investigational centers in the US. Of these subjects, 253 were randomized to receive ONEXTON Gel and 245 were randomized to receive Vehicle Gel. Overall, 447 of the 498 subjects (89.8%) completed the study, including 234 subjects (92.5%) in the ONEXTON Gel group and 213 subjects (86.9%) in the Vehicle Gel group.

Within the ACYC Gel group, the most common reasons for study discontinuation were lost to follow-up (11 subjects; 57.9%) and withdrawal by subject (5 subjects; 26.3%). Additional reasons for discontinuation included noncompliance with the study drug (1 subject; 5.3%), withdrawal by parent/guardian (1 subject; 5.3%), and "other" (1 subject; 5.3%). No subject in

the ONEXTON Gel group died, discontinued due to an AE, or discontinued due to lack of efficacy.

Within the Vehicle Gel group, the most common reasons for study discontinuation were withdrawal by subject (13 subjects; 40.6%) and lost to follow-up (12 subjects; 37.5%). Additional reasons for discontinuation included AE (3 subjects; 9.4%), withdrawal by parent/guardian (3 subjects; 9.4%), and pregnancy (1 subject; 3.1%). No subject in the Vehicle Gel group died or discontinued due to lack of efficacy.

6.1.4 Analysis of Primary Endpoint(s)

A total of 498 subjects were randomized into the study at 28 investigational centers. All 498 subjects were included in the ITT analysis set, and 421 randomized subjected were in the PP analysis set.

Table 18: Baseline Disease Characteristics (ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
EGSS		
3 - Moderate	212 (83.8%)	200 (81.6%)
4 - Severe	41 (16.2%)	45 (18.4%)
Inflammatory Lesion Count		
Mean (SD)	27.2 (6.0)	26.7 (6.1)
Median	26.0	25.0
Range	20 - 40	20 - 46
Non-inflammatory Lesion Count		
Mean (SD)	38.3 (18.6)	37.2 (17.1)
Median	32	31
Range	20 - 98	20 - 96

Source: Biostatistical Reviewer's Analysis
SD: Standard Deviation

The ONEXTON Gel was clinically and statistically better to than the Vehicle Gel for the co-primary efficacy endpoints. Statistically significant differences between treatment groups were observed for the absolute change from Baseline in inflammatory lesion counts ($p<0.001$), the absolute change from Baseline in non-inflammatory lesion counts ($p<0.001$), and the percentage of subjects who achieved a 2-grade reduction from Baseline in the EGSS ($p<0.001$). The least squares (LS) mean (SD) absolute change from Baseline in inflammatory lesion counts was greater in the ONEXTON Gel group than in the Vehicle Gel group (16.3 vs 8.2, respectively), and the LS mean (SD) absolute change from Baseline in non-inflammatory lesion counts was greater in the ONEXTON Gel group than in the Vehicle Gel group (19.2 vs 9.6, respectively). The percentages of subjects who achieved a 2-grade reduction from Baseline in the EGSS were also greater in the ONEXTON Gel group than in the Vehicle Gel group (35% vs 17%, respectively).

Table 19: Results for the Co-Primary Efficacy Endpoints at Week 12 (MI-MCMC, ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value
EGSS: 2-grade reduction*	89 (35.2%)	41.6 (17.0%)	<0.001(1)
Absolute Change in Inflammatory Lesions:			
Mean*	16.3	8.2	
LS Mean(2)	16.2	8.3	<0.001(2)
Absolute Change in Non-inflammatory Lesions:			
Mean*	19.2	9.6	
LS Mean(2)	18.8	9.6	<0.001(2)

Source: Reviewer's Analysis
(1) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
(2) Least squares means and p-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model.
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

Reviewer's comment: *Efficacy was demonstrated adequately in this clinical trial. The statistical co-primary endpoints were observed consistently across study visits for the change from Baseline in both inflammatory and non-inflammatory lesion counts. The product is effective in the treatment of acne vulgaris as demonstrated by the co-primary endpoints.*

6.1.5 Analysis of Secondary Endpoints(s)

ONEXTON gel was statistically superior ($p < 0.001$) to vehicle gel on all three secondary efficacy endpoints. The results from the ITT and PP analyses were similar.

Table 20: Results for the Co-Primary Efficacy Endpoints at Week 12 (MI-MCMC, ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value
EGSS: Clear or Almost Clear*	72.1 (28.5%)	35.5 (14.5%)	<0.001(1)
Percent Change in Inflammatory Lesions:			
Mean*	60.4%	31.3%	
LS Mean(2)	60.6%	31.4%	<0.001(2)
Percent Change in Non-inflammatory Lesions:			
Mean*	51.8%	27.6%	
LS Mean(2)	51.6%	27.4%	<0.001(2)

Source: Reviewer's Analysis
(1) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
(2) Least squares means and p-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model.
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

6.1.6 Other Endpoints

Other endpoints were evaluated by the applicant in the clinical trial included:

- Oily/Shiny Skin Assessment Responses
- Subject self-assessment Responses
- Patient Satisfaction Survey Responses
- Summary of Acne-QoL Questionnaire Responses

Reviewer's comment: *The "other" endpoints described in the clinical trial were exploratory. The applicant did not provide validation to these Patient Reported Outcomes (PRO) and these endpoints will not be acceptable to include in the label of the product.*

6.1.7 Subpopulations

The results for the co-primary efficacy endpoints by gender, race (white and non-white), age (12-17 and 18-40) and baseline disease severity (EGSS) subgroups are presented in **Table 21**. For all three co-primary endpoints, the treatment effect was slightly greater in females than in males. This was also observed in the Acanya® Gel trials. For race, the effects of either treatment (ONEXTON or vehicle) were less pronounced for non-whites in comparison to whites; however, a small proportion of subjects (16.0%) were non-white and therefore inference from this subgroup lacks reliability. For all three co-primary endpoints, the treatment effect was greater in subjects aged 12-17 versus subjects aged 18-40 and the treatment effect was smaller in moderate subjects versus severe subjects; however, a small proportion of subjects (18%) were had a baseline disease severity of severe.

Table 21: Co-Primary Efficacy Results at Week 12 by Gender, Race, Age, and Baseline Disease Severity (MI-MCMC, ITT)

	EGSS (2-grade reduction)		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
Subgroup (N_o, N_v)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
Gender						
Male (130, 126)	28.2%	13.6%	15.4	8.7	17.4	8.8
Female (123, 119)	42.5%	20.5%	17.3	7.6	21.1	10.5
Race						
White (208, 210)	35.7%	18.8%	16.6	8.8	19.7	11.0
Non-White (45, 35)	32.8%	6.3%	14.7	4.5	17.0	1.3
Age						
12-17 (155, 134)	33.1%	8.5%	16.4	6.2	19.4	8.3
18-40 (98, 111)	38.5%	27.2%	16.2	10.5	18.8	11.3
Baseline Disease Severity (EGSS)						
Moderate (212, 200)	31.3%	16.7%	16.0	8.7	18.7	9.5
Severe (41, 45)	55.1%	18.3%	17.8	5.7	22.0	10.1

Source: Reviewer's Analysis
N_o: number of subjects in the ONEXTON treatment arm
N_v: number of subjects in the vehicle treatment arm
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

The results of the secondary efficacy endpoints by gender, race (white and non-white), age (12-17 and 18-40) and baseline disease severity (EGSS) subgroups are presented in **Tables 22**. The results for percent change in inflammatory and non-inflammatory lesion counts are similar to those for absolute change. For subjects with a baseline EGSS of moderate, an EGSS score of clear or almost clear at Week 12 is equivalent to ≥ 2-grade reduction; however, for subjects with a baseline EGSS of severe, an EGSS score clear or almost clear at Week 12 is a higher efficacy bar than a ≥ 2-grade reduction. Therefore, it is not surprising that the response rate for the secondary endpoint of EGSS score of clear or almost clear is less in the severe subgroup compared to the moderate subgroup.

Table 22: Secondary Efficacy Results at Week 12 by Gender, Race, Age, and Baseline Disease Severity (MI-MCMC, ITT)

	EGSS (clear or almost clear)		Percent Change in Inflammatory Lesions		Percent Change in Non-Inflammatory Lesions	
Subgroup (N_o, N_v)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
Gender						
Male (130, 126)	21.5%	12.3%	55.8%	32.3%	48.1%	30.2%
Female (123, 119)	35.9%	16.8%	65.3%	30.3%	55.7%	25.2%
Race						
White (208, 210)	28.7%	15.9%	60.5%	33.3%	52.9%	30.8%
Non-White (45, 35)	27.8%	6.2%	59.8%	19.3%	46.9%	8.4%
Age						
12-17 (155, 134)	27.6%	7.2%	59.9%	22.6%	50.5%	21.3%
18-40 (98, 111)	30.0%	23.2%	61.3%	41.8%	54.0%	35.3%
Baseline Disease Severity (EGSS)						
Moderate (212, 200)	31.3%	16.7%	61.9%	34.3%	52.1%	28.3%
Severe (41, 45)	14.1%	4.7%	52.6%	18.0%	50.5%	24.8%

Source: Reviewer's Analysis
N_o: number of subjects in the ONEXTON treatment arm
N_v: number of subjects in the vehicle treatment arm
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose-response evaluation of the drug product was completed. The clinical dosing regimen has been established with other products that contain the combination of clindamycin phosphate and benzoyl peroxide.

Subjects in the V01-ACYC-301 were instructed to use a pea-sized amount of the study drug applied to the entire face once daily for 12 weeks. Subjects were >90% compliant with this regimen and there were no findings during the study that would alter this dosing recommendation.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Based on the results from study V01-ACYC-301, ONEXTON Gel was effective in the treatment of moderate to severe acne vulgaris when used once daily for 12 weeks. The study demonstrated that there was no loss of efficacy over the 12 week treatment period and, efficacy improved from baseline through week 12. These data demonstrate that efficacy persists through the 12 week treatment period and there does not appear to be any tolerance effect.

6.1.10 Additional Efficacy Issues/Analyses

Comparison to Acanya® Gel

For the approval of Acanya® (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/2.5%, the applicant, Dow Pharmaceutical Sciences, conducted two identically designed Phase 3 trials (Study 012 and Study 017). Both studies were multicenter, randomized, double-blind, 4-arm (Acanya®, each monad, and vehicle) trials. The trials enrolled subjects aged 12 years or older, who had an EGSS of 3 (moderate) or 4 (severe), 17 to 40 inflammatory facial lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory facial lesions (open and closed comedones), and ≤ 2 facial nodules. The protocol specified co-primary and secondary efficacy endpoints are the same for the Acanya® Gel trials and the ONEXTON Gel trial.

The demographics of the Acanya® Gel trials are generally similar to those of the ONEXTON gel trial. The baseline disease characteristics of EGSS and inflammatory lesion counts are very similar between the Acanya® Gel trials and the ONEXTON trial. The average baseline non-inflammatory lesion count was higher in the Acanya® Gel trials compared to the ONEXTON trial.

Table 23 displays the efficacy results at Week 12 presented in the label for Acanya® Gel. For all endpoints presented in the table, Acanya® Gel was statistically superior to both monads and vehicle (all p-values less than 0.012). **Table 24** presents a side-by-side comparison of the results from the ONEXTON gel trial and the Acanya® Gel trials. The results are very similar for ONEXTON gel and Acanya® Gel.

Table 23: Efficacy Results for Acanya® Gel at Week 12 (ITT, LOCF)

		Acanya® Gel (N=399)	Clindamycin Gel (N=408)	BPO Gel (N=406)	Vehicle Gel (N=201)
Study 012	**EGSS[(1)]:**				
	Clear or Almost Clear	115 (29%)	84 (21%)	76 (19%)	29 (14%)
	2-grade reduction from baseline	131 (33%)	100 (25%)	96 (24%)	38 (19%)
	Inflammatory Lesions:				
	Mean Absolute Change	14.8	12.2	13.0	9.0
	Mean Percent Change	55.0%	47.1%	49.3%	34.5%
	Non-inflammatory Lesions:				
	Mean Absolute Change	22.1	17.9	20.6	13.2
	Mean Percent Change	45.3%	38.0%	40.2%	28.6%
		Acanya® Gel (N=398)	**Clindamycin Gel (N=404)**	**BPO Gel (N=403)**	**Vehicle Gel (N=194)**
Study 017	**EGSS[(1)]:**				
	Clear or Almost Clear	113 (28%)	94 (23%)	94 (23%)	21 (11%)
	2-grade reduction from baseline	147 (37%)	114 (28%)	114 (28%)	27 (14%)
	Inflammatory Lesions:				
	Mean Absolute Change	13.7	11.3	11.2	5.7
	Mean Percent Change	54.2%	45.3%	45.7%	23.3%
	Non-inflammatory Lesions:				
	Mean Absolute Change	19.0	14.9	15.2	8.3
	Mean Percent Change	41.2%	34.3%	34.5%	19.2%

Source: The label for Acanya® Gel (NDA 50819)
(1) EGSS was a 6-point scale, where the 6th category was "very severe."

Table 24: Comparison of the Efficacy Results at Week 12 for the ONEXTON Gel Trial and the Acanya® Gel Trials (ITT, MI-MCMC(1), LOCF(2))

			Study 012		Study 017	
	ONEXTON (N=253)	Vehicle (N=245)	Acanya (N=399)	Vehicle (N=201)	Acanya (N=398)	Vehicle (N=194)
EGSS(3):						
Clear or Almost Clear	29%	15%	29%	14%	28%	11%
2 grade reduction from baseline	35%	17%	33%	19%	37%	14%
Inflammatory Lesions:						
Mean Absolute Change	16.3	8.2	14.8	9.0	13.7	5.7
Mean Percent Change	60.4%	31.3%	55.0%	34.5%	54.2%	23.3%
Non-inflammatory Lesions:						
Mean Absolute Change	19.2	9.6	22.1	13.2	19.0	8.3
Mean Percent Change	51.8%	27.6%	45.3%	28.6%	41.2%	19.2%

Source: Reviewer's analysis and the label for Acanya® Gel (NDA 50819)
(1) Missing data for the ONEXTON gel trial was imputed using MI-MCMC.
(2) Missing data for the Acanya® gel trials was imputed using LOCF.
(3) EGSS for the ONEXTON gel trial was a 5-point scale while EGSS was a 6-point scale for the Acanya® gel trials.

Reviewer's comments: *The above analysis by the Agency Biostatistcal Reviewer provides some confidence of the efficacy in the single Phase 3 pivotal trial.*

The Agency Reviewer recommends for approval given the collective evidence provided by the applicant.

7 Review of Safety

Safety Summary

A single safety and efficacy Phase 3 clinical trial was completed with ONEXTON (clindamycin phosphate/benzoyl peroxide) 1.2%/3.75% Gel in subjects 12 years and older with moderate to severe acne vulgaris. This study compared the ONEXTON to-be-marketed formulation to Vehicle Gel. The safety of the product was similar to that observed in studies with lower and higher concentrations of benzoyl peroxide (BenzaClin and Acanya). Overall, the most frequent treatment emergent adverse event was nasopharyngitis (Drug 7.4% vs. Vehicle 5.1%). Few treatments related adverse events were observed. There were no serious adverse events or deaths observed in this clinical trial.

7.1 Methods

Clinical trial V01-ACYC-301 was conducted to evaluate the safety and efficacy of ONEXTON Gel for the treatment of subjects with moderate to severe acne vulgaris. A detailed discussion of the Phase 3 design is available in Section 5 of this review. The safety evaluation of this clinical trial demonstrated that the drug product was well tolerated and comparable to other drug products in this class. The applicant did not conduct a standard four-arm trial comparing the

combination to its respective monads due to the available data from Acanya and BenzaClin, as well as, (b) (4), which is a generic marketed product.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

V01-ACYC-301 is the only clinical trial conducted for ONEXTON Gel.

7.1.2 Categorization of Adverse Events

Adverse events are categorized by MedDRA version 15.1.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Not Applicable.

7.2 Adequacy of Safety Assessments

This safety review will discuss the single clinical trial conducted with ONEXTON Gel in subjects 12 years and older with acne vulgaris in detail. In addition to the data generated by the Phase 3 clinical trial, the sponsor presented safety information for Acanya Gel and BenzaClin Gel, which brackets the strength of the ONEXTON Gel.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 498 subjects were randomized into the trial. Of the 498 subjects, 479 were included in the safety population. The 19 subjects excluded from the safety analysis did not have post-baseline evaluations conducted and were excluded by protocol.

Table 25: V01-ACYC-301: Extent of Exposure (Safety)

	ONEXTON Gel (N=243)	Vehicle Gel (N=236)
Number of Application		
N	239	230
Mean	81.3	78.8
Standard deviation	6.56	14.31
Median	83.0	83.0
Minimum to maximum	50 to 96	8 to 98
Compliant, n (%) [a]		
Yes	233 (95.9)	228 (96.6)
No	10 (4.1)	8 (3.4)
Study Medication Used (g)		
N	231	224
Mean	46.2	48.3
Standard deviation	28.17	28.53
Median	39.6	44.4
Minimum to maximum	2 to 158	1 to 142

[a] A subject was considered compliant with dosing regimen if the subject applied at least 80% but no more than 120% of the expected applications, and did not miss more than 5 consecutive applications.

The mean amount applied did not seem to differ from the ONEXTON Gel arm to the Vehicle Gel arm. The compliancy numbers were also very similar in both arms. The safety population had essentially similar exposure to drug product.

7.2.2 Explorations for Dose Response

Dose-response was not explored with ONEXTON Gel.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed with the ONEXTON Gel.

7.2.4 Routine Clinical Testing

No clinical laboratory assessments were conducted in study V01-ACYC-301.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new metabolic, clearance, or interaction evaluation was completed with ONEXTON Gel. Class labeling will indicate that all clindamycin containing products will have a similar drug interaction section in the label. Specifically, avoid using ONEXTON Gel in combination with topical or oral erythromycin-containing products and avoid concomitant topical therapy due to

cumulative irritancy effects. Clindamycin has also been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents.

Reviewer's comment: *The label will have sufficient DRUG INTERACTIONS section to cover the clindamycin containing product class labeling.*

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Similar drug product class for combination products containing clindamycin phosphate and benzoyl peroxide will have similar CONTRAINDICATION section and WARNINGS AND PRECAUTION section. These will contain language for hypersensitivity, colitis/enteritis, and avoidance of sun exposure.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in V01-ACYC-301.

7.3.2 Nonfatal Serious Adverse Events

The treatment emergent adverse events (TEAEs) that occurred in this trial were similar in both arms. None of the TEAEs were serious, most were mild or moderate in severity, and most were not related to the study drug.

The most frequent TEAE was nasopharyngitis (7.4% in ONEXTON and 5.1% in Vehicle). No other TEAEs occurred at a frequency more than 5% and none of the individual TEAEs that occurred at a frequency of 1% or more were assessed by the investigator as treatment-related or were associated with skin and subcutaneous tissue disorders.

Table 26: Summary of Treatment-Emergent Adverse Events (≥ 1%) in V01-ACYC-301

Preferred adverse event term, n (%) [a]	ONEXTON Gel (N=243)	Vehicle Gel (N=236)	P-Value [b]
Abdominal discomfort	0 (0.0)	3 (1.3)	0.199
Headache	3 (1.2)	5 (2.1)	0.498
Influenza	5 (2.1)	5 (2.)	1.000
Nasopharyngitis	18 (7.4)	12 (5.1)	0.348
Pyrexia	3 (1.2)	2 (0.8)	1.000
Sinusitis	7 (2.9)	1 (0.4)	0.068
Upper respiratory tract infection	2 (0.8)	3 (1.3)	0.682

Note: TEAE are those with an onset after the first application of study medicine.
[a] Counts reflect numbers of subjects reporting 1 or more adverse events that map to the MedDRA dictionary (Version 15.1). Subjects are only counted once.
[b] P-value for the difference between treatment groups from a Fisher's exact test.

Within the ONEXTON Gel group, there were 4 treatment-related TEAEs experienced by 3 subjects: burning sensation, contact dermatitis, pruritus, and rash. In the Vehicle group, there were 7 treatment-related TEAEs experienced by 6 subjects: acne cystic, contact dermatitis, facial pain, hypersensitivity, lip swelling, pruritus, and swelling face. Only the treatment-related events of contact dermatitis and pruritus were reported in both treatment groups. No treatment-related event was reported by more than 1 subject in a treatment group.

Reviewer's comment: *Few adverse events are experienced by the subjects in this clinical trial was specifically due to the investigational product. Sinusitis is unlikely to be a treatment-related AE. Labeling will reflect that adverse events were rare.*

7.3.3 Dropouts and/or Discontinuations

The trial enrolled and randomized a total of 498 subjects (253 to ONEXTON and 245 to vehicle) from 28 centers in the United States. A total of 51 randomized subjects prematurely discontinued from the study. The vehicle arm had a higher rate of discontinuation (13.1%) compared to the ONEXTON arm (7.5%). The reasons for discontinuation are presented in **Table 27**.

Table 27: Disposition of Subjects (ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
Completed	234 (92.5%)	213 (85.0%)
Discontinued	19 (7.5%)	32 (13.1%)
Adverse Event	0	3
Lost to Follow-Up	11	12
Non-Compliance with Study Drug	1	0
Other	1	0
Pregnancy	0	1
Parent/Guardian Request	1	3
Subject's Request	5	13

Source: Reviewer's Analysis

Reviewer's comment: *There were no discontinuations due to adverse events in the ONEXTON Gel group.*

7.3.4 Significant Adverse Events

Specific adverse events that are treatment-related include: burning sensation, contact dermatitis, pruritus, and rash. In the ONEXTON Gel group, there were 4 treatment related AE experienced by 3 subjects and within the Vehicle Gel group, there were 7 treatment-related AE experienced by 6 subjects.

Table 28: Summary of Treatment-Related AE in V01-ACYC-301

Preferred adverse event term, n (%) [a]	ONEXTON Gel (N=243)	Vehicle Gel (N=236)
Acne cystic	0 (0.0%)	1 (0.4%)
Burning sensation	1 (0.4%)	0 (0.0%)
Dermatitis contact	1 (0.4%)	1 (0.4%) [b]
Facial pain	0 (0.0%)	1 (0.4%)
Hypersensitivity	0 (0.0%)	1 (0.4%) [b]
Lip swelling	0 (0.0%)	1 (0.4%)
Pruritus	1 (0.4%)	1 (0.4%)
Rash	1 (0.4%)	0 (0.0%)
Swelling face	0 (0.0%)	1 (0.4%)

Note: Treatment-related AE are those with an onset after the first application of study medication. Treatment-related AE are those with an investigator-assessed relationship of "possibly related" or "related".

[a] Counts reflect numbers of subjects reporting 1 or more adverse events that map to the MedDRA dictionary (Version 15.1). Subjects are only counted once under the greatest reported relationship.

[b] Within the Vehicle Gel group, the events of dermatitis contact and hypersensitivity resulted in subject discontinuation from the study. No subject in either study drug group discontinued the study due to any other treatment-emergent, treatment-related adverse event.

Reviewer's comment: *The Vehicle Gel group had more treatment-related adverse events as described in the table above. Several of the subjects from the Vehicle Gel group discontinued the study due to contact dermatitis or hypersensitivity. These events were rare. Treatment-*

specific adverse events were all under 1% of AEs. Product labeling will reflect the rarity of these AEs.

7.3.5 Submission Specific Primary Safety Concerns

Cutaneous safety is a primary concern in topical acne treatments. The applicant performed assessment including erythema and scaling in their Phase 3 clinical trial. Overall, more than 80% of the subjects in the ONEXTON group had no erythema at any post-Baseline study visit and more than 88% of the subjects in the ONEXTON Gel group had no scaling at any post-Baseline study visit. At Week 12, the mean erythema score was the same in both treatment groups, and the mean scaling score was slightly lower in the Vehicle Gel group.

Figure 2: Mean Erythema Score by Visit

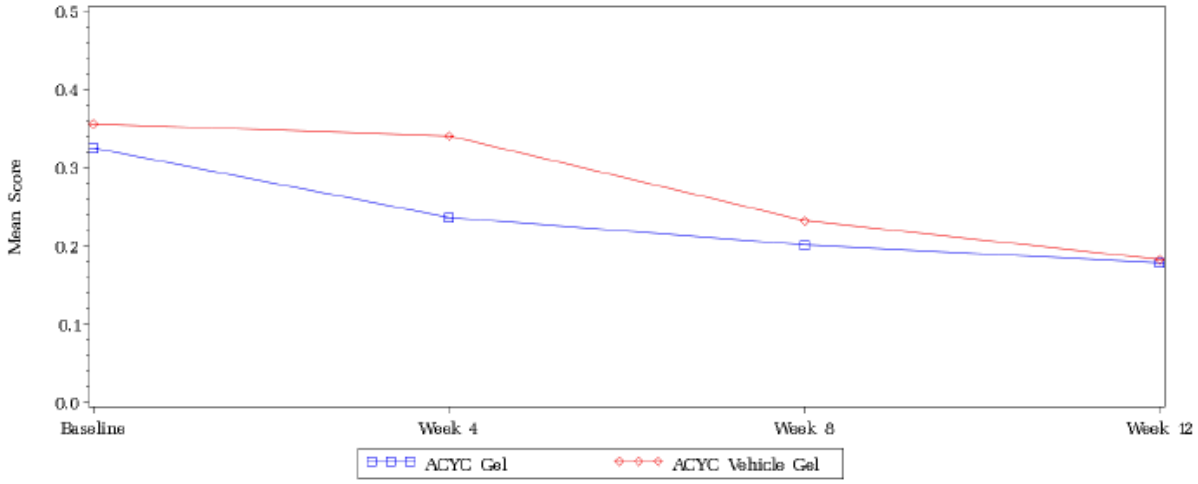
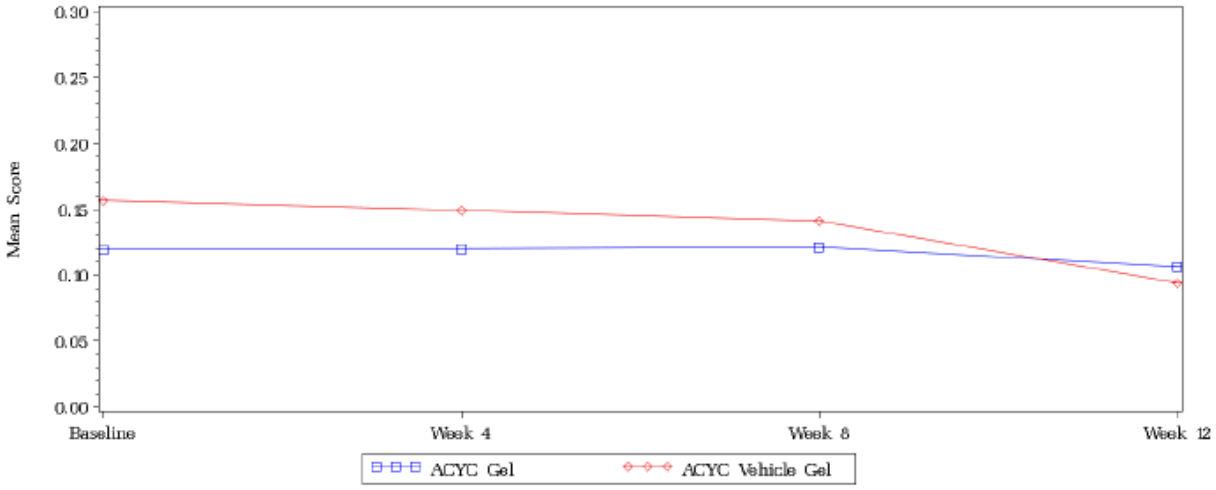


Figure 3: Mean Scaling Scores by Visit



Other cutaneous tolerability assessments include itching, burning, and stinging. The figures below depict the changes in the assessments at Baseline, Week 4, Week 8, and Week 12. The mean scores were lower for mean itch and mean stinging scores when comparing ONEXTON Gel and Vehicle Gel. The mean burning score were higher in the ONEXTON Gel group after Week 8 and into Week 12.

Figure 4: Mena Itching Scores by Visit

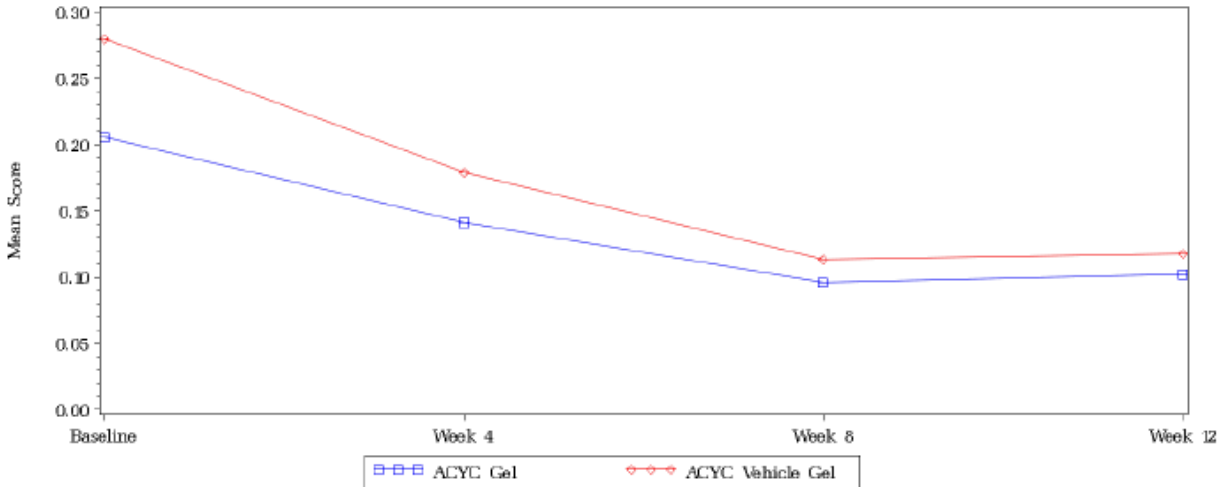


Figure 5: Mean Burning Score by Visit

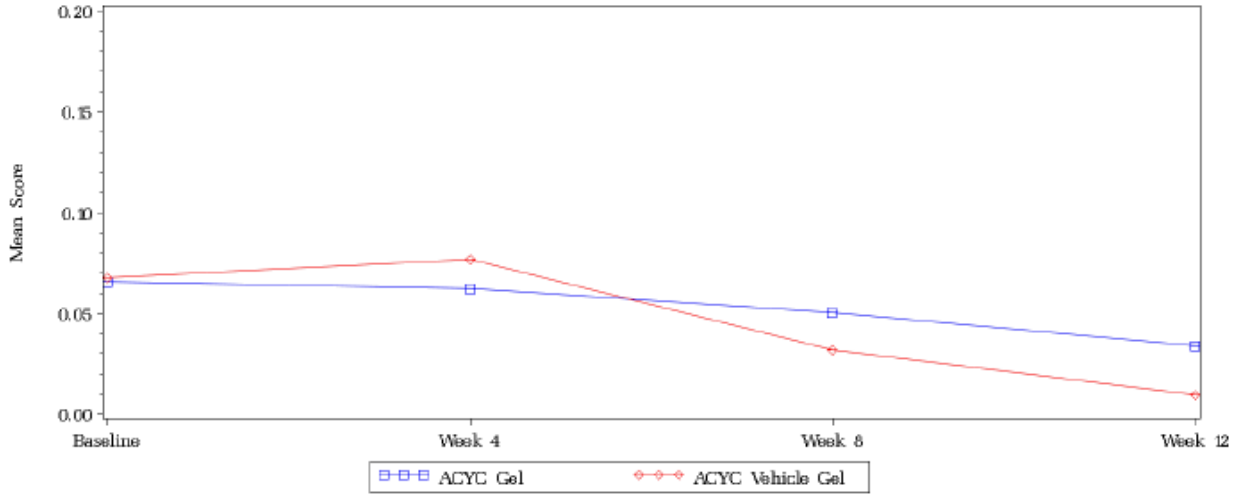


Figure 6: Mean Stinging Scores by Visit

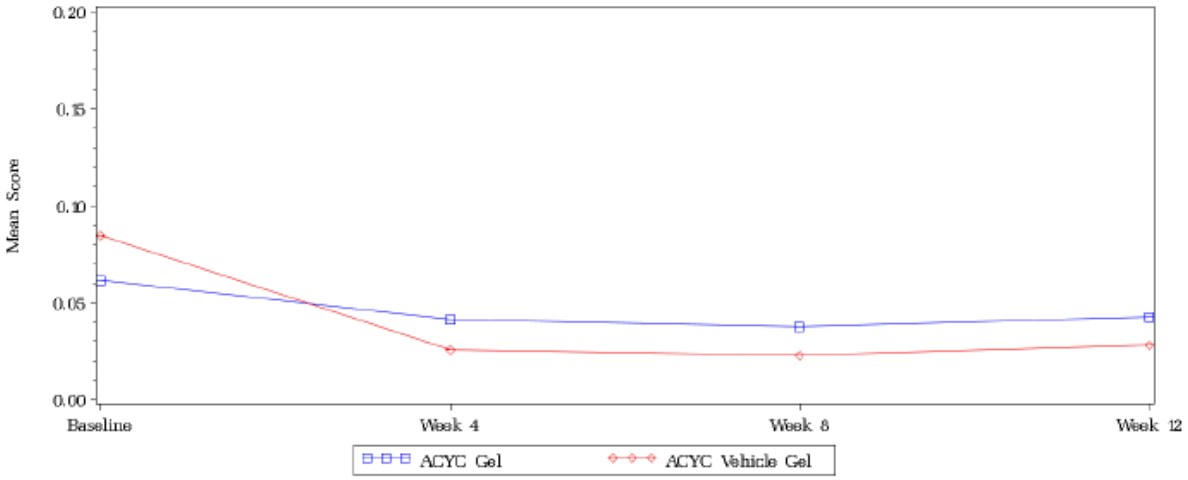


Table 29: Local Skin Reactions - Percent of Subjects with Symptoms Present. Results from the Phase 3 Trial of ONEXTON Gel 1.2%/3.75% (N = 243)

	Before Treatment (Baseline)			During Treatment			End of Treatment (Week 12)		
	Mild	**Mod.***	**Severe**	**Mild**	**Mod.***	**Severe**	**Mild**	**Mod.***	**Severe**
Erythema	20	6	0	28	5	<1	15	2	0
Scaling	10	1	0	19	3	0	10	<1	0
Itching	14	3	<1	15	3	0	7	2	0
Burning	5	<1	<1	7	1	<1	3	<1	0
Stinging	5	<1	0	7	0	<1	3	0	<1

Reviewer's comment: *During the clinical trial, subjects were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions either were the same as baseline or increased and peaked around week 4 and were near or improved from baseline levels by week 12. Table 29 will be presented in the label for ONEXTON Gel in section ADVERSE REACTIONS.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The adverse events are described above. Nearly all reported adverse events that occurred in V01-ACYC-301 were associated with local treatment. No analysis of adverse events by organ system or syndrome was needed.

7.4.2 Laboratory Findings

No laboratory data was collected in this clinical trial.

7.4.3 Vital Signs

Abbreviated physical examinations (including height, weight, and vital signs) were conducted at Baseline and Week 12, urine pregnancy tests were performed at every study visit on premenarchal females and females of childbearing potential, and concomitant medication uses were documented throughout the study; results of these assessments are provided by subject. No formal analyses of these safety-related parameters were conducted. It should be noted that relevant changes in concomitant medications and abnormal physical examination findings or vital sign measurements were to have been reported as AEs.

7.4.4 Electrocardiograms (ECGs)

None

7.4.5 Special Safety Studies/Clinical Trials

The sponsor requested a waiver for dermal safety studies.

Reviewer's comment: *The waiver request was granted for ONEXTON Gel.* (b) (4) *ONEXTON* (b) (4) *Acanya Gel* (b) (4) *in the concentration of benzoyl peroxide (3.75% versus 2.5%, respectively). Dermal safety studies were previously conducted for the approval of Acanya Gel, and adequate information is available for labeling.*

7.4.6 Immunogenicity

None

7.6 Pediatrics

This supplemental application did not trigger PREA.

8 Postmarket Experience

There is no postmarket experience with ONEXTON GEL (clindamycin phosphate 1.2%/benzoyl peroxide 3.75%).

9 Appendices

None

9.1 Literature Review/References

1. Ceilley RI. Advances in topical delivery systems in acne: new solutions to address concentration dependent irritation and dryness. Skinmed 2011 Jan-Feb;9(1):15-21.
2. Feldman S, Careccia RE, Barham KL, Hancox J. Diagnosis and treatment of acne. Am Fam Physician. 2004;69(9):2123-30.
3. Gollnick HP, Zouboulis CC, Akamatsu H, Kurokawa I, Schulte A. Pathogenesis and pathogenesis related treatment of acne. J Dermatol 1991;18:489-99.
4. Milstone EB, McDonald AJ, Scholhamer Jr CF. Pseudomembranous colitis after topical application of clindamycin. Arch Dermatol 1981; 117 (3): 154-5.
5. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol 1986; 122 (5): 583-4.

9.2 Labeling Recommendations

Final labeling will be contained in the approval letter.

12 page(s) has been Withheld in Full as draft labeling (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

An Advisory meeting was not held for this supplement application.

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

/s/

GARY T CHIANG
10/10/2014

DAVID L KETTL
10/21/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 50819/ S-12 **Applicant:** DOW Pharmaceutical Sciences **Stamp Date:** 30-JAN-2014

Drug Name: ONEXTON (clindamycin phosphate/benzoyl peroxide Gel, 1.2%/3.75%) **NDA/BLA Type:** Supplement

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			The application is a 505 (b)(2) with the reference product DUAC (NDA 50741); the applicant owns the data to BenzaClin and Acanya
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	The proposed strength is clindamycin phosphate 1.2% with increase benzoyl peroxide strength of 3.75%. This is a bracketed strength to Acanya and

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					BenzaClin/DUAC.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Phase 3 two arm clinical study of clindamycin phosphate/ benzoyl peroxide 1.2%/3.75% compared to vehicle Indication: Acne		X		A single Phase 3 clinical trial is provided. The applicant intends to use reference safety data from Acanya (BPO 2.5%) and BenzaClin (BPO 5.0%) to describe safety events related to the bracketed strength.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			MedDRA 15.1
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	The potential for cardiotoxicity was explored in the original NDA for Acanya
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	Sufficient evidence of post marketing safety is included with use of Acanya since it's approval
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			A Full waiver is requested for pediatrics age 0-11 years old.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			This review is in the process of full financial disclosure review

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

Reviewer's comment: *An efficacy supplement to an original 505(b)(2) application is considered a 505(b)(2) supplement because it is inherently relying once again on the same source(s) of information that the original application relied on for approval.*

When the original application relied on listed drug(s), the applicant would need to again provide in the supplement an appropriate patent certification or statement to address reliance on the listed drug(s).

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

NONE

Gary T Chiang MD, MPH 27-MAR-2014

Reviewing Medical Officer Date

David Kettl MD 27-MAR-2014

Clinical Team Leader Date

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/s/

GARY T CHIANG
03/27/2014

DAVID L KETTL
03/27/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div II, Branch VI and HFD-540	**50-819**

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Dow Pharmaceutical Sciences, Inc 1330 Redwood Way Petaluma, CA 94952	Supplement: **S-012, Efficacy** Submission Date: January 30, 2014 PDUFA Date: November 30, 2014

5. PROPRIETARY NAME	6. ESTABLISHED NAME	7. AMENDMENTS, REPORT, DATE
Acanya Gel (already approved) Onexton (proposed)	Clindamycin phosphate, Benzoyl peroxide	Amendments dated 02/19/2014, 03/14/2014 (labeling), 04/24/2014 (labeling), 04/28/2014, 06/26/2014, 07/03/2014, 08/14/2014, 09/03/2014

8. SUPPLEMENT PROVIDES FOR:

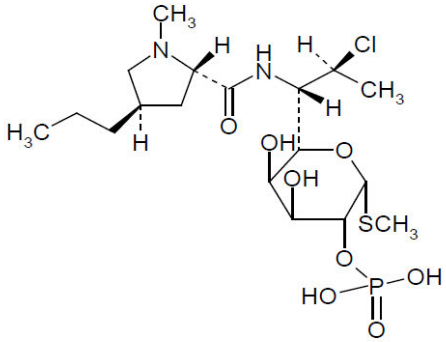
introduction of a 3.75% benzoyl peroxide strength in addition to the already approved 2.5% benzoyl peroxide strength in Acanya Gel. The 3.5% strength will be marketed under different proprietary name.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Acne vulgaris	Rx	
12. DOSAGE FORM	**13. POTENCY**	
gel	1.2% clindamycin phosphate; 2.5% benzoyl peroxide (already approved) 3.75% benzoyl peroxide (proposed)	

14. CHEMICAL NAME AND STRUCTURE

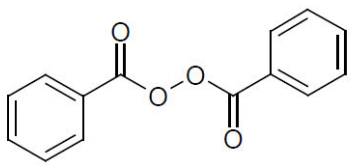
Clindamycin Phosphate, USP

- Methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate)
- $C_{18}H_{34}ClN_2O_8PS$



Benzoyl Peroxide (BPO)

- Peroxide, Dibenzoyl
- $C_{14}H_{10}O_4$



15. COMMENTS

This efficacy supplement (**S-012 to NDA 50-819**) provided for the introduction of 3.75% benzoyl peroxide strength, a new and higher strength of benzoyl peroxide than the already approved Acanya (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/ 2.5%. **Name Onexton™ is also proposed.**

(b) (4) the corresponding higher concentration of benzoyl peroxide. The manufacturers (b) (4) are identical to those already approved for Acanya Gel, 2.5%. The already approved container closure systems used for the marketed Acanya Gel, 2.5% (3.5 g physician samples packaged in (b) (4) and 50 g commercial product packaged in (b) (4) are proposed for Onexton™ Gel, 3.75%.

(b) (4)

CDER Office of Compliance has issued overall "ACCEPTABLE' recommendation to the manufacturing and testing facilities.

As a result, this supplement is recommended for APPROVAL pending the resolution of the recommended labeling changes.

16. CONCLUSION AND RECOMMENDATION

Recommend **APPROVAL** from the CMC perspective.

17. NAME	18. REVIEWER'S SIGNATURE	19. DATE COMPLETED
Yubing Tang, Ph.D. Chemist	See appended electronic signature sheet	September 25, 2014

REVIEW NOTES

Dow Pharmaceutical Sciences (DPS) submitted this efficacy supplement proposing to **add 3.75% benzoyl peroxide (BPO) strength** in addition to the already approved 2.5% benzoyl peroxide in Acanya Gel. The new proprietary name, Onexton is also proposed for this new drug product.

(b) (4)

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(b) (4)

V. Labeling

Presented here is preliminary review on Packaging Insert (PI) and container/carton labels provided in the amendment dated 04/24 (the most recent label/labeling update).

1. For the expression of "… **10 mg (1%) clindamycin as phosphate …**" appeared in Carton and container labels and PI Section 3 and 11, change to read"… **12mg clindamycin phosphate equivalent to 10mg (1%) clindamycin**..."
2. In Section "Dosage form and strength" of PI Highlight, use the expression in Section 3 of Full Prescribing Information, i.e. "**Each gram of ONEXTON Gel contains 12 mg (1.2%) clindamycin phosphate, equivalent to 10 mg (1%) clindamycin, and 37.5 mg (3.75%) benzoyl peroxide.** (b) (4)"
3. For Section 11 of PI, in addition to the change in point 1 above, the (b) (4) list should be re-arranged in alphabetic order, i.e., move "**purified water**" as the last (b) (4)
4. Add "**Store pump upright**" in Section 16 and 17 of PI to be consistent with those instructed in labels and with the sample storage condition in stability study.
5. Add descriptive words in Section 16 for the drug product so that the first sentence reads like "**ONEXTON Gel 1.2%/3.75% is a white to off-white smooth gel supplied as a 50 g pump (NDC 0187-3050-50)"**
6. For carton and container labels for physician and 50gram size: change "**for external use only**" to "**for topical use only**".

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/s/

YUBING TANG
09/30/2014

THOMAS F OLIVER
09/30/2014

Initial Quality Assessment
Division of New Drug Quality Assessment II

OND Division:	Division of Dermatology and Dental Products
NDA/Supplement:	**50-819/S-012**
Category:	**Efficacy**
Provides for:	1. A new benzoyl peroxide strength, 3.75%. The current approved strength is 2.5%. 2. A new trade name, ONEXTON, for the new 3.75% strength
Applicant:	Dow Pharmaceutical Sciences.
Stamp Date:	Jan. 30, 2014
Procedural/PDUFA Date	Nov. 30, 2014
Product :	ONEXTON (clindamycin phosphate and benzoyl peroxide) topical gel, 1.2%/3.75%
CMC Lead:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-day Letter:	☒	☐

SUMMARY

This efficacy supplement provides for a new benzoyl peroxide strength, 3.75%, for the approved Acanya (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/2.5%. A new trade name, ONEXTON, is also proposed for the new strength.

ONEXTON 3.75% uses the **same drug subtances**, clindamycin phosphate and benzoyl peroxide, as the approved Acanya 2.5%. The applicant stated in Section 3.2.P.2 Pharmaceutical Development that [redacted (b) (4)] for the increased concentration of benzoyl peroxide to 3.75%. [redacted (b) (4)] The proposed [redacted (b) (4)] for ONEXTON 3.75% is [redacted (b) (4)] to that approved for Acanya 2.5%. There is [redacted (b) (4)] **assay acceptance criterion among the various strengths**.

Formulation Comparision

Ingredient	Grade	% w/w	
		ACANYA 2.75%	**ONEXTON 3.75%**
Benzoyl peroxide	USP	2.50 [a]	3.75[a]
Clindamycin Phosphate	USP	1.20	1.20
Propylene Glycol	USP	[redacted (b) (4)]	
Carbomer 980	NF		
Potassium Hydroxide	NF		
Purified Water	USP		

[a]Benzoyl peroxide [redacted (b) (4)] is proposed for ONEXTON 3.75% to [redacted (b) (4)] The same [redacted (b) (4)] has been approved for Acnaya 2.75% (p. 24 of 79 of CMC review #1 original NDA).

The approved manufacturing facility, Contract Pharmaceuticals Limited Canada, for Acanya 2.5% is proposed for the manufacture of ONEXTON 3.75%. Testing facilities also remain the same. The proposed commercial batch size for ONEXTON 3.75% is (b) (4) and is approximately (b) (4) the batch size of the approved and marketed Acanya 2.5%. The (b) (4) for both ONEXTON 3.75% and Acanya 2.5% is (b) (4)

The proposed container closure system for ONEXTON 3.75% is 50 gram (b) (4) pump for trade size, and a 3.5 gram tube for physician's sample. Both systems are currently approved for Acanya 2.5%.

Drug product stability data from (b) (4) batch (Batch DP1550, Batch size (b) (4) are provided in the initial submission to support the proposed expiry period and in-use period for each packaging configuration. The table below shows the amount of data and study conditions:

Submitted Stability Data and Proposed Expiration Dating Period

	3.5 g tube	50 g Pump
Proposed expiration dating period	(b) (4)	
Registration stability studies # of Batch Long term (5°C) Accelerated 25°C/60% RH orientation		
In-life study at 25°C/60% RH		
In-use stability study		

CONSULTS: **None except** possible consultation to **EA** group for categorical exclusion claim.

EER/DMF: Statement of readiness for inspection for each drug product facility involved in the new strength, and updated Form 356h with complete drug product establishment and DMF information are provided in the amendment dated Feb. 14, 2014. The applicant also confirms that the establishment and DMF information is identical to that provided in the original NDA. No new DMF is referenced in this efficacy supplement. Neither is there any new facility.

The applicant stated that there are no changes in drug substance. Therefore, Establishment Evaluation will be requested **only for drug product facilities**.

ENVIRONMENTAL ASSESSMENT: The applicant requests a categorical exclusion based on 21 CFR 25.31(a).

FILLING ISSUES: None. Executed batch and Master batch records were not provided in the initial submission but provided in the amendment dated Feb. 14, 2014.

CRITICAL REVIEW ISSUES:

1. The proposed benzoyl peroxide (b) (4) needs a critical review. The justification for the (b) (4) is provided in Module 2 Quality Overall Summary under the header "Pharmaceutical Development."

2. The registration stability study and in-use stability study need a critical review. (b) (4)

(b) (4)

3. All Type III DMFs need to be checked for any new submissions that have not been reviewed.

4. The categorical exclusion claim from the preparation of Environmental Analysis report needs a critical review. (b) (4)

5. The applicant did not provide (b) (4)

COMMENTS TO BE CONVEYED in 74-DAY LETTER:

Request the applicant to provide the following information to facilitate the review:

1. Representative samples for the trade size and physician sample.
2. (b) (4)
3.
4. Information/data supporting the proposed (b) (4) for benzoyl peroxide should be added to Module 3. Additionally, indicate the proposed (b) (4) in the Formulation Composition table in Section 3.2.P.1.

COMMENT/RECOMMENDATION:

The submission is fileable from the CMC and quality perspective.

Shulin Ding
Pharmaceutical Assessment Lead

Tom Oliver
Chief, Branch VI

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			n/a

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		x	The applicant stated that there are no changes in drug substance.
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		Categorical exclusion claimed based on EIC below (b)(4)ppb.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		x	No change.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	No change.
14.	Does the section contain information regarding the characterization of the DS?		x	No change.
15.	Does the section contain controls for the DS?		x	No change.
16.	Has stability data and analysis been provided for the drug substance?		x	No change.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			n.a

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?			n/a
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			n/a

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		x	Method validation reports are provided in Section 3.2.P.5.3 for assay and related substances of clindamycin and benzoyl peroxide.

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	9/7/07	
	II			10/6/05	
	III			??	
	III			9/28/2006	
	III			11/11/05	
	III			3/19/07	
	III			11/16/05	
	III			12/8/06	
	III			3/18/08	
	III			9/16/09	
	III			6/19/08	
	III			7/7/08	
	III			3/14/08	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		

33.	Have the immediate container and carton labels been provided?	x		

See appended electronic signature page}
Shulin Ding
CMC-Lead
Division II
Office of New Drug Quality Assessment

{See appended electronic signature page}
Thomas Oliver
Branch Chief
Division VI
Office of New Drug Quality Assessment

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/s/

SHULIN DING
03/14/2014

THOMAS F OLIVER
03/18/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

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:	50,819
Supporting document/s:	SDNs 292 and 317
Applicant's letter date:	1-30-2014 and 4/24/2014
CDER stamp date:	1-30-2014 and 4/24/2014
Product:	ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%
Indication:	Acne Vulgaris
Applicant:	Dow Pharmaceutical Sciences
Review Division:	Dermatology and Dental Products
Reviewer:	Jiaqin Yao, Ph.D.
Supervisor/Team Leader:	Barbara Hill, Ph.D.
Acting Division Director:	Tatiana Oussova, M.D.
Project Manager:	Strother Dixon

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 50,819 are owned by Dow Pharmaceutical Sciences or are data for which Dow Pharmaceutical Sciences has obtained a written right of reference.
Any information or data necessary for approval of NDA 50,819 that Dow Pharmaceutical Sciences does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 50,819.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

The sponsor owns the approved drugs BenzaClin Gel ((b) (4) clindamycin phosphate and 5% benzoyl peroxide, NDA 50-756) and Acanya Gel (1.2% clindamycin phosphate and 2.5% benzoyl peroxide, NDA 50-819) for the treatment of acne vulgaris. Within the supplement submissions, the sponsor has developed a drug product (Onexton Gel) with 1.2% clindamycin phosphate and 3.75% benzoyl peroxide in the (b) (4) as Acanya Gel for the same indication.

1.2 Brief Discussion of Nonclinical Findings

Clindamycin is an antibiotic that decreases Propionibacterium acnes (P. acnes) colonization of skin follicles and reduces the inflammatory aspect of acne. Benzoyl peroxide is an antibacterial agent effective against P. acnes through oxidation. Additionally, benzoyl peroxide reduces non-inflammatory lesions, possibly through induction of keratolysis and desquamation. Because the sponsor owns both BenzaClin Gel ((b) (4) clindamycin phosphate and 5% benzoyl peroxide) and Acanya Gel (1.2% clindamycin phosphate and 2.5% benzoyl peroxide), no new nonclinical studies have been submitted to support this sNDA for Onexton Gel (1.2% clindamycin phosphate and 3.75% benzoyl peroxide) in the (b) (4) as Acanya Gel for the same indication.

1.3 Recommendations

1.3.1 Approvability

This sNDA is approvable from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The following wording was proposed by the sponsor for the nonclinical sections in the label of this sNDA. Reviewer recommended revisions to the nonclinical sections are provided in this review. It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the ONEXTON Gel label.

HIGHTLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

ONEXTON Gel is a combination of clindamycin phosphate (a lincosamide antibacterial- (b) (4) and benzoyl peroxide indicated for the topical treatment of acne vulgaris.

Reviewer's comments: The established pharmacologic class for clindamycin is "lincosamide antibacterial". There is no established pharmacologic class for benzyol peroxide.

8.1 Pregnancy
Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women treated with ONEXTON Gel. ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ONEXTON Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

Reviewer's comments: This section has been modified by the sponsor per current PLR labeling standards and the information is the same as that in the label of Acanya Gel.

12.1 Mechanisms of Action
Clindamycin: Clindamycin is a lincosamide antibacterial *[see Clinical Pharmacology~~Microbiology~~ (12.4)]*.
Benzoyl Peroxide: Benzoyl peroxide is an oxidizing agent with bacteriocidal and keratolytic effects, but the precise mechanism of action is unknown.

Reviewer's comments: The mechanism of action for the two active moieties for the treatment of acne vulgaris is unknown. The established pharmacologic class for clindamycin is "lincosamide antibacterial". The mechanism of action for benzoyl peroxide is as shown in the label of Acanya Gel, although there is no established pharmacologic class for benzoyl peroxide.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity, mutagenicity and impairment of fertility testing of ONEXTON Gel have not been performed.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced (b) (4) skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8,

5.4, and 30 times amount of clindamycin and 2.4, 7.2, and 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, respectively) did not cause any increase in tumors. However, topical treatment (b) (4) formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900, and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 1.6, 4.8, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, respectively) for up to 97 weeks did not cause any increase in tumors. In a 52 week dermal photocarcinogenicity study in hairless mice (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the (b) (4) formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation.

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies have not been performed with ONEXTON Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g ONEXTON Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

Reviewer's comments: The information in this section is the same as that in the label of Acanya Gel, except that the animal to human dose multiples of benzoyl peroxide (marked as red) have been changed accordingly due to the concentration change of benzoyl peroxide from 2.5% in Acanya Gel to 3.75% in ONEXTON Gel.

2 Drug Information

2.1 Drug

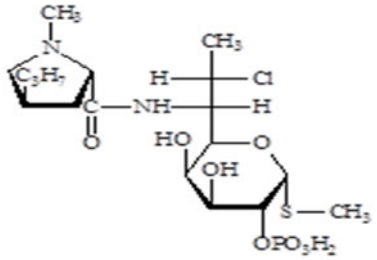
CAS Registry Number
Clindamycin phosphate: 24729-96-2
Benzoyl peroxide: 94-36-0

Chemical Name
Clindamycin phosphate: Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-theo-α-D-galacto-octopyranoside-2-(dihydrogen phosphate)

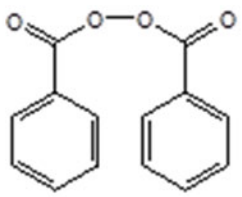
Benzoyl peroxide (BPO): Dibenzoyl peroxide

Molecular Formula/Molecular Weight
Clindamycin phosphate: $C_{18}H_{34}ClN_2O_8PS$ / 504.97
Benzoyl peroxide: $C_{14}H_{10}O_4$ / 242.23

Structure or Biochemical Description



Clindamycin phosphate



Benzoyl peroxide

Pharmacologic Class
Clindamycin phosphate: Lincosamide antibacterial
Benzoyl peroxide: Not established yet, but with bacteriocidal and keratolytic effects

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 41,733, NDAs 50-741 and 50-756, ANDA 65,443

2.3 Drug Formulation

The product is a two-component product consisting of a benzoyl peroxide gel and clindamycin phosphate concentrate. The components are mixed by the pharmacist at time of dispensing. The composition of the mixture is as follows.

Ingredient	%w/w (as dispensed to patient)		
	Acanya Gel	Acanya 3.75%	Toxicology Formulation
(b) (4) benzoyl peroxide, USP	2.50	3.75	(b) (4)
Clindamycin phosphate, USP	1.20	1.20	
Propylene Glycol, USP (b) (4)		(b) (4)	
Carbomer 980 (b) (4)			
Potassium Hydroxide, NF			
Purified Water, USP			

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

ONEXTON Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older. ONEXTON Gel should be applied to the affected areas once daily or as directed by the physician.

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/s/

JIAQIN YAO
08/28/2014

BARBARA A HILL
08/28/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 50819/S-012 **Applicant:** Dow Pharmaceutical **Stamp Date:** 1-30-2014

Drug Name: Onexton (clindamycin and benzoyl peroxide) gel, 1.2%/3.75% **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not Applicable (NA). No new nonclinical studies are required to support this NDA.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			NA
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			No new nonclinical studies are needed.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Refer to CMC review.
11	Has the applicant addressed any abuse potential issues in the submission?			NA
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

NA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Jiaqin Yao — see sign off date

Reviewing Pharmacologist — Date

Barbara Hill — see sign off date

Supervisor — Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

JIAQIN YAO
03/13/2014

BARBARA A HILL
03/13/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	50819
Supplement #:	012
Drug Name:	ONEXTON (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75%
Indication(s):	Acne Vulgaris
Applicant:	Dow Pharmaceutical Sciences
Date(s):	Submitted: 1/30/2014
	PDUFA: 11/30/2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Matthew Guerra, Ph.D.
Concurring Reviewer:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
Clinical Team:	Gary Chiang, MD / David Kettl, MD
Project Manager:	Strother Dixon

Keywords: Acne vulgaris, single pivotal trial, superiority trial, combination product

Table of Contents

1 EXECUTIVE SUMMARY

The applicant, Dow Pharmaceutical Sciences, is seeking approval of ONEXTON (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75% for the topical treatment of acne vulgaris. The proposed combination product has the same concentration of clindamycin phosphate and intermediate concentration of benzoyl peroxide of the following approved products:

- BenzaClin® (clindamycin phosphate and benzoyl peroxide) gel, (b) (4)/5%
- Acanya® (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/2.5%

BenzaClin® gel (NDA 50756) and Acanya® gel (NDA 50819) were approved for the topical treatment of acne vulgaris in 2000 and 2008, respectively.

The applicant submitted data from a single, randomized, multicenter, vehicle-controlled, parallel-group, Phase 3 trial (V01-ACYC-301). A total of 498 subjects with moderate to severe acne vulgaris were enrolled from 28 centers in the U.S. and randomized to either ONEXTON gel or vehicle gel. The co-primary and co-secondary efficacy endpoints were all statistically significant ($p < 0.001$), see Table 1. From the information submitted in this application, it appears the applicant has not conducted any trials that directly compare the efficacy of ONEXTON gel to either Acanya® gel or BenzaClin® gel. This reviewer compared the efficacy results of ONEXTON gel in this trial to the results of Acanya® gel in the trials used for its approval and found the results to be very similar, see Table 16 on page 13.

Table 1: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (ITT)

Endpoints	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value
Co-Primary:			
EGSS (2-grade reduction): n (%)	89 (35.2%)	41.6 (17.0%)	<0.001(1)
Absolute Change in Inflammatory Lesions: Mean	16.3	8.2	<0.001(2)
Absolute Change in Non-Inflammatory Lesions: Mean	19.2	9.6	<0.001(2)
Co-Secondary:			
EGSS (clear or almost clear): n (%)	72.1 (28.5%)	35.5 (14.5%)	<0.001(1)
Percent Change in Inflammatory Lesions: Mean	60.4%	31.3%	<0.001(2)
Percent Change in Non-Inflammatory Lesions: Mean	51.8%	27.6%	<0.001(2)

Source: Reviewer's Analysis
(1) P-value based on a logistic regression model (Firth's Penalized Likelihood) with treatment and analysis center as factors.
(2) P-value based on an ANCOVA model with treatment, analysis center, and baseline lesion counts as factors.
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).
ITT: Intent-to-Treat

2 INTRODUCTION

2.1 Overview

The applicant, Dow Pharmaceutical Sciences, is seeking approval of ONEXTON (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75% for the topical treatment of acne vulgaris. The proposed combination product has the same concentration of clindamycin phosphate and intermediate concentration of benzoyl peroxide of the following approved products:

- BenzaClin® (clindamycin phosphate and benzoyl peroxide) gel, (b) (4)/5%
- Acanya® (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/2.5%

BenzaClin® gel (NDA 50756) and Acanya® gel (NDA 50819) were approved for the topical treatment of acne vulgaris in 2000 and 2008, respectively.

On May 2, 2012, the applicant met with the Agency for a Type C Guidance meeting for NDA 50819 to gain agreement on the evidentiary requirements for submission of a sNDA for the proposed product; however, at the beginning of the meeting the applicant informed the Agency that BenzaClin® is now owned by their parent company, Valeant Pharmaceuticals. In addition, the applicant proposed a new set of questions related to a NDA submission that would include no new clinical studies. The Agency stated they could not provide feedback on this new proposal and the applicant should submit the questions to the IND or a new meeting request. No further meetings were held between the applicant and the Agency for the development program of the proposed product.

2.2 Clinical Studies Overview

The applicant submitted data from a single trial (Study V01-ACYC-301). An overview of the trial is presented in Table 2.

Table 2: Clinical Study Overview

Location	Study Population	Treatment Arms	Number of Subjects	Dates
28 Centers in US	Age 12-40, EGSS of 3 (moderate) or 4 (severe), 20-40 inflammatory lesions, and 20-100 non-inflammatory lesions	ONEXTON Gel	253	10/10/2012 - 5/23/2013
		Vehicle Gel	245	

*Note that one subject randomized to vehicle had a baseline inflammatory lesion count of 46.

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and entirely electronic. The datasets in this review are archived at the following locations:
\\cdsesub1\evsprod\NDA050819\0085\m5\datasets\v01-acyc-301\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The databases for the study required minimal data management prior to performing analyses. In the Filing Communication Letter, this reviewer made the following request:

> "In Table 11-4 (page 56 of the study report), you presented the efficacy results for the three co-primary endpoints at Week 12. It is not clear how you obtained the presented response rates for the 2-grade reduction from baseline in EGSS. Submit the SAS code used to generate these rates."

The applicant submitted the requested information on April 28, 2014.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study V01-ACYC-301 was a 12-week, multicenter, randomized, double-blind, vehicle-controlled, parallel-group, Phase 3 trial investigating the safety and efficacy of ONEXTON (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75% for the treatment of acne vulgaris. For enrollment, the protocol specified the following key inclusion criteria:

- Male or female between the ages of 12 and 40 (inclusive)
- Evaluator's Global Severity Score (EGSS) of 3 (moderate) or 4 (severe), see Table 3 for details on the EGSS category descriptions
- 20-40 inflammatory facial lesions (papules, pustules, and nodules)
- 20-100 non-inflammatory facial lesions (open and closed comedones)
- $\leq$ 2 facial nodules

Table 3: Evaluator's Global Severity Score (EGSS)

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost Clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; non nodulocystic lesions)
3	Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesion evident: several to many comedones and papules/pustules, and there may or may not be one nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papule/pustules and more than 2 nodulocystic lesions

Subjects applied study product once daily to the face for 12 weeks. Subject had scheduled visits at screening, baseline, and Weeks 4, 8, and 12.

The protocol specified the following as co-primary efficacy endpoints:

- Absolute change in inflammatory lesion count from baseline to Week 12
- Absolute change in non-inflammatory lesion count from baseline to Week 12
- Proportion of subjects who achieve at least a 2-grade reduction from baseline to Week 12 in the EGSS

The protocol specified the following as "secondary co-primary efficacy endpoints":

- Percent change in inflammatory lesion count from baseline to Week 12
- Percent change in non-inflammatory lesion count from baseline to Week 12
- Proportion of subjects who are clear or almost clear and 2-grade reduction from baseline in EGSS at Week 12

3.2.2 Statistical Methodologies

The primary analysis population specified in the protocol was the intent-to-treat (ITT) population, which was defined in the protocol as all randomized subjects. Efficacy analyses were performed using the per-protocol (PP) population as supportive analyses. The PP population included all randomized subjects that completed the 12-week evaluation without study protocol violations, which are listed below:

- Failed any of the inclusion/exclusion criteria
- Had taken any interfering concomitant medications
- Did not attend the Week 12 visit, with the exception of a discontinuation from the study due to an adverse event related to study treatment or documented lack of treatment effect
- Missed both the Week 4 and Week 8 visits
- Was not compliant with the dosing regimen (i.e., subjects may not miss more than five consecutive days of dosing and must take 80-120% of expected doses. The number of expected doses will be determined for each subject based on the length of their participation in the study)
- Out of visit window at the Week 12 visit

The protocol specified a pooling strategy for centers that enrolled less than 8 subjects in each treatment arm. These centers were pooled by ordering and combining the smallest with the largest until all centers meet the minimum of 8 subjects in each treatment arm. For Study V01-ACYC-301, 12 of the 28 centers did not meet the minimum and the pooling strategy yielded a total of 21 analysis centers.

For the co-primary endpoint of the proportion of subjects with a 2-grade reduction in the EGSS, the protocol-specified analysis method was a logistic regression model with treatment and analysis center as factors. It should be noted that the applicant used "Firth's Penalized Likelihood" option in SAS, which was not specified in protocol or the SAP. Using standard logistic regression resulted in SAS producing the following message: "Validity of the model fit is questionable." The treatment-by-center interaction was included in the model if significant at $\alpha = 0.10$. If the test was significant, the protocol specified a sensitivity analysis where the data will

be analyzed excluding one analysis center at a time to identify the impact of each analysis center on the overall results.

For the co-primary endpoints of absolute change from baseline in inflammatory and non-inflammatory lesions, the protocol-specified method was an analysis of covariance (ANCOVA) model with factors for treatment and analysis center, and the respective baseline lesion count as a covariate. The treatment-by-center interaction was included in the model if significant at $\alpha = 0.10$. If the test was significant, the protocol specified a sensitivity analysis where the data will be analyzed excluding one analysis center at a time to identify the impact of each analysis center on the overall results. The protocol specified conducting a skewness test (based on the methods presented by J.H. Zar (1984)) to the residuals from the ANCOVA models. The protocol specified that if the two-sided p-value for the skewness test is significant at the 0.01 level, then the ANCOVA model would be based on the ranked lesion counts.

The protocol-specified methods for the secondary endpoints mirrored the co-primary endpoints (i.e., binary endpoint analyzed using logistic regression and continuous endpoint analyzed using an ANCOVA model). The protocol did not specify a method to control the Type I error rate for multiple secondary endpoints; however, the secondary endpoints are designated as "secondary co-primary efficacy endpoints" in the protocol.

For handling of missing data, the primary imputation method specified in the protocol was the multiple imputation (MI) approach using the Markov Chain Monte Carlo (MCMC) method.

For the binary co-primary endpoint of success on EGSS (2-grade reduction from baseline), the protocol specified the following sensitivity analyses for handling of missing data:

1. Analyze the dichotomized EGSS using repeated measures logistic regression (generalized estimating equations), with treatment, analysis center, and visit as factors. For this analysis, data from all post-baseline visits will be included with no imputation for missing data.
2. Impute missing data using multiple imputation where the imputation model is a logistic regression model with factors of treatment group and analysis center.

For the co-primary endpoints of absolute change in inflammatory and non-inflammatory lesion counts, the protocol specified the following sensitivity analyses for handling of missing data:

1. Analyze change in absolute lesion count using repeated measures ANCOVA, with treatment, analysis center, and visit as factors and the respective baseline lesion count as a covariate. For this analysis, data from all post-baseline visits will be included with no imputation for missing data.
2. Impute missing data using multiple imputation where the imputation model is a linear regression model with factors for treatment group and analysis center, and the respective baseline lesion count as a covariate.

3.2.3 Patient Disposition, Demographics and Baseline Characteristics

The trial enrolled and randomized a total of 498 subjects (253 to ONEXTON and 245 to vehicle) from 28 centers in the United States. A total of 51 randomized subjects prematurely discontinued from the study. The vehicle arm had a higher rate of discontinuation (13.1%) compared to the ONEXTON arm (7.5%). The reasons for discontinuation are presented in Table 4. Baseline demographics were generally balanced across the treatment arms. Subjects in the ONEXTON arm were on average slightly older than subjects in the vehicle arm. The demographics are presented in Table 5. The baseline disease characteristics are presented in Table 6. The baseline disease characteristics were generally balanced across the treatment arms. For enrollment, the protocol specified that subjects have 20 to 40 inflammatory lesions at baseline. One subject randomized to vehicle had a baseline inflammatory lesion count of 46.

Table 4: Disposition of Subjects (ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
Completed	234 (92.5%)	213 (85.0%)
Discontinued	19 (7.5%)	32 (13.1%)
Adverse Event	0	3
Lost to Follow-Up	11	12
Non-Compliance with Study Drug	1	0
Other	1	0
Pregnancy	0	1
Parent/Guardian Request	1	3
Subject's Request	5	13

Source: Reviewer's Analysis

Table 5: Demographics (ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
Age		
Mean (SD)	18.2 (5.6)	19.3 (6.0)
Median	16.0	17.0
Range	12 - 40	12 - 39
Gender		
Male	130 (51.4%)	126 (51.4%)
Female	123 (48.6%)	119 (48.6%)
Race		
White	208 (82.2%)	210 (85.7%)
Black	33 (13.0%)	24 (9.8%)
Asian	6 (2.4%)	4 (1.6%)
Other	6 (2.4%)	7 (2.9%)
Ethnicity		
Hispanic or Latino	64 (25.3%)	72 (29.4%)
Not Hispanic or Latino	189 (74.7%)	173 (70.6%)

Source: Reviewer's Analysis
SD: Standard Deviation

Table 6: Baseline Disease Characteristics (ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
EGSS		
3 - Moderate	212 (83.8%)	200 (81.6%)
4 - Severe	41 (16.2%)	45 (18.4%)
Inflammatory Lesion Count		
Mean (SD)	27.2 (6.0)	26.7 (6.1)
Median	26.0	25.0
Range	20 - 40	20 - 46
Non-inflammatory Lesion Count		
Mean (SD)	38.3 (18.6)	37.2 (17.1)
Median	32	31
Range	20 - 98	20 - 96

Source: Reviewer's Analysis
SD: Standard Deviation

3.2.4 Primary Efficacy Endpoints Results

ONEXTON gel was statistically superior ($p < 0.001$) to vehicle gel on all three co-primary efficacy endpoints. The results from the ITT and PP analyses were similar. The ITT and PP results are presented in Tables 7 and 8, respectively.

For the change in inflammatory and non-inflammatory lesion counts, it should be noted that the pre-specified skewness tests were statistically significant ($p <0.001$); therefore, the applicant also analyzed these endpoints using the rank transformed data. The results using the ranked data were very similar to those of the unranked data ($p < 0.001$).

Table 7: Results for the Co-Primary Efficacy Endpoints at Week 12 (MI-MCMC, ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value
EGSS: 2-grade reduction*	89 (35.2%)	41.6 (17.0%)	<0.001[(1)]
Absolute Change in Inflammatory Lesions:			
Mean*	16.3	8.2	
LS Mean[(2)]	16.2	8.3	<0.001[(2)]
Absolute Change in Non-inflammatory Lesions:			
Mean*	19.2	9.6	
LS Mean[(2)]	18.8	9.6	<0.001[(2)]

Source: Reviewer's Analysis
(1) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
(2) Least squares means and p-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model.
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

Table 8: Results for the Co-Primary Efficacy Endpoints at Week 12 (PP)

	ONEXTON Gel (N=217)	Vehicle Gel (N=204)	P-value
EGSS: 2-grade reduction	79 (36.4%)	33 (16.2%)	<0.001[(1)]
Absolute Change in Inflammatory Lesions:			
Mean	16.4	7.8	
LS Mean[(2)]	16.2	8.1	<0.001[(2)]
Absolute Change in Non-inflammatory Lesions:			
Mean	19.3	8.9	
LS Mean[(2)]	18.9	8.9	<0.001[(2)]

Source: Reviewer's Analysis
(1) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
(2) Least squares means and p-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model.

3.2.5 Handling of Missing Data

Table 9 provides the number of subjects with missing data for the co-primary efficacy endpoints by week and treatment arm. Approximately 7% of the subjects in the ONEXTON arm and approximately 13% of the subjects in the vehicle arm had missing data at Week 12.

Table 9: Missing Data for the Co-Primary Efficacy Endpoints by Week (ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
Week 4	12 (4.7%)	10 (4.1%)
Week 8	14 (5.5%)	25 (10.2%)
Week 12	18 (7.1%)	32 (13.1%)

Source: Reviewer's Analysis

For the co-primary of success on EGSS (2-grade reduction from baseline) at Week 12, the applicant conducted three sensitivity analyzes for the handling of missing data: (i) impute missing data using multiple imputations based on a logistic regression model (MI-Regression), (ii) not impute missing data and analyze using repeated measures logistic regression, and (iii) impute missing data using LOCF (not pre-specified in the protocol). This reviewer conducted an additional sensitivity analysis where the missing data was imputed as failures. The results of the sensitivity analyses that imputed the missing data as well as the primary imputation method (i.e., multiple imputation using the Markov Chain Monte Carlo method (MI-MCMC)) are presented in Table 10. The results were very similar across the different sensitivity analyses. The results for the repeated measures logistic regression (observed cases only) were also statistically significant ($p < 0.001$).

Table 10: Results for EGSS (2-grade reduction from baseline) at Week 12 with Different Approaches for Handling Missing Data (ITT)

Imputation Method	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value[(1)]
MI-MCMC (primary)*	89 (35.2%)	41.6 (17.0%)	<0.001
MI-Regression*	88.2 (34.8%)	41.9 (17.1%)	<0.001
LOCF	83 (32.8%)	38 (15.5%)	<0.001
Impute as Failure	82 (32.4%)	36 (14.7%)	<0.001

Source: Reviewer's Analysis
(1) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
*The values displayed are the averages over the 250 imputed datasets.

For the co-primary endpoints of absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12, the applicant conducted three sensitivity analyses for the handling missing data: (i) impute missing data using multiple imputations using a linear regression model (MI-Regression), (ii) not impute missing data and analyze using repeated measures ANCOVA, and (iii) impute missing data using LOCF (not pre-specified in the protocol). The results of the sensitivity analyses that imputed the missing data as well as the primary imputation method (i.e., MI-MCMC) are presented in Tables 11 and 12 for inflammatory lesions and non-inflammatory lesions, respectively. The results were similar across the different sensitivity analyses. The results for the repeated measures ANCOVA (observed cases only) were also statistically significant ($p < 0.001$).

Table 11: Results for Absolute Change in Inflammatory Lesion Counts at Week 12 with Different Approaches for Handling Missing Data (ITT)

Imputation Method	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value[(1)]
MI-MCMC (primary)*	16.3	8.2	<0.001
MI-Regression*	16.2	8.3	<0.001
LOCF	15.6	7.7	<0.001

Source: Reviewer's Analysis
(1) P-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model.
*The values displayed are the averages over the 250 imputed datasets.

Table 12: Results for Absolute Change in Non-Inflammatory Lesion Counts at Week 12 with Different Approaches for Handling Missing Data (ITT)

Imputation Method	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value[(1)]
MI-MCMC (primary)*	19.2	9.6	<0.001
MI-Regression*	19.2	9.6	<0.001
LOCF	18.3	9.2	<0.001

Source: Reviewer's Analysis
(1) P-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model.
*The values displayed are the averages over the 250 imputed datasets.

3.2.6 Secondary Efficacy Endpoints Results

ONEXTON gel was statistically superior ($p < 0.001$) to vehicle gel on all three secondary efficacy endpoints. The results from the ITT and PP analyses were similar. The ITT and PP results are presented in Tables 13 and 14, respectively.

Table 13: Results for the Co-Primary Efficacy Endpoints at Week 12 (MI-MCMC, ITT)

	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value
EGSS: Clear or Almost Clear*	72.1 (28.5%)	35.5 (14.5%)	<0.001(1)
Percent Change in Inflammatory Lesions:			
Mean*	60.4%	31.3%	
LS Mean(2)	60.6%	31.4%	<0.001(2)
Percent Change in Non-inflammatory Lesions:			
Mean*	51.8%	27.6%	
LS Mean(2)	51.6%	27.4%	<0.001(2)

Source: Reviewer's Analysis
(1) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
(2) Least squares means and p-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model.
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

Table 14: Results for the Co-Primary Efficacy Endpoints at Week 12 (PP)

	ONEXTON Gel (N=217)	Vehicle Gel (N=204)	P-value
EGSS: Clear or Almost Clear	65 (30.0%)	29 (14.2%)	<0.001(1)
Percent Change in Inflammatory Lesions:			
Mean	60.7%	29.9%	
LS Mean(2)	61.1%	29.9%	<0.001(2)
Percent Change in Non-inflammatory Lesions:			
Mean	53.3%	27.0%	
LS Mean(2)	52.8%	26.7%	<0.001(2)

Source: Reviewer's Analysis
(1) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
(2) Least squares means and p-value from an ANCOVA model with treatment, analysis center, and baseline lesion counts in the model.

3.2.7 Comparison to Acanya® Gel

For the approval of Acanya® (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/2.5%, the applicant, Dow Pharmaceutical Sciences, conducted two identically designed Phase 3 trials (Study 012 and Study 017). Both studies were multicenter, randomized, double-blind, 4-arm (Acanya®, each monad, and vehicle) trials. The trials enrolled subjects aged 12 years or older, who had an EGSS of 3 (moderate) or 4 (severe), 17 to 40 inflammatory facial lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory facial lesions (open and closed comedones), and ≤ 2 facial nodules. The protocol specified co-primary and secondary efficacy endpoints are the same for the Acanya® gel trials and the ONEXTON gel trial.

The demographics of the Acanya® gel trials are generally similar to those of the ONEXTON gel trial, see Tables A.1 and A.2 in Appendix. The baseline disease characteristics of EGSS and inflammatory lesion counts are very similar between the Acanya® gel trials and the ONEXTON trial. The average baseline non-inflammatory lesion count was higher in the Acanya® gel trials compared to the ONEXTON trial.

Table 15 displays the efficacy results at Week 12 presented in the label for Acanya® gel. For all endpoints presented in the table, Acanya® gel was statistically superior to both monads and vehicle (all p-values less than 0.012). Table 16 presents a side-by-side comparison of the results from the ONEXTON gel trial and the Acanya® gel trials. The results are very similar for ONEXTON gel and Acanya® gel.

Table 15: Efficacy Results for Acanya® Gel at Week 12 (ITT, LOCF)

		Acanya® Gel (N=399)	Clindamycin Gel (N=408)	BPO Gel (N=406)	Vehicle Gel (N=201)
Study 012	**EGSS[(1)]:**				
	Clear or Almost Clear	115 (29%)	84 (21%)	76 (19%)	29 (14%)
	2-grade reduction from baseline	131 (33%)	100 (25%)	96 (24%)	38 (19%)
	Inflammatory Lesions:				
	Mean Absolute Change	14.8	12.2	13.0	9.0
	Mean Percent Change	55.0%	47.1%	49.3%	34.5%
	Non-inflammatory Lesions:				
	Mean Absolute Change	22.1	17.9	20.6	13.2
	Mean Percent Change	45.3%	38.0%	40.2%	28.6%
		Acanya® Gel (N=398)	**Clindamycin Gel (N=404)**	**BPO Gel (N=403)**	**Vehicle Gel (N=194)**
Study 017	**EGSS[(1)]:**				
	Clear or Almost Clear	113 (28%)	94 (23%)	94 (23%)	21 (11%)
	2-grade reduction from baseline	147 (37%)	114 (28%)	114 (28%)	27 (14%)
	Inflammatory Lesions:				
	Mean Absolute Change	13.7	11.3	11.2	5.7
	Mean Percent Change	54.2%	45.3%	45.7%	23.3%
	Non-inflammatory Lesions:				
	Mean Absolute Change	19.0	14.9	15.2	8.3
	Mean Percent Change	41.2%	34.3%	34.5%	19.2%

Source: The label for Acanya® Gel (NDA 50819)
(1) EGSS was a 6-point scale, where the 6th category was "very severe."

Table 16: Comparison of the Efficacy Results at Week 12 for the ONEXTON Gel Trial and the Acanya® Gel Trials (ITT, MI-MCMC[(1)], LOCF[(2)])

			Study 012		Study 017	
	ONEXTON (N=253)	**Vehicle (N=245)**	**Acanya (N=399)**	**Vehicle (N=201)**	**Acanya (N=398)**	**Vehicle (N=194)**
EGSS[(3)]:						
Clear or Almost Clear	29%	15%	29%	14%	28%	11%
2 grade reduction from baseline	35%	17%	33%	19%	37%	14%
Inflammatory Lesions:						
Mean Absolute Change	16.3	8.2	14.8	9.0	13.7	5.7
Mean Percent Change	60.4%	31.3%	55.0%	34.5%	54.2%	23.3%
Non-inflammatory Lesions:						
Mean Absolute Change	19.2	9.6	22.1	13.2	19.0	8.3
Mean Percent Change	51.8%	27.6%	45.3%	28.6%	41.2%	19.2%

Source: Reviewer's analysis and the label for Acanya® Gel (NDA 50819)
(1) Missing data for the ONEXTON gel trial was imputed using MI-MCMC.
(2) Missing data for the Acanya® gel trials was imputed using LOCF.
(3) EGSS for the ONEXTON gel trial was a 5-point scale while EGSS was a 6-point scale for the Acanya® gel trials.

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

The extent of exposure to study product is presented in Table 17. The planned duration of exposure for was 12 weeks (i.e., 84 applications of study product).

Table 17: Extent of Exposure (Safety Population)

	ONEXTON Gel (N=243)	Vehicle Gel (N=236)
Number of Applications		
N	239	230
Mean (SD)	81.3 (6.6)	78.8 (14.3)
Median	83	83
Range	50 - 96	8 - 98
Amount Used (g)		
N	231	224
Mean (SD)	46.2 (28.2)	48.3 (28.5)
Median	39.6	44.4
Range	2 - 158	1 - 142
Compliant[(1)]	233 (95.9%)	228 (96.6)

Source: pg. 74 of Study Report.
(1) A subject was considered compliant with the dosing regimen if the subject applied at least 80% but no more than 120% of the expected applications, and did not miss more than 5 consecutive applications.
SD: Standard Deviation

3.3.2 Adverse Events

Approximately 22% of ONEXTON subjects and 24% of vehicle subjects reported at least one adverse event. Table 18 presents an overview of adverse events reported during the trial. The adverse events reported in at least 1% of subjects are presented in Table 19.

Table 18: Overview of Adverse Events Reported (Safety Population)

	ONEXTON Gel (N=243)	Vehicle Gel (N=236)
Subjects Reporting at Least 1 AE	54 (22.2%)	57 (24.2%)
AEs Reported	68	71
Relationship to Study Drug		
Not Related	59	63
Unlikely Related	5	1
Possibly Related	2	5
Related	2	2
Severity		
Mild	42	40
Moderate	24	27
Severe	2	4
Serious AEs Reported	0	0

Source: pg. 75 of Study Report.

Table 19: Adverse Events in >1% of Subjects in any Treatment Group (Safety Population)

Preferred Term	ONEXTON Gel (N=243)	Vehicle Gel (N=236)
Abdominal discomfort	0	3 (1.3%)
Headache	3 (1.2%)	5 (2.1%)
Influenza	5 (2.1%)	5 (2.1%)
Nasopharyngitis	18 (7.4%)	12 (5.1%)
Pyrexia	3 (1.2%)	2 (0.8%)
Sinusitis	7 (2.9%)	1 (0.4%)
Upper respiratory tract infection	2 (0.8%)	3 (1.3%)

Source: pg. 76 of Study Report.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Baseline Disease Severity

The results for the co-primary efficacy endpoints by gender, race (white and non-white), age (12-17 and 18-40) and baseline disease severity (EGSS) subgroups are presented in Tables 20. For all three co-primary endpoints, the treatment effect was slightly greater in females than in males. This was also observed in the Acanya® gel trials. For race, the effects of either treatment (ONEXTON or vehicle) were less pronounced for non-whites in comparison to whites; however, a small proportion of subjects (16.0%) were non-white and therefore inference from this subgroup lacks reliability. For all three co-primary endpoints, the treatment effect was greater in subjects aged 12-17 versus subjects aged 18-40 and the treatment effect was smaller in moderate subjects versus severe subjects; however, a small proportion of subjects (18%) were had a baseline disease severity of severe.

Table 20: Co-Primary Efficacy Results at Week 12 by Gender, Race, Age, and Baseline Disease Severity (MI-MCMC, ITT)

	EGSS (2-grade reduction)		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
Subgroup (N_o, N_v)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	ONEXTON Gel (N=253)	Vehicle Gel (N=245)
Gender						
Male (130, 126)	28.2%	13.6%	15.4	8.7	17.4	8.8
Female (123, 119)	42.5%	20.5%	17.3	7.6	21.1	10.5
Race						
White (208, 210)	35.7%	18.8%	16.6	8.8	19.7	11.0
Non-White (45, 35)	32.8%	6.3%	14.7	4.5	17.0	1.3
Age						
12-17 (155, 134)	33.1%	8.5%	16.4	6.2	19.4	8.3
18-40 (98, 111)	38.5%	27.2%	16.2	10.5	18.8	11.3
Baseline Disease Severity (EGSS)						
Moderate (212, 200)	31.3%	16.7%	16.0	8.7	18.7	9.5
Severe (41, 45)	55.1%	18.3%	17.8	5.7	22.0	10.1

Source: Reviewer's Analysis

N_o: number of subjects in the ONEXTON treatment arm

N_v: number of subjects in the vehicle treatment arm

*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

The results of the secondary efficacy endpoints by gender, race (white and non-white), age (12-17 and 18-40) and baseline disease severity (EGSS) subgroups are presented in Tables 21. The results for percent change in inflammatory and non-inflammatory lesion counts are similar to those for absolute change. For subjects with a baseline EGSS of moderate, an EGSS score of clear or almost clear at Week 12 is equivalent to ≥ 2-grade reduction; however, for subjects with a baseline EGSS of severe, an EGSS score clear or almost clear at Week 12 is a higher efficacy bar than a ≥ 2-grade reduction. Therefore, it is not surprising that the response rate for the secondary endpoint of EGSS score of clear or almost clear is less in the severe subgroup compared to the moderate subgroup.

Table 21: Secondary Efficacy Results at Week 12 by Gender, Race, Age, and Baseline Disease Severity (MI-MCMC, ITT)

	EGSS (clear or almost clear)		Percent Change in Inflammatory Lesions		Percent Change in Non-Inflammatory Lesions	
Subgroup (N_o, N_v)	**ONEXTON Gel (N=253)**	**Vehicle Gel (N=245)**	**ONEXTON Gel (N=253)**	**Vehicle Gel (N=245)**	**ONEXTON Gel (N=253)**	**Vehicle Gel (N=245)**
Gender						
Male (130, 126)	21.5%	12.3%	55.8%	32.3%	48.1%	30.2%
Female (123, 119)	35.9%	16.8%	65.3%	30.3%	55.7%	25.2%
Race						
White (208, 210)	28.7%	15.9%	60.5%	33.3%	52.9%	30.8%
Non-White (45, 35)	27.8%	6.2%	59.8%	19.3%	46.9%	8.4%
Age						
12-17 (155, 134)	27.6%	7.2%	59.9%	22.6%	50.5%	21.3%
18-40 (98, 111)	30.0%	23.2%	61.3%	41.8%	54.0%	35.3%
Baseline Disease Severity (EGSS)						
Moderate (212, 200)	31.3%	16.7%	61.9%	34.3%	52.1%	28.3%
Severe (41, 45)	14.1%	4.7%	52.6%	18.0%	50.5%	24.8%

Source: Reviewer's Analysis
N_o: number of subjects in the ONEXTON treatment arm
N_v: number of subjects in the vehicle treatment arm
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

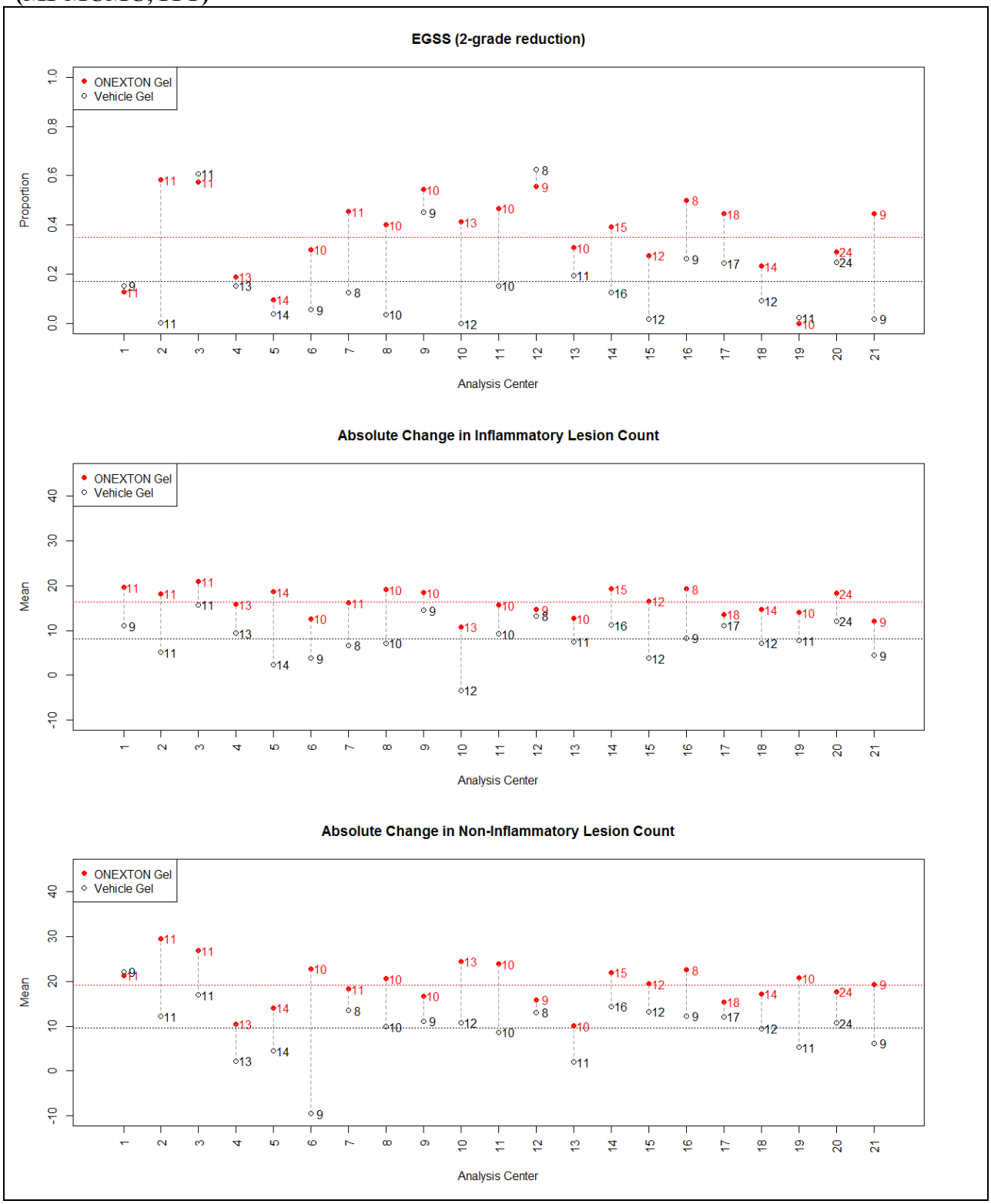
4.2 Center

Study V01-ACYC-301 was conducted at 28 centers in the United States. The protocol specified a pooling strategy for centers that enrolled less than 8 subjects in each treatment arm. These centers were pooled by ordering and combining the smallest with the largest until all centers meet the minimum of 8 subjects in each treatment arm. For Study V01-ACYC-301, 12 of the 28 centers did not meet the minimum and the pooling strategy yielded a total of 21 analysis centers.

Figure 1 presents the results for the co-primary efficacy endpoints at Week 12 by analysis centers. For success on EGSS (2-grade reduction) at Week 12, there was some variability in the treatment effect across the analysis centers, with four analysis centers having the response rate slightly higher in the vehicle arm than in the ONEXTON arm. For absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12, the treatment effects were generally consistent across the analysis centers. There was slightly more variability in the non-inflammatory lesion counts compared to the inflammatory lesion counts.

The applicant investigated the consistency of results across analysis centers by testing interaction in the logistic regression and ANCOVA models. If the interaction was significant at $\alpha = 0.10$ level, the protocol specified a sensitivity analysis were each analysis would be systemically removed to explore the possible source of the interaction effect. The p-values for all three co-primary efficacy endpoints were not significant ($\alpha = 0.10$); therefore, the applicant did not conduct the sensitivity analysis. As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. For all three co-primary endpoints, the removal of any one center did not affect the overall conclusions ($p < 0.001$).

Figure 1: Results for the Co-Primary Efficacy Endpoints at Week 12 by Analysis Centers (MI-MCMC, ITT)



Source: Reviewer's Analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues affecting overall conclusions. For the handling of missing data, the results were similar between the primary imputation method (i.e., multiple imputation using the Markov Chain Monte Carlo method (MI-MCMC)) and the applicant's pre-specified sensitivity analyses. Treatment effects were generally consistent across subgroups. The applicant's investigation of the treatment-by-center interaction focused on the effects after pooling (i.e., analysis centers). As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. For all three co-primary efficacy endpoints, the removal of any one center did not affect the overall conclusions ($p < 0.001$).

5.2 Collective Evidence

ONEXTON (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75% was superior to vehicle gel in the topical treatment of acne vulgaris. The trial enrolled subjects aged 12 to 40 years, who had an Evaluator's Global Severity Score (EGSS) of 3 (moderate) or 4 (severe), 20 to 40 inflammatory facial lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory facial lesions (open and closed comedones), and ≤ 2 facial nodules. The protocol-specified co-primary efficacy endpoints were the proportion of subjects who achieve at least a 2-grade reduction from baseline to Week 12 in the EGSS, absolute change in inflammatory lesion counts from baseline to Week 12, and absolute change in non-inflammatory lesion counts from baseline to Week 12. The protocol specified three co-secondary efficacy endpoints: the proportion of subjects who achieve an EGSS of 0 (clear) or 1 (almost clear) at Week 12, percent change in inflammatory lesion counts from baseline to Week 12, and percent change in non-inflammatory lesion counts from baseline to Week 12. The co-primary and co-secondary efficacy endpoints were all statistically significant ($p < 0.001$), see Table 22.

Table 22: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (MI-MCMC, ITT)

Endpoints	ONEXTON Gel (N=253)	Vehicle Gel (N=245)	P-value
Co-Primary:			
EGSS (2-grade reduction): n (%)	89 (35.2%)	41.6 (17.0%)	<0.001[(1)]
Absolute Change in Inflammatory Lesions: Mean	16.3	8.2	<0.001[(2)]
Absolute Change in Non-Inflammatory Lesions: Mean	19.2	9.6	<0.001[(2)]
Co-Secondary:			
EGSS (clear or almost clear): n (%)	72.1 (28.5%)	35.5 (14.5%)	<0.001[(1)]
Percent Change in Inflammatory Lesions: Mean	60.4%	31.3%	<0.001[(2)]
Percent Change in Non-Inflammatory Lesions: Mean	51.8%	27.6%	<0.001[(2)]

Source: Reviewer's Analysis
(1) P-value based on a logistic regression model (Firth's Penalized Likelihood) with treatment and analysis center as factors.
(2) P-value based on an ANCOVA model with treatment, analysis center, and baseline lesion counts as factors.
*The values displayed are the averages over the 250 imputed datasets (MI-MCMC).

This reviewer also compared the efficacy results of ONEXTON gel, 1.2%/3.75% in this trial to the results of Acanya® gel, 1.2%/2.5% in the trials used for its approval and found the results to be very similar, see Table 16 on page 13.

5.3 Conclusions and Recommendations

Efficacy findings from the single pivotal trial (Study V01-ACYC-301) established that of ONEXTON (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75% was superior to vehicle gel for the topical treatment of acne vulgaris in subjects 12 years of age and older.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Matthew Guerra, Ph.D.
Date: October 3, 2014

Statistical Team Leader: Mohamed Alosh, Ph.D.
Date: October 3, 2014

cc:
DDDP/Marcus
DDDP/Oussova
DDDP/Kettl
DDDP/ Chiang
DDDP/Gould
DDDP/Dixon
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Guerra

APPENDIX

Table A.1: Demographics and Baseline Disease Characteristics for Acanya® Gel Study 012 (ITT)

	Acanya Gel (N=399)	Clindamycin Gel (N=408)	BPO Gel (N=406)	Vehicle Gel (N=201)
Age				
Mean (SD)	19.3 (6.5)	19.7 (7.2)	19.4 (7.0)	19.7 (7.1)
Median	17.0	17.2	16.7	16.9
Range	12.2 - 46.6	12.1 - 49.1	12.0 - 53.8	12.2 - 44.4
Gender				
Male	184 (46.1%)	193 (47.3%)	167 (41.1%)	107 (53.2%)
Female	215 (53.9%)	215 (52.7%)	239 (58.9%)	94 (46.8%)
Race				
White	308 (77.2%)	311 (76.2%)	295 (72.7%)	155 (77.1%)
Black	65 (16.3%)	70 (17.2%)	82 (20.2%)	34 (16.9%)
Asian	8 (2.0%)	16 (3.9%)	8 (2.0%)	6 (3.0%)
Other	22 (5.5%)	16 (3.9%)	24 (5.9%)	12 (6.0%)
EGSS				
3 - Moderate	328 (82.2%)	332 (81.4%)	341 (84.1%)	163 (81.1%)
4 - Severe	71 (17.8%)	76 (18.6%)	65 (16.0%)	38 (18.9%)
Inflammatory Lesion Count				
Mean (SD)	26.8 (6.9)	26.8 (6.8)	26.3 (6.7)	26.9 (6.9)
Median	26	26	25	26
Range	17 - 42	17 - 48	17 - 42	16 - 41
Non-inflammatory Lesion Count				
Mean (SD)	48.4 (21.7)	45.8 (20.3)	48.9 (21.3)	44.0 (20.2)
Median	43	41	44	37
Range	20 - 100	20 - 100	20 - 100	20 - 100

Source: Tables 21 and 22 from Dr. Clara Kim's statistical review for NDA 50819 (Acanys® gel)
SD: Standard Deviation

Table A.2: Demographics and Baseline Disease Characteristics for Acanya® Gel Study 017 (ITT)

	Acanya Gel (N=398)	Clindamycin Gel (N=404)	BPO Gel (N=403)	Vehicle Gel (N=194)
Age				
Mean (SD)	19.1 (7.1)	19.6 (7.4)	18.9 (7.1)	18.9 (6.5)
Median	16.6	17	16.3	16.4
Range	12.1 - 54.7	12.1 - 70.2	12.0 - 48.4	12.3 - 50.9
Gender				
Male	205 (51.5%)	199 (49.3%)	187 (46.4%)	187 (49.5%)
Female	193 (48.5%)	205 (50.7%)	216 (53.6%)	98 (50.5%)
Race				
White	310 (77.9%)	317 (78.5%)	303 (75.2%)	150 (77.3%)
Black	63 (15.8%)	63 (15.6%)	83 (20.6%)	34 (17.5%)
Asian	9 (2.3%)	11 (2.7%)	10 (2.5%)	5 (2.6%)
Other	21 (5.3%)	19 (4.7%)	15 (3.7%)	6 (3.1%)
EGSS				
3 - Moderate	315 (79.1%)	321 (79.5%)	326 (80.9%)	156 (80.4%)
4 - Severe	83 (20.9%)	83 (20.5%)	77 (19.1%)	38 (19.6%)
Inflammatory Lesion Count				
Mean (SD)	26.0 (7.0)	25.7 (6.8)	25.3 (6.8)	25.3 (6.4)
Median	24.5	24	23	24
Range	17 - 41	17 - 41	17 - 42	17 - 40
Non-inflammatory Lesion Count				
Mean (SD)	46.5 (21.1)	44.9 (20.1)	44.7 (20.8)	44.1 (18.2)
Median	40	39	39	40
Range	20 - 100	20 - 100	20 - 100	20 - 94

Source: Tables 21 and 22 from Dr. Clara Kim's statistical review for NDA 50819 (Acanys® gel)
SD: Standard Deviation

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/s/

MATTHEW W GUERRA
10/03/2014

MOHAMED A ALOSH
10/03/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 050819 / S-12 **Applicant:** Dow Pharmaceutical Sciences **Stamp Date:** 1/30/2014

Drug Name: (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75% **NDA/BLA Type:** Supplement

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Comment for 74-day letter:
In Table 11-4 (page 56 of the study report), you presented the efficacy results for the three co-primary endpoints at Week 12. It is not clear how you obtained the presented response rates for the 2-grade reduction from baseline in EGSS. Submit the SAS code used to generate these rates.

Matthew Guerra, Ph.D.	March 14, 2014
Reviewing Statistician	Date
Mohamed Alosh, Ph.D.	March 14, 2014
Supervisor/Team Leader	Date

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

/s/

MATTHEW W GUERRA
03/14/2014

MOHAMED A ALOSH
03/14/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 50819/S-12	Submission Date(s): 1/31/2014
Brand Name	Onexton Gel
Generic Name	Clindamycin phosphate/benzoyl peroxide 1.2%/3.75%
Primary Reviewer	An-Chi Lu, M.S., Pharm.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Dow
Submission Type	Efficacy supplement
Dosage Form	Gel
Indication	Topical treatment of acne vulgaris in patients 12 years or older

Table of Contents

1 Executive Summary

This efficacy supplement is for the introduction of Onexton Gel (clindamycin phosphate and benzoyl peroxide), 1.2%/3.75%, in addition to the already approved Acanya Gel, 1.2%/2.5%. Acanya® (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/2.5% for the treatment of acne vulgaris was approved on October 23, 2008. The difference between the proposed Onexton Gel and the approved Acanya Gel is the concentration of benzoyl peroxide (3.75% vs. 2.5%).The efficacy supplement contains data from one Phase 3 safety and efficacy trial V01-ACYC-301. This trial did not include pharmacokinetic (PK) assessments. The sponsor requests a waiver for conduct of PK trial with Onexton Gel.

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

1.2 Phase IV Commitments/Requirements

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted an efficacy and safety Phase 3 trial V01-ACYC-301 for the submission of Onexton Gel. This trial did not evaluate any pharmacokinetics. The sponsor requested a PK waiver by asserting that the exposure of clindamycin from Onexton Gel would be low and similar to Acanya Gel, and less than BenzaClin Gel.

The systemic exposures of clindamycin for Acanya Gel (once daily dosing) and BenzaClin Gel (twice daily dosing) are listed in Table 1. At steady state, the Cmax for Acanya Gel ranges from 0.51 to 3.30 ng/mL, and 1.43 to 7.18 ng/mL for BenzaClin Gel. The mean AUC is 8.42±6.007 ng*hr/mL for Acanya Gel, and 30.34±17.39 ng*hr/mL for BenzaClin Gel.

Table 1: The Systemic Exposures of Clindamycin for Acanya Gel and BenzaClin Gel

	Measured	Lower Limit of Quantitation	Mean AUC[a] (ng·hr/mL)	C_{max}[b] (ng/mL)
Acanya Gel	Day 30	0.5 ng/mL	8.42 ± 6.007	0.51 to 3.30
BenzaClin Gel	Day 5	1 ng/mL	30.34 ± 17.394	1.43 to 7.18

[a] AUC presented is AUC_{0-t} (n=6) for Acanya Gel and AUC_{SS} (n=12) for BenzaClin Gel. The $AUC_{0-\infty}$ for Acanya Gel is 24.26 (n=1).

[b] C_{max} presented is the range from minimum to maximum. Values BLQ were excluded for Acanya Gel and set to 0 to BenzaClin Gel.

In terms of [(b) (4)] Onexton Gel is the [(b) (4)] Acanya Gel [(b) (4)] for the concentration of benzoyl peroxide (3.75% and 2.5%, respectively), [(b) (4)] from

BenzaClin Gel. BenzaClin Gel has an approved generic form, [redacted] (ANDA 65443), which was shown to be bioequivalent to BenzaClin Gel in a bioequivalence (BE) trial with clinical endpoint and [redacted] Onexton Gel [redacted] for the concentration of benzoyl peroxide (5% vs. 3.75%) and propylene glycol [redacted] Table 2 is an abbreviated table of select components (active ingredients and propylene glycol) of these formulations. The propylene glycol concentration in [redacted] than Onexton Gel [redacted]. Propylene glycol is [redacted]. This reviewer notes that the sponsor had the ownership of all four products at one time.

Table 2: Product Composition Comparison between Acanya Gel, Onexton Gel, and [redacted] for Benzoyl Peroxide, Clindamycin Phosphate, and Propylene Glycol

Ingredients	Acanya Gel (%)	Onexton Gel (%)	[redacted] (%)
Benzoyl Peroxide	2.50	3.75	5.00
Clindamycin Phosphate	1.20	1.20	1.20
Propylene Glycol	[redacted]		

Regarding absorption of benzoyl peroxide, because the metabolism of benzoyl peroxide to benzoic acid in the skin is complete and rapid, its plasma concentration is not assessed. Since benzoic acid is an endogenous compound and it is also widely used as a food additive (that is considered safe in humans), it would be difficult to accurately evaluate treatment-related exposure of benzoic acid. The contribution of benzoic acid from exogenously administered benzoyl peroxide in Onexton Gel is also expected to be limited.

Lastly, in the Phase 3 trial of Onexton Gel (V01-ACYC-301), the sponsor stated there were no events associated with gastrointestinal disorders which would be expected with high circulating levels of clindamycin. As additional secondary supporting evidence, there are six approved products with 1.2% clindamycin phosphate. These products, including Ziana Gel (clindamycin phosphate 1.2% and tretinoin 0.025%), Veltin Gel (clindamycin phosphate 1.2% and tretinoin 0.025%), Cleocin Solution 1% (clindamycin phosphate [redacted]), Clindagel 1% (clindamycin phosphate [redacted], Evoclin Foam (clindamycin phosphate [redacted]), and Duac Gel (clindamycin phosphate 1.2% and benzoyl peroxide 5%), appear to have low clindamycin systemic exposure.

In conclusion, based on the available data, the systemic exposure of clindamycin following once daily administration of Onexton Gel would likely be low and bracketed by concentration observed for approved products Acanya Gel (NDA 50819) and [redacted] (ANDA 65443) and not expected to cause systemic safety concerns. [redacted] was previously bridged to BenzaClin Gel via a BE trial with clinical endpoint. Under the aforementioned circumstances, the PK waiver for this application is acceptable.

Clinical Pharmacology Briefing:
An optional intra-division level Clinical Pharmacology briefing was conducted on 9/25/2014 with the following in attendance: Edward D Bashaw, Hae-Young Ahn, Doanh Tran, Chinmay Shukla, and An-Chi Lu.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the formulation composition of Onexton Gel, 1.2%/3.75%? Was the to-be-marketed formulation used in the pivotal Phase 3 trial?

(b) (4) Onexton Gel, 1.2%/3.75% (b) (4) as the marketed Acanya Gel, 1.2%/2.5%, (b) (4) for the increased concentration of benzoyl peroxide. The composition of Onexton Gel is shown in Table 3. This formulation was used in the pivotal Phase 3 trial V01-ACYC-301.

Table 3: Composition of Onexton Gel (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%

Ingredients	Grade	%w/w	Function
Benzoyl Peroxide	USP	3.75[1]	Drug Substance
Clindamycin Phosphate	USP	1.20[2]	Drug Substance
Propylene Glycol	USP	(b) (4)	
Carbomer 980	NF		
Potassium Hydroxide	NF		
Purified Water	USP		

[1] A (b) (4) overage is added to (b) (4)
[2] Equivalent to 1% Clindamycin

2.1.2 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action: The mechanism of action as per Acanya Gel label approved on 2/28/2014 is as follows:

Clindamycin: Clindamycin is a lincosamide antibacterial.

Benzoyl Peroxide: Benzoyl peroxide is an oxidizing agent with bacteriocidal and keratolytic effects but the precise mechanism of action is unknown.

Therapeutic indication: Topical treatment of acne vulgaris in patients 12 years or older.

2.1.3 What is the proposed route of administration and dosage?

Proposed route of administration: Topical

Proposed dosage: Apply a pea-sized amount to the face once daily.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies used to support dosing or claims? Is the PK waiver for Onexton Gel acceptable?

The original NDA was approved on October 23, 2008 for the treatment of acne vulgaris in patients 12 years or older. This efficacy supplement introduces Onexton gel (clindamycin phosphate and benzoyl peroxide), 1.2%/3.75%, in addition to the already approved Acanya Gel, 1.2%/2.5%. The sponsor submitted one Phase 3 trial V01-ACYC-301 for the safety and efficacy evaluation of Onexton Gel.

In this submission, the sponsor did not perform pharmacokinetic (PK) assessments and requested a waiver for conduct of PK trial with Onexton Gel, and asserted that plasma levels of clindamycin would be similar to Acanya Gel (NDA 50819) and lower than BenzaClin Gel (NDA 50756). In addition, since benzoic acid is an endogenous compound and it is also widely used as a food additive (that is considered safe in humans), it would be difficult to accurately evaluate treatment-related exposure of benzoic acid.

The systemic exposures for the two approved products are listed in Table 1. The product composition comparison between Acanya Gel, Onexton Gel, (b) (4) and BenzaClin Gel is shown in Table 4. (b) (4) Onexton Gel (b) (4) to the approved Acanya gel (1.2%/2.5%) (b) (4) the concentration of benzoyl peroxide and corresponding purified water, and is also (b) (4) to (b) (4) the generic form of BenzaClin gel (clindamycin phosphate and benzoyl peroxide gel, (b) (4) /5%) (b) (4) the concentration of benzoyl peroxide and propylene glycol. (b) (4) (ANDA 65443) was approved in August 2009 based on bioequivalence trial with clinical endpoints to BenzaClin Gel. In the ANDA clinical bioequivalence review for (b) (4) Dr. Sarah Seung noted that (b) (4) contains (b) (4) propylene glycol while the RLD (reference listed drug) BenzaClin Gel contains none. The potential for increased systemic absorption of clindamycin and associated adverse events had been considered, and the OGD (Office of Generic Drugs) concluded that the formulation with (b) (4) (b) (4)

Table 4: Product Composition Comparison between Acanya Gel, Onexton Gel, [redacted], and BenzaClin Gel

Ingredients	Grade	%w/w			
		Acanya Gel	Onexton Gel	[redacted]	BenzaClin Gel
Benzoyl Peroxide	USP	2.50	3.75	5.00	5.00
Clindamycin Phosphate	USP	1.20	1.20	1.20	[redacted]
Propylene Glycol	[redacted]				
Carbomer 980					
Potassium Hydroxide					
Purified Water					

For the systemic exposure of BenzaClin Gel, based on the label and clinical pharmacology review (dated 11/20/2008 in DARRTS), thirteen (13) subjects with acne vulgaris were treated with ~2 grams topically to the face and back twice daily for 4.5 days. On Day 5, twelve subjects (92.3%) had quantifiable (>LOQ=1 ng/mL) clindamycin concentrations. The mean C_{max} was 3.59 ± 1.82 ng/mL (range 1.43-7.18 ng/mL n=12), and the mean AUC_{0-t} was 30.34 ± 17.39 h.ng/mL (range 11.40-69.68 h.ng/mL, n=12). Considering that the formulation of BenzaClin Gel is different from Onexton Gel, definitive inferences cannot be made to determine clindamycin concentration of Onexton Gel. However, it is noted that BenzaClin Gel is bioequivalent to [redacted] and [redacted] has a [redacted] to Onexton Gel [redacted] the content of propylene glycol. In addition, since propylene glyco [redacted]

For the systemic exposure of Acanya Gel, in the maximal use PK trial for Acanya Gel 2.5% (DPSI-IDP-110-P4-01[redacted]; NDA 050-819; SN0072) in which 16 adult subjects with moderate to severe acne vulgaris were treated with 1 gram applied to the face once daily for 30 days, twelve subjects (75%) had at least one quantifiable clindamycin plasma concentration above the lower limit of quantification (LOQ = 0.5 ng/mL) on Day 1 or Day 30. On Day 30, the mean C_{max} was 1.22 ± 0.88 ng/mL (range 0.51-3.30 ng/mL, n=10 with measurable concentrations), and the mean AUC_{0-t} was 8.42 ± 6.01 h.ng/mL (range 2.39-18.51 h.ng/mL, n=6). The [redacted] of Acanya Gel 2.5% and Onexton Gel is the [redacted] for the concentration of benzoyl peroxide (2.5% and 3.75%, respectively). Since the approved [redacted] has a higher concentration of benzoyl peroxide, even if benzoyl peroxide does affect the absorption of clindamycin, the

effect of 3.75% of benzoyl peroxide in Onexton Gel would be bracketed by the 2.5% and 5% in the two approved products (Acanya Gel and (b) (4) respectively).

The sponsor stated that in the Phase 3 trial of Onexton Gel (V01-ACYC-301), there were no systemic effects for the topically applied Onexton Gel; specifically, there were no events associated with gastrointestinal disorders which would be expected with high circulating levels of clindamycin.

As secondary supportive evidence, there are other approved products with 1.2% clindamycin phosphate, and the systemic exposures of clindamycin are illustrated below in Table 5. It appears that with various different formulations, they do not show significant clindamycin exposure when used as a topical drug.

Table 5: Approved Products with 1.2% Clindamycin Phosphate and their PK data

NDA # and approval date	Trade Name	Active ingredients	PK data in the label	PK Study Design
50802 11/7/2006	Ziana	clindamycin phosphate 1.2% and tretinoin 0.025%	Plasma concentrations for clindamycin generally did not exceed 3.5 ng/mL, with the exception of one subject whose plasma concentration reached 13.1 ng/mL.	12 subjects with moderate to severe acne were administered 4 g once daily for 14 days. (face, neck, back and chest)
50803 7/16/2010	Veltin	clindamycin phosphate 1.2% and tretinoin 0.025%	All subjects had quantifiable plasma clindamycin concentrations and were all ≤5.56 ng/mL on the last day, with the exception of one subject who had a C_{max} of 8.73 ng/mL at 4 hours post-dose.	17 subjects with moderate to severe acne were administered 3 g once daily for 5 days. (face, neck, upper chest, and upper back)
50537 7/9/1980	Cleocin Solution	clindamycin phosphate (b) (4)	0–3 ng/mL of clindamycin in serum and less than 0.2% of the dose is recovered in urine as clindamycin following multiple topical applications	Study design unclear. Clindamycin phosphate was at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution
50782 11/27/2000	Clindagel 1%	clindamycin phosphate (b) (4)	C_{max} were less than 5.5 ng/ml following five days of once daily applications (range on Day 5: 0.505-5.299 ng/mL)	24 patients with acne vulgaris were administered with 3-12 g once daily for 5 days. (13-37 years old found to have 25–100 inflammatory facial lesions and 20 - 100 noninflammatory lesions at Screening)

50801 10/22/2004	Evoclin Foam	clindamycin phosphate (b) (4)	Mean C_{max} and $AUC_{(0-12)}$ were 23% and 9% lower, respectively, than for the clindamycin gel, 1%. (C_{max} 1.56±0.81 ng/mL, AUC_{0-12h} 13.69±6.25 ng.h/mL)	24 subjects with acne vulgaris, 12 subjects applied 4 grams of Evoclin Foam once-daily for five days, and 12 subjects applied 4 grams of a clindamycin gel, 1%, once daily for five days. (mild to moderate facial acne vulgaris)
50741 8/26/2002	Duac	clindamycin phosphate and benzoyl peroxide, 1.2%/5%	Mean plasma clindamycin levels during the 4-week dosing period were <0.5 ng/mL	Study design unclear. 78 subjects in a comparative trial of DUAC Gel and 1% clindamycin solution alone.
50162 2/22/1970	Clindamycin hydrochloride capsule (oral)		An average peak serum level of 2.50 mcg/mL was reached in 45 minutes; serum levels averaged 1.51 mcg/mL at 3 hours and 0.70 mcg/mL at 6 hours	a 150 mg oral dose of clindamycin hydrochloride in 24 normal adult volunteers

From all of the supporting evidence discussed above, the PK waiver for this application is acceptable.

2.2.2 What is the Sponsor's pediatric development plan?

The sponsor has conducted a Phase 3 clinical trial to support the proposed indication of treatment of acne vulgaris in patients 12 years or older. The sponsor requests a waiver for pediatric subjects age 0 to 11 years old for reason that Onexton Gel does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients.

2.3 Intrinsic Factors

No new information provided in this sNDA.

2.4 Extrinsic Factors

No new information provided in this sNDA.

2.5 Analytical Section

The Sponsor did not assess any PK in this application and hence did not carry out any bioanalysis.

3 Detailed Labeling Recommendations

The following changes are recommended for sections 7 and 12 of the label. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

7 DRUG INTERACTIONS

7.1 Erythromycin

Avoid using ONEXTON Gel ~~should not be used~~ in combination with topical or oral erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this in vitro antagonism is not known.

7.2 Concomitant Topical Medications

Concomitant topical acne therapy should be used with caution since a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. If irritancy or dermatitis occurs, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

(b) (4) **Neuromuscular Blocking Agents**

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ONEXTON Gel should be used with caution in patients receiving such agents.

12 CLINICAL PHARMACOLOGY

12.1 Mechanisms of Action

Clindamycin: Clindamycin is a lincosamide antibacterial [see Clinical Pharmacology ~~Microbioloty~~ (12.4)].

Benzoyl Peroxide: Benzoyl peroxide is an oxidizing agent with bacteriocidal and keratolytic effects, but the precise mechanism of action is unknown.

12.3 Pharmacokinetics

The systemic absorption of ONEXTON Gel has not been evaluated. The systemic absorption of clindamycin was investigated in an open-label, multiple-dose trial in 16 adult subjects with moderate to severe acne vulgaris treated with 1 gram of a marketed gel containing clindamycin 1%/benzoyl peroxide 2.5% (b) (4) applied to the face once daily for 30 days. This product has the same formulation as ONEXTON Gel but with a ~~higher~~ lower concentration of benzoyl peroxide. Twelve subjects (75%) had at least one quantifiable clindamycin plasma concentration above the lower limit of quantification (LOQ = 0.5 ng/mL) on Day 1 or Day 30. On Day 1, the mean (± standard deviation) peak plasma concentrations (Cmax) was 0.78 ± 0.22 ng/mL (n=9 with measurable concentrations), and the mean AUC0-t was 5.29 ± 0.81 h.ng/mL (n=4). On Day 30, the mean Cmax was 1.22 ± 0.88 ng/mL (n=10), and the mean AUC0-t was 8.42 ± 6.01 h ng/mL (n=6). Clindamycin plasma concentrations were below LOQ in all subjects at 24 hours post-dose on the three tested days (Day 1, 15, and 30).

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid.

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/s/

AN-CHI LU
09/26/2014

DOANH C TRAN
09/26/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 50819, S-12, SDN292 **Applicant: Dow** **Stamp Date: 1/31/2014**

Drug Name: clindamycin phosphate and benzoyl peroxide gel, 1.2%/3.75%. **NDA/BLA Type: Efficacy Supplement**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
Criteria for Assessing Quality of an NDA					
	Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?			X	
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			X	
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			X	
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
11	Is the appropriate pharmacokinetic information submitted?		X		The sponsor requests a waiver from conducting bioavailability trial. This will be considered during NDA review.
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	

	General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?			X	
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?			X	
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?			X	
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
17	Was the translation from another language important or needed for publication?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

See end of filing memorandum.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**50819/S-012**	**Brand Name**	**(b) (4) gel, 1.2%/3.75%.**
OCP Division	**Division of Clinical Pharmacology 3**	**Generic Name**	**Clindamycin phosphate and benzoyl peroxide 1.2%/3.75% gel**
Medical Division	**Division of Dermatology and Dental Product**	**Drug Class**	**Antibiotic**
OCP Primary Reviewer	**An-Chi Lu, M.S., Pharm.D.**	**Indication(s)**	**Topical treatment of acne vulgaris in patients 12 years or older**
OCP Secondary Reviewer	**Doanh Tran, R.Ph., Ph.D**	**Dosage Form**	**Gel**
		Dosing Regimen	**Once daily**
Date of Submission	**1/31/2014**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**9/30/2014**	**Sponsor**	**Dow**
PDUFA Due Date	**11/30/2014**	**Priority Classification**	**Standard**
Division Due Date	**9/30/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is the sponsor's request for a waiver to conduct maximal use PK trial acceptable?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memorandum

Clinical Pharmacology Review

NDA: 50819
Compound: Clindamycin phosphate and benzoyl peroxide gel, 1.2%/3.75%.
Sponsor: Dow
Date: 3/12/2014
Reviewer: An-Chi Lu

Background:
This efficacy supplement is for the introduction of ACYC Gel (clindamycin phosphate and benzoyl peroxide), 1.2%/3.75%, in addition to the already approved Acanya Gel, 1.2%/2.5%. Acanya® (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/2.5% for the treatment of acne vulgaris was approved on October 23, 2008. The difference between the proposed ACYC Gel and the approved Acanya Gel is the concentration of benzoyl peroxide (3.75% vs. 2.5%).The efficacy supplement contains data from one Phase 3 trial V01-ACYC-301. This trial did not perform pharmacokinetic (PK) assessments.

Pharmacokinetic waiver request:
The sponsor did not conduct PK trials with ACYC Gel, and requests a waiver for conduct of PK trial with ACYC Gel. The sponsor stated that plasma levels of clindamycin would be bracketed by levels determined for Acanya Gel (NDA 50819) and BenzaClin Gel (NDA 50756). In addition, benzoyl peroxide component in both of these products is rapidly converted in the skin to benzoic acid and not measurable systemically. The sponsor stated that since the only difference of ACYC Gel from Acanya Gel and BenzaClin Gel is the concentration of benzoyl peroxide (3.75% vs. 2.5% and 5%), the PK of these three products would be measured by the plasma levels of the clindamycin phosphate 1.2% that is common to all three products. The systemic exposures in the two approved products are listed in Table 1. The sponsor stated that an additional pharmacokinetics trial with ACYC Gel would demonstrate levels consistent with those observed with Acanya Gel (with the (b) (4) as ACYC Gel) and BenzaClin Gel.

Table 1: Systemic Exposure in Approved Products with Clindamycin Phosphate 1.2%

	Measured	Lower Limit of Quantitation	Mean AUC[a] (ng·hr/mL)	C_{max}[b] (ng/mL)
Acanya Gel	Day 30	0.5 ng/mL	8.42 ± 6.007	0.51 to 3.30
BenzaClin Gel	Day 5	1 ng/mL	30.34 ± 17.394	1.43 to 7.18

[a] AUC presented is AUC_{0-t} (n=6) for Acanya Gel and AUC_{SS} (n=12) for BenzaClin Gel. The $AUC_{0-\infty}$ for Acanya Gel is 24.26 (n=1).
[b] C_{max} presented is the range from minimum to maximum. Values BLQ were excluded for Acanya Gel and set to 0 to BenzaClin Gel.

Internal Comments:
[redacted] ACYC Gel [redacted] to the approved Acanya gel (1.2%/2.5%) [redacted] the concentration of benzoyl peroxide and corresponding purified water, and is also [redacted], the generic form of BenzaClin gel (clindamycin phosphate and benzoyl peroxide gel, [redacted]/5%) [redacted] the concentration of benzoyl peroxide and propylene glycol. It is [redacted] of BenzaClin gel. The waiver request will be considered during NDA review.

Clinical vs. to-be-marketed formulation:
The to-be-marketed formulation was used in the Phase 3 safety and efficacy trial V01-ACYC-301.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the submission for the efficacy supplement (s-12) for NDA 50819 is fileable.

Comments for Sponsor:
1. We acknowledge that you request a waiver for conduct of pharmacokinetic trial with ACYC Gel and state that plasma levels of clindamycin would be bracketed by levels determined for Acanya Gel and BenzaClin Gel. However, we note that although the [redacted] of ACYC Gel is [redacted] to Acanya Gel [redacted] difference in concentration of benzoyl peroxide), it is [redacted] of BenzaClin Gel. Provide rationale on how the plasma levels of clindamycin would be bracketed between Acanya Gel (containing 2.5% benzoyl peroxide) and BenzaClin Gel (containing 5% benzoyl peroxide) when [redacted]

2. Provide a summary of product composition for Acanya Gel, 1.2%/2.5%, BenzaClin Gel, and [redacted] (product used in bioequivalent trial with BenzaClin Gel).

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/s/

AN-CHI LU
03/14/2014

DOANH C TRAN
03/14/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

OTHER REVIEW(S)

Division of Dermatology and Dental Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 050819 S-012

Name of Drug: Onexton (clindamycin phosphate and benzoyl peroxide) topical gel, 1.2%/3.75%

Applicant: Dow Pharmaceutical Sciences

Labeling Reviewed

Submission Date: January 30, 2014

Receipt Date: January 30, 2014

Background and Summary Description:
The efficacy supplement provides for introduction of 3.75% benzoyl peroxide strength in addition to the already approved 2.5% benzoyl peroxide in Acanya Gel. The PDUFA date is November 30, 2014. The labeling for this supplement is based on the already approved Acanya Gel label and their clinical trial entitled "A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of ACYC and ACYC Vehicle Gel in the Treatment of Acne Vulgaris."

Review

The sponsor based the initial submission of the NDA 050819 S-012 Onexton™ label, dated January 30, 2014, on the label in their August 30, 2013 NDA 050819 S-010 Acanya submission. The Agency approved NDA 050819 S-010 Acanya on February 28, 2014. The sponsor submitted a revised NDA 050819 S-012 Onexton™ label based on the approved NDA 050819 S-010 Acanya label on March 14, 2014.

In a review of the approved Acanya label and the Onexton label, the sponsor proposed the following:

1. Replaced references to "Acanya" with "Onexton";
2. Addition of tables containing trial results for Onexton™;
3. Deletion of tables containing the Acanya trial results; and
4. Minor editorial changes.

Recommendations

There were no additional changes between the approved NDA 050819 S-010 Acanya and the NDA 050819 S-012 Onexton™ labels.

Strother D. Dixon	31 Oct 2014
Regulatory Project Manager	Date
Barbara Gould	03 Nov 2014
Chief, Project Management Staff	Date

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/s/

STROTHER D DIXON
11/03/2014

BARBARA J GOULD
11/03/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 050819	NDA Supplement #: S- 012	Efficacy Supplement Type SE- 2
Proprietary Name: Onexton Established/Proper Name: (clindamycin phosphate and benzoyl peroxide) Dosage Form: Gel Strengths: 1.2%/3.75%		
Applicant: Dow Pharmaceutical Sciences		
Date of Receipt: January 30, 2014		
PDUFA Goal Date: November 30, 2014	Action Goal Date (if different): November 17, 2014	
RPM: Strother D. Dixon		
Proposed Indication(s): For the treatment of acne vulgaris		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 050741 Duac (clindamycin and benzoyl peroxide) topical gel, 1%/5%	Non-Clinical, Clinical Pharmacology & Clinical

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant stated, "The sponsor intends to rely on data from Acanya Gel and BenzaClin to bracket the ACYC Gel. The Sponsor owns the original data for both of these products. The Sponsor has established a clinical bridge to the safety and efficacy of ACYC Gel through bracketing of the BPO concentrations and performance of a single Phase 3 safety and efficacy study comparing ACYC Gel to Vehicle Gel (V01-ACYC-301)."

The original approval for Acanya (NDA 050819) relied on literature to support the nonclinical requirements, and the clinical pharmacology bioequivalence information was agreed to be conducted as a postmarketing commitment. The applicant provided safety and efficacy data in two adequate and well-controlled four armed clinical trials.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒
*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐
*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
BenzaClin (clindamycin and benzoyl peroxide) topical gel, 1%/5%	050756	Y
Duac (clindamycin and benzoyl peroxide) topical gel, 1%/5%	050741	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☒ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The supplement provides for introduction of a 3.75% benzoyl peroxide strength in addition to the already approved 2.5% benzoyl peroxide in Acanya Gel.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): ANDA 090979 (clindamycin phosphate and benzoyl peroxide) 1.2%/5%

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):
ANDA 090979 (clindamycin phosphate and benzoyl peroxide) 1.2%/5%
ANDA 065443 (clindamycin phosphate and benzoyl peroxide) 1%/5%

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

STROTHER D DIXON
10/27/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 24, 2014

To: Strother Dixon
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Tara Turner, Pharm.D., MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer, OPDP

CC: Adora Ndu, Pharm.D., Team Leader, OPDP

Subject: **NDA 050819/S-012**
ONEXTON™ (clindamycin phosphate and benzoyl peroxide)
Gel, 1.2%/3.75%, for topical use

On February 14, 2014, DDDP consulted OPDP to review the draft Package Insert labeling (PI), carton and container labeling, and Patient Package Insert (PPI) for ONEXTON™ (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%, for topical use (Onexton) for the supplemental NDA submission (supplement 012), which provides for the introduction of a 3.75% benzoyl peroxide strength in addition to the already approved 2.5% benzoyl peroxide in Acanya Gel. The sponsor intends to continue marketing the 2.5% benzoyl peroxide product under the trade name, Acanya Gel.

OPDP reviewed the proposed substantially complete versions of the PI and PPI provided by DDDP via e-mail on September 10, 2014. OPDP also reviewed the revised carton and container labeling submitted to the electronic document room by the sponsor on April 23, 2014. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the PPI for Onexton under separate cover. OPDP's comments on the PI and carton and container labeling are provided below.

Thank you for your consult. If you have any questions about OPDP's comments, please contact Tara Turner at 6-2166 or at Tara.Turner@fda.hhs.gov.

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/s/

TARA P TURNER
09/24/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 24, 2014
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)** Melinda McLawhorn, Pharm.D., BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
From:	Morgan Walker, PharmD, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Tara Turner, Pharm.D., MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name) Dosage Form and Route:	ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%, For topical use
Application Type/Number:	NDA 50819
Supplement Number:	S-012
Applicant:	Dow Pharmaceutical Sciences

1 INTRODUCTION

On January 27, 2014, Dow Pharmaceutical Sciences submitted for the Agency's review an efficacy supplement to their New Drug Application (NDA) 50819/S-012 ACANYA (clindamycin phosphate and benzoyl peroxide) Gel. This efficacy supplement proposes the introduction of a new benzoyl peroxide strength (3.75%) in addition to the approved 2.5% benzoyl peroxide in ACANYA Gel. The efficacy supplement also includes a request for proprietary name review for the proposed name ONEXTON for the new 3.75% benzoyl peroxide strength. The Applicant states in their cover letter that they intend to continue to market the approved 2.5% benzoyl peroxide dosage form as ACANYA Gel.

ACANYA (clindamycin phosphate and benzoyl peroxide) 1.2%/2.5% Gel was originally approved on October 23, 2008, and is indicated for the topical treatment of acne vulgaris.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on February 14, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ONEXTON (clindamycin phosphate and benzoyl peroxide) 1.2%/3.75% Gel.

2 MATERIAL REVIEWED

- Draft ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel PPI received on January 30, 2014, further revised by the Applicant throughout the review cycle, and received by DMPP and OPDP on February 14, 2014.
- Draft ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel Prescribing Information (PI) received on January 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 10, 2014.
- Approved ACANYA (clindamycin phosphate and benzoyl peroxide) Gel comparator labeling dated February 28, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
09/24/2014

MELINDA W MCLAWHORN
09/24/2014

MELINDA W MCLAWHORN on behalf of TARA P TURNER
09/24/2014

BARBARA A FULLER
09/24/2014

LASHAWN M GRIFFITHS
09/24/2014

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 22, 2014
Application Type and Number:	NDA 050819/S-012
Product Name and Strength:	Onexton (Clindamycin Phosphate and Benzoyl Peroxide) Gel, 1.2%/3.75%
Product Type:	Multiple-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Dow Pharmaceutical Sciences
Submission Date:	January 31, 2014
Panorama #:	2014-16880
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Onexton, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an external name study, conducted by Med ERRS, for this product.

1.1 REGULATORY HISTORY

NDA 050819 was approved on October 21, 2008 under the proprietary name Acanya for clindamycin phosphate and benzoyl peroxide gel 1.2%/2.5%.

1.2 PRODUCT INFORMATION

The following product information is provided in the 2/4/2014 proprietary name submission.

- Intended Pronunciation: on-ex-tun
- Active Ingredient: Clindamycin phosphate and benzoyl peroxide
- Indication of Use: Acne vulgaris
- Route of Administration: Topical
- Dosage Form: Gel
- Strength: 1.2%/3.75%
- Dose and Frequency: Apply to the affected area(s) once daily
- How Supplied: 50 g pump
- Storage: Pharmacist: Prior to Dispensing Store in a refrigerator, 2°C to 8°C (36°F to 46°F). Patient: Store at room temperature at or below 25°C (77°F)
- Container and Closure Systems: (b) (4)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Dermatology and Dental Products (DDDP) concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[1].

2.2.2 Components of the Proposed Proprietary Name

The Applicant did not provide a derivation or intended meaning for the proposed name, Onexton in their submission. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.2.1 Dual Proprietary Name

The applicant, Dow Pharmaceuticals, currently markets clindamycin phosphate and benzoyl peroxide gel 1.2%/2.5% under the proprietary name Acanya. However, for the proposed new strength 1.2%/3.75% Dow is pursuing the proposed proprietary name Onexton. Dow argues that a separate proprietary name will help to easily differentiate the higher strength component (3.75%) as a stand-alone name that describes the product in terms that physicians understand and use. Dow also claims that in addition to convenience, a new name affords an additional measure of assurance that the appropriate strength is prescribed and dispensed. Finally, Dow referenced other marketed products where there is a precedent for dual trade names.

DMEPA considered the safety implications of having a dual proprietary name for this product line (i.e. concomitant administration leading to over dose), including discussions with the review division. However, the risk of concomitant administration of Acanya with Onexton is no different from the risk of concomitant administration of Onexton with any of the multiple clindamycin phosphate and benzoyl peroxide products currently available (branded and generics). Therefore, a distinct proprietary name for Dow's clindamycin phosphate and benzoyl peroxide 1.2%/3.75% strength is acceptable.

2.2.3 FDA Name Simulation Studies

One hundred fifty-six practitioners participated in DMEPA's prescription studies. One participant misinterpreted the study name Onexton for the marketed product Orudis. We note that Orudis was not identified by POCA nor by the external study submitted by the applicant. This misinterpretation is evaluated as part of our overall Failure Modes and Effects Analysis (FMEA) in section 2.2.6.

Sixty-three participants interpreted the name correctly (outpatient n=39, voice n=13, inpatient n=11). A total of 37 participants misinterpreted the letter 'n'; 20 for a 'v'

[1]USAN stem search conducted on April 11, 2014.

(outpatient n=9, inpatient n=11), 7 for an 'u' (inpatient n=7), 5 for an 'm' (outpatient n=2, inpatient n=3), and 5 for an 'r' (outpatient n=1, inpatient n=4). A total of 35 participants misinterpreted the final letter 'o'; 30 for an 'i' (voice = 28, outpatient n=1, inpatient n=1), and 5 for an 'e' (voice n=5). Twenty-one participants in the inpatient study misinterpreted the letter 'x' for an 'r'. (Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, February, 18, 2014 e-mail, to the Division of Dermatology and Dental Products (DDDP) the clinical team leader indicated that "the etymology of the name 'Onexton' itself is not an issue for us. However, the issue of this product having a distinct trade name from 'Acanya' needs to be considered. The clinical preference would be to keep the same brand name." Although DMEPA concurs with the review division's preference to keep the name Acanya for this new strength, there is not a safety argument to object to a dual proprietary name as discussed in the section 2.2.2.1.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Table 1 lists the number of names with the combined orthographic and phonetic score of ≥50% retrieved from our POCA search organized as highly similar, moderately similar or low similarity for further evaluation. In addition, the table includes the names identified in the prescription simulation study and the names identified by Med-Errs that were not identified by POCA.

Table 1. POCA Search Results	**Number of Names**
Highly similar name pair: combined match percentage score ≥70%	2
Moderately similar name pair: combined match percentage score ≥50% to ≤ 69%	245
Low similarity name pair: combined match percentage score ≤49%	2

2.2.6 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 249 names contained in Table 1 determined that none of the names will pose a risk for confusion as described in Appendices C through E.

We evaluated the potential for confusion between Onexton and Orudis in detail due to the misinterpretation in the FDA prescription study (see section 2.2.3 and Appendix B).

Orudis (ketoprofen) is a non-steroidal antiinfamatory drug used for the treatment of rheumatoid arthritis (RA), osteoarthritis (OA), management of pain, and primary dysmenorrhea. Orudis was approved in 25 mg, 50 mg, and 75 mg capsules. Recommended dosing for RA and OA range from 75 mg tid to 25-50 mg qid, and for pain management and dysmenorrhea from 25-75 mg every 6-8 hours prn. Although Orudis is a discontinued drug product, there are generic equivalent products available. Therefore, we considered the potential for misinterpretation between Onexton and Orudis.

The Phonetic and Orthographic Computer Analysis (POCA) software program identified the name pair with a combined score of less than 50, indicating low similarity between the names. The strengths of the products provide differentiation that would help prevent misinterpretations. Onexton is a single strength product (i.e. 1.2%/3.75%) that does not require a strength to be included on a prescription. However, Orudis is available in multiple strengths, thus requiring a strength to be included on a prescription. In addition, there is no strength overlap or similarity. Finally, the frequency of administration and usual dose between the products are significantly different. Onexton could be ordered as "UAD", "Use as directed, or "Apply once daily" where Orudis would contain instructions for use such as "1 cap three times daily" or "1 cap every 6 hours as needed for pain".

Based on these factors, the risk for confusion between Onexton and Orudis is minimized, thus we believe both proprietary names can safely co-exist in the market.

2.2.7 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Dermatology and Dental Products (DDDP) via e-mail on April 18, 2014. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DDDP on April 18-22, 2014, they stated no additional concerns or comments with the proposed proprietary name, Onexton.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Teena Thomas, OSE project manager, at 301-796-0549.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Onexton, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your January 31, 2014 submission are altered, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name.

1. **Promotional Assessment**: For prescription drug products, the promotional review of the proposed name is conducted by OPDP. For over-the-counter (OTC) drug products, the promotional review of the proposed name is conducted by DNCE. OPDP or DNCE evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP or DNCE provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [2]

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Affirmative answers to these questions indicate a potential area of concern.
Y/N	Does the name have obvious Similarities in Spelling and Pronunciation to other Names?
Y/N	Are there Manufacturing Characteristics in the Proprietary Name?
Y/N	Are there Medical and/or Coined Abbreviations in the Proprietary Name?
Y/N	Are there Inert or Inactive Ingredients referenced in the Proprietary Name?
Y/N	Does the Proprietary Name include combinations of Active Ingredients
Y/N	Is there a United States Adopted Name (USAN) Stem in the Proprietary Name?
Y/N	Is this the same Proprietary Name for Products containing Different Active Ingredients?
Y/N	Is this a Proprietary Name of a discontinued product?

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.

[2] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

- Moderately similar pair: combined match percentage score ≥50% to ≤ 69%.
- Low similarity: combined match percentage score ≤49%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. Based on our root cause analysis of post marketing experience errors, we find the expression of strength and dose, which is often located in close proximity to the drug name itself on prescriptions and medication orders, is an important factor in mitigating or potentiating confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion is limited (e.g., route, frequency, dosage form, etc.).

- For highly similar names, there is little that can mitigate a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are likely to be rejected by FDA. (See Table 3)
- Moderately similar names with overlapping or similar strengths or doses represent an area for concern for FDA. The dosage and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics (e.g., route, frequency, dosage form, etc.) to mitigate confusion may be limited when the strength or dose overlaps. FDA will review these names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4)
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist (See Table 5).

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair do not share a common strength or dose (see Step 1 of the Moderately Similar Checklist).			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		

Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥50% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths have a higher potential for confusion and should be evaluated further (see Step 2). For single strength products, also consider circumstances where the strength may not be expressed. For any combination drug products, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: o Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. o Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. o Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion between moderately similar names **with** overlapping or similar strengths or doses.

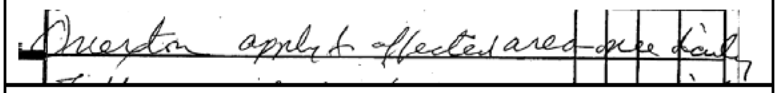
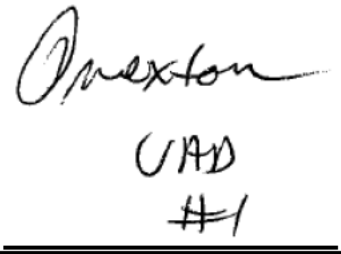
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤49%).

In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where there are data that suggest a name with low similarity might be vulnerable to confusion with your proposed name (for example, misinterpretation of the proposed name as a marketed product in a prescription simulation study). In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Onexton Study (Conducted on February 14, 2014)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order:  Outpatient Prescription: 	Onexton Use once daily Dispense # 1

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

As of Date 4/14/2014

275 People Received Study
156 People Responded

Study Name: Onexton

Total	56	50	50	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
ANEXTON	0	0	1	1
AVERTON	0	0	1	1
DON'T KNOW	1	0	0	1
OLNEXTON	0	1	0	1
OMERTON	0	0	2	2
OMERXTRA	0	0	1	1
OMEXEL	1	0	0	1
OMEXTON	5	0	0	5
ONERDON	0	0	1	1
ONERTAN	0	0	1	1
ONERTON	0	0	6	6
ONESTIEN	0	1	0	1
ONEXTAN	0	1	1	2
ONEXTEN	0	4	0	4
ONEXTEND	0	1	0	1
ONEXTIN	0	28	0	28
ONEXTON	39	13	11	63
ONEXTRA	0	0	1	1
ORIERXTON	0	0	1	1
ORIEXTON	0	0	3	3
ORUDIS	1	0	0	1
OUERDON	0	0	1	1
OUERTA	0	0	1	1
OUERTON	0	0	1	1
OUEXTON	0	0	3	3
OVERTON	0	0	5	5
OVERXTON	0	0	3	3
OVEXTIN	0	0	1	1
OVEXTON	9	0	3	12
OVEXTRA	0	0	1	1
QUEXTON	0	0	1	1
UNKNOWN	0	1	0	1

Appendix C: Highly Similar Names (i.e., combined POCA score is ≥70%)

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	Orthographic and/or phonetic differences in the names sufficient to prevent confusion
1.	Onexton	100	Proposed proprietary name subject of this review.
2.	Nacton	72	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.

Appendix D: Moderately Similar Names (i.e., combined POCA score is ≥50% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Proposed Name	POCA Score (%)
3.	Nexiclon	66
4.	Cenestin	65
5.	Doxepin	58
6.	Lanoxin	58
7.	Loniten	58
8.	Mestinon	58
9.	Necon	58
10.	Extensa***	56
11.	Bosentan	55
12.	Edoxaban*** (established name for IND (b) (4)	52
13.	Panixine	52
14.	(b) (4) ***	51
15.	Tolectin	58
16.	Olmesartan	57
17.	Nexium	55
18.	Yodoxin	55

No.	Proposed Name	POCA Score (%)
19.	Ondansetron	54
20.	Zonegran	54
21.	Cinoxacin	53
22.	Ceftin	52
23.	Exelon	52
24.	Vectrin	52
25.	Ancobon	51
26.	Dexone	51
27.	Amnesteem	50
28.	Digoxin	50
29.	MS Contin	50
30.	Omnipen	50
31.	Otrexup	50
32.	Oxycontin	50
33.	Orudis	<50 Rx Study Hit

Appendix E: Moderately Similar Names (i.e., combined POCA score is ≥50% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
34.	Obestin-30 Note: Discontinued product but other branded and generic phentermine products available.	69	**Dose**: xx mg or xx tab vs. apply to affected area or UAD **Orthographic**: The additional upstroke letter 'b' in Obestin-30 and the modifier 30 provide sufficient orthographic differences between the names.
35.	Senexon (OTC product available in tablet and syrup dosage forms)	68	**Dose:** xx mg or xx tab or xx mL vs. apply to affected area or UAD **Orthographic:** The prefixes of this name pair and the additional upstroke letter 't' in Onexton provide sufficient orthographic differences. **Phonetic:** The first syllables of this name pair have sufficient phonetic differences.
36.	Anectine	66	**Dose**: xx mg vs. apply to affected area or UAD **Other:** Anectine is a high alert medication used in the Emergency Room or Operating Room vs. Onexton will primarily be used in the home setting.
37.	Avonex Pen	66	**Dose:** xx mcg vs. apply to affected area or UAD **Orthographic**: The prefixes of this name pair have sufficient orthographic differences.
38.	Momexin	66	**Orthographic:** The capital letters in this name pair and the upstroke letter 't' in Onexton provide sufficient orthographic differences.
39.	Anextuss	65	**Dose:** xx tablets vs. apply to affected area or UAD **Orthographic:** The suffixes of this name pair have sufficient orthographic differences. **Phonetic:** The last syllables of this name pair have sufficient phonetic differences.
40.	Anestacon	64	**Orthographic:** The suffixes and length of this name pair provide sufficient orthographic differences.

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
41.	Tinactin (OTC)	63	**Orthographic:** The suffixes of this name pair have sufficient orthographic differences.
42.	Apexicon	60	**Orthographic:** The prefixes and suffixes of this name pair have have sufficient orthographic differences.
43.	Fareston	60	**Dose:** 1 tablet or 60 mg vs. apply to affected area or UAD **Orthographic:** The capital letters of this name pair have sufficient orthographic differences. **Phonetic:** The first syllables of this name pair have sufficient phonetic differences.
44.	Nexplanon	60	**Orthographic:** The capital letters and length of this name pair provide sufficient orthographic differences. **Other:** Nexplanon is an subdermal implant that requires a HCP intervientionfor insertion/removal.
45.	Nexterone	60	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The capital letters and length of this name pair provide sufficient orthographic differences.
46.	Podactin	60	**Orthographic:** The prefixes and infixes of this name pair provide sufficient orthographic differences.
47.	Sumaxin	60	**Orthographic:** The prefixes and infixes of this name pair provide sufficient orthographic differences.
48.	Extina	59	**Orthographic:** The prefixes of this name pair provide sufficient orthographic differences.
49.	Mephyton	59	**Dose:** xx mg or xx tablets vs. apply to affected area or UAD **Orthographic:** The prefixes and infixes of this name pair provide sufficient orthographic differences.
50.	Metreton	59	**Orthographic:** The prefixes and infixes of this name pair provide sufficient orthographic differences.

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
51.	Arestin	58	**Other:** Arestin is indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. It is administer in a dental office by a trained healthcare professional.
52.	Dexacen-4	58	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences.
53.	Oxytocin	58	**Dose:** xx mU or xx mL vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences.
54.	Icodextrin	58	**Orthographic:** The prefixes and length of this name pair provide sufficient orthographic differences. **Other:** Extraneal is intended for intraperitoneal administration only. It should be administered only as a single daily exchange for the long dwell in continuous ambulatory peritoneal dialysis or automated peritoneal dialysis.
55.	Maxolon	58	**Dose**: xx mg or xx tablets vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences.
56.	Naftin	58	**Orthographic:** The prefixes and infixes of this name pair provide sufficient orthographic differences.
57.	Omniscan	58	**Dose:** xx mL or xx mmol vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences.

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
58.	Senexon-S	58	**Dose:** xx tabs vs. apply to affected area or UAD **Orthographic:** The capital letters and the upstroke 't' in Onexton provide sufficient orthographic differences. **Phonetic:** The first syllables in the names sound different when spoken.
59.	Iron Dextran	57	**Dose:** xx mL vs. apply to affected area or UAD **Orthographic:** The prefixes of this name pair and the length of the names provide sufficient orthographic differences.
60.	Bendectin	56	**Dose:** xx tablets vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair and the length of the name provide sufficient orthographic differences
61.	Fenex DM	56	**Dose:** xx tabs vs. apply to affected area or UAD **Orthographic:** The prefixes of this name pair have sufficient orthographic differences
62.	Hextend	56	**Dose:** xx mL vs. apply to affected area or UAD **Orthographic:** The prefixes of this name pair and the ending upstroke letter 'd' in Hextend provide sufficient orthographic differences
63.	Maxiphen	56	**Dose:** xx tabs vs. apply to affected area or UAD **Orthographic:** The prefixes and infixes of this name pair have sufficient orthographic differences
64.	Metastron	56	**Dose:** xx MBq or xx mCi vs. apply to affected area or UAD **Orthographic:** The prefixes of this name pair and the length of the name provide sufficient orthographic differences
65.	Nikzon	56	**Orthographic:** The capital letters and infixes of this name pair provide sufficient orthographic differences

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
66.	Nystatin	56	**Orthographic:** The prefixes and infixes of this name pair have sufficient orthographic differences
67.	Oncovin	56	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
68.	Umecta PD	56	**Orthographic:** The infixes of this name pair have sufficient orthographic differences **Other:** Umecta is the family name for a product line of moisturizing products (i.e. Umecta PD, Umecta mousse, Umecta nail film). A prescriber would need to indicate the specific product.
69.	Doxidan	55	**Dose:** xx tab vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
70.	Robaxin	55	**Dose:** xx tab or xx mg vs. apply to affected area or UAD **Orthographic:** The capital letters and infixes of this name pair provide sufficient orthographic differences
71.	Akineton	54	**Dose:** xx tab or xx mg vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
72.	Aldex AN	54	**Dose:** xx tab vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
73.	Amlactin	54	**Orthographic:** The infixes of this name pair have sufficient orthographic differences
74.	Dex-Tuss	54	**Dose:** xx mL or xx tsp vs. apply to affected area or UAD **Orthographic:** The suffixes of this name pair have sufficient orthographic differences

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
75.	Elixicon	54	**Dose:** xx mL or xx tsp vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
76.	Entex T	54	**Dose:** xx tab vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
77.	Maxidone	54	**Dose:** xx tab vs. apply to affected area or UAD **Orthographic:** The capital letters and infixes of this name pair provide sufficient orthographic differences
78.	Naphcon	54	**Orthographic:** The capital letters and infixes of this name pair provide sufficient orthographic differences
79.	Nexafed	54	**Dose:** xx tab vs. apply to affected area or UAD **Orthographic:** The capital letters and the ending upstroke letter 'd' in Nexafed provide sufficient orthographic differences between the names
80.	Nitrotan	54	**Orthographic:** The capital letters and infixes of this name pair provide sufficient orthographic differences
81.	Reumacetin	54	**Orthographic:** The capital letters, infixes and length of this name pair provide sufficient orthographic differences
82.	Rynex DM	54	**Dose:** xx mL or xx tsp vs. apply to affected area or UAD **Orthographic:** The capital letters and infixes of this name pair have sufficient orthographic differences
83.	Vanacon	54	**Dose:** xx mL or xx tsp vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
84.	Natesto*** Note: Proposed name found conditionally acceptable for NDA 205488	54	**Orthographic:** The prefixes of this name pair have sufficient orthographic differences.

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
85.	Betaxon	53	**Orthographic:** The capital letters and infixes of this name pair have sufficient orthographic differences
86.	Desitin	53	**Orthographic:** The infixes of this name pair have sufficient orthographic differences **Other:** Desitin is the family name for a product line of diaper rash products (i.e. Desitin rapid relief cream, Desitin maximum strength paste, and Desitin multi purpose ointment). A prescriber would need to indicate the specific product.
87.	Dexasone	53	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
88.	Konakion	53	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The capital letters and infixes of this name pair provide sufficient orthographic differences
89.	Optison	53	**Dose:** xx mL vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
90.	Bronitin	52	**Orthographic:** The capital letters and infixes of this name pair provide sufficient orthographic differences
91.	Concept OB	52	**Dose:** 1 capsule vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
92.	Conivaptan	52	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The infixes and length of this name pair provide sufficient orthographic differences
93.	Donatussin	52	**Dose:** xx mL or xx tsp vs. apply to affected area or UAD **Orthographic:** The infixes, suffixe and length of this name pair provide sufficient orthographic differences

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
94.	Eloxatin	52	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
95.	Exefen	52	**Dose:** xx tabs vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences **Other:** Exefen is the family name for a product line of cold/cough products (i.e. Exefen IR and Exefen DMX). A prescriber would need to indicate the specific product.
96.	Gamastan S/D	52	**Dose:** xx mL vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
97.	Phenetron	52	**Dose:** xx tabs vs. apply to affected area or UAD **Orthographic:** The prefixes of this name pair have sufficient orthographic differences
98.	Plexion	52	**Orthographic:** The prefixes of this name pair have sufficient orthographic differences
99.	Rondex-DM	52	**Dose:** xx mL or xx tsp vs. apply to affected area or UAD **Orthographic:** The prefixes of this name pair have sufficient orthographic differences
100.	Secretin	52	**Dose:** xx mcg vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
101.	Datscan	51	**Dose:** xx MBq or xx mCi vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
102.	Eulexin	51	**Dose:** xx caps vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences.

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
103.	Humegon	51	**Dose:** xx International Units vs. apply to affected area or UAD **Orthographic:** The prefixes and infixes of this name pair provide sufficient orthographic differences.
104.	Neoscan	51	**Dose:** xx mCi vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
105.	Nicotine	51	**Dose:** 1 patch or 1 lozenge or 1 gum vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
106.	Noroxin	51	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
107.	Opcicon***	51	**Dose:** xx tablets vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences.
108.	U-Lactin	51	**Orthographic:** The infixes of this name pair have sufficient orthographic differences.
109.	Anacin	50	**Dose:** xx tablets or xx capsules vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences.
110.	Anefrin	50	**Orthographic:** The infixes of this name pair have sufficient orthographic differences.
111.	Cogentin	50	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences

No.	**Proposed name: Onexton** **Strength:** 1.2%/3.75% **Usual Dose:** Apply once daily	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
112.	Conex	50	**Dose:** xx tabs or xx mL or xx tsp vs. apply to affected area or UAD **Orthographic:** The suffixes and length of this name pair provide sufficient orthographic differences
113.	Humatin	50	**Dose:** xx caps vs. apply to affected area or UAD **Orthographic:** The prefixes and suffixes of this name pair provide sufficient orthographic differences
114.	Ivermectin	50	**Orthographic:** The infixes and length of this name pair provide sufficient orthographic differences
115.	Mexsana	50	**Orthographic:** The capital letters, infixes and suffixes of this name pair provide sufficient orthographic differences
116.	Monistat	50	**Orthographic:** The capital letters and suffixes of this name pair provide sufficient orthographic differences
117.	Myoxin	50	**Orthographic:** The capital letters and infixes of this name pair provide sufficient orthographic differences
118.	Natacyn	50	**Orthographic:** The infixes of this name pair have sufficient orthographic differences
119.	Neutrexin	50	**Dose:** xx mg vs. apply to affected area or UAD **Orthographic:** The infixes and length of this name pair provide sufficient orthographic differences
120.	Oncaspar	50	**Dose:** xx International Units vs. apply to affected area or UAD **Orthographic:** The infixes of this name pair have sufficient orthographic differences
121.	Ongo-Fin	50	**Orthographic:** The infixes of this name pair have sufficient orthographic differences
122.	Overtime	50	**Orthographic:** The suffixes of this name pair have sufficient orthographic differences

Appendix F: Low Similarity Names (i.e., combined POCA score is ≤49%)

No.	Name	POCA Score (%)
123.	Crestor	<50

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
124.	Dextran	67	Component used in eye drops. Component of intravenous products (antithrombotic, to reduce blood viscosity, and as a volume expander in anemia).
125.	Canesten	66	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
126.	(b) (4)		
127.			
128.	Oradexon	64	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
129.	(b) (4)		
130.			

No.	Name	POCA Score (%)	Failure preventions
131.	(b) (4)		
132.	Promectin	61	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
133.	Clonixin	60	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
134.	Enoxacin	60	Established name for Penetrex. No branded or generic products available. NDA 019616 was withdrawn FR effective on 4/4/2005.
135.	(b) (4)		
136.	Mectizan	60	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
137.	Ondanestron	60	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
138.	Oreton	60	ANDA 080281 was withdrawn FR effective on 2/21/2001. All methyltestosterone buccal tablets have been discontinued; only oral tablets are available.
139.	(b) (4)		
140.	Ponstan	60	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
141.	(b) (4)		

No.	Name	POCA Score (%)	Failure preventions
142.	(b) (4)		
143.	Bimectin	58	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
144.	Entsufon	58	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
145.	Nystan	58	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
146.	(b) (4)		
147.			
148.			
149.	Uni Decon	58	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
150.	Endoxan	57	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
151.	Nioxin	57	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
152.	(b) (4)		
153.	Coracten	56	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
154.	Cydectin	56	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
155.	(b) (4)		
156.	Dynaxin	56	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
157.	(b) (4)		
158.			
159.	Monensin	56	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
160.	Nexgard	56	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
161.	Opustan	56	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
162.	Redoxon	56	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
163.			(b) (4)
164.	Dexcon DM	55	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
165.	Dexcon PE	55	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
166.	Genaton	55	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
167.	Ilex Skin	55	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
168.	Pectin	55	This is not a drug name, but a compounding ingredient.
169.	Coactin	54	NDA 050565 was withdrawn FR effective on 10/2/1996. There are no generic equivalents available.
170.	Dexphen M	54	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
171.	Doramectin	54	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
172.	Emete-Con	54	NDA 016818 and NDA 016820 were withdrawn FR effective on 6/25/97 and 12/7/2007, respectively. There are no generic equivalents available.
173.	Endo-mectin	54	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
174.	Flunixin	54	This is not a drug name, but a compounding ingredient.
175.	Moctanin	54	NDA 019368 was withdrawn FR effective on 11/12/2002. There are no generic equivalents available.
176.	Nacon	54	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
177.	Noromectin	54	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
178.	(b) (4)		
179.	Perestan	54	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
180.	(b) (4)		
181.			
182.	Unitensen	54	NDA 008814 and NDA 009217 were withdrawn FR effective on 3/2/1994. There are no generic equivalents available.
183.	(b) (4)		
184.	Uni-tussin	54	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
185.	Amoxidin	53	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
186.	(b) (4)		
187.			
188.			
189.			
190.			
191.	Acticon	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
192.	Ancestim	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
193.	(b) (4)		
194.			
195.			

No.	Name	POCA Score (%)	Failure preventions
196.	Endacon	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
197.	Enoximone	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
198.	Lunestar	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
199.	Maxaquin	52	NDA 020013 was withdrawn FR effective on 6/18/2009. There are no generic equivalents available.
200.	Moxidectin	52	Establised name for a veterinary drug. Orphan drug designation on 9/29/10 for treatment of onchocerciasis volvulus in children and adults. Unable to find product characteristics for human orphan drug designation.
201.	Neoplatin	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
202.	Nescon PD	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
203.	[redacted]		(b) (4)
204.	Ornacyn	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
205.	Ornex	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
206.	Oxygen	52	Name identified in Rx Norm database. Not a drug product name.
207.	(b) (4)		
208.			
209.			
210.	Testolin	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
211.	(b) (4)		
212.			
213.	Uniferon	52	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
214.	Alexan	51	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
215.	Conex LA	51	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
216.	Duphaston	51	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
217.	Ebastine	51	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
218.	Encron	51	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
219.	Formestane	51	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
220.	(b) (4)		
221.	Nexium 24R***	51	Name identified in 'Name entered by safety evaluator' database. Unable to find this name in any internal database.
222.	Regroton	51	NDA 015103 was withdrawn FR effective on 6/4/2004. There are no generic equivalents available.
223.	Antepsin	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
224.	Bromatan	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
225.	(b) (4)		

No.	Name	POCA Score (%)	Failure preventions
226.	Cofex-DM	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
227.	Conacetol	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
228.	Congestant	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
229.	Dexacine	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
230.	Dextran HM	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
231.	Evoxin	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
232.	Flexon	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
233.	Gondafon	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
234.	Mesantoin	50	NDA 006008 was withdrawn FR effective on 8/20/2010. There are no generic equivalents available.
235.	M-Eslon	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
236.	Monooctanoin	50	Generic name for an orphan drug with designation date of 5/30/84 for dissolution of cholesterol gallstones retained in the common bile duct. Unable to find product characteristics for orphan drug.
237.	Emedastine	50	Name identified in 'Name entered by safety evaluator' database. However, emedastine difumarate is the established name for Emadine.
238.			(b) (4)
239.	Nicosyn	50	Name identified in Rx Norm database. Unable to find product characteristics in commonly used drug databases.
240.	One Touch	50	Not a drug product. One Touch is a product line of glucose meters.
241.	Osteoscan	50	NDA 017454 was withdrawn FR effective on 5/29/2002. There are no generic equivalents available.
242.			(b) (4)
243.			
244.	Pentaspan	50	Trade name for an orphan drug with a designation date of 8/28/85 for adjunct in leukapheresis to improve the harvesting and increase the yield of leukocytes by centrifugal means. Unable to find product characteristics for orphan drug.

No.	Name	POCA Score (%)	Failure preventions
245.	Taractan	50	NDA 012486 and NDA 012487 were withdrawn FR effective on 1/9/1997 and 6/25/1997, respectively. NDA 016149 was withdrawn pending FR notice as of 1/9/1997. There are no generic equivalents available.
246.	(b) (4)		
247.	Trexofin***	50	Name identified in 'Name entered by safety evaluator' database. Unable to find this name in any internal database.
248.	Trexydin***	50	Name identified in 'Name entered by safety evaluator' database. Unable to find this name in any internal database.
249.	(b) (4)		

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

/s/

CARLOS M MENA-GRILLASCA
04/22/2014

LUBNA A MERCHANT
04/22/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 050819/S-012

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: Onexton (clindamycin phosphate and benzoyl peroxide) gel, 1.2%, 3.75%

Applicant: Dow Pharmaceutical Sciences

Receipt Date: January 30, 2014

Goal Date: November 30, 2014

1. Regulatory History and Applicant's Main Proposals

This efficacy supplement provides for the introduction of 3.75% benzoyl peroxide strength in addition to the already approved 2.5% benzoyl peroxide in Acanya Gel.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by Wednesday April 18, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *The margins are not 1/2 inch.*

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *The heading is not presented in the center of a horizontal line and the horizontal line proceeding adverse reaction is not consistent.*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

NO 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment: *The proposed trade name and established name need to be on the same line.*

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.****"*).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Selected Requirements of Prescribing Information

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

NO 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *Add a period at the end of the statement.*

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *RPM will update the month at time of action.*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *10- no overdose information; 15- no references*

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

NO 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *This statement is not verbatim in the label.*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JENNIFER M DAO
03/28/2014

STROTHER D DIXON
03/28/2014
On behalf of Barbara Gould

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 050819	NDA Supplement #:S- 012	Efficacy Supplement Type SE- 2
Proprietary Name: Onexton gel Established/Proper Name: (clindamycin phosphate and benzoyl peroxide) Dosage Form: gel Strengths: 1.2%, 3.75%		
Applicant: Dow Pharmaceutical Sciences Agent for Applicant (if applicable):		
Date of Application: January 30, 2014 Date of Receipt: January 30, 2014 Date clock started after UN:		
PDUFA Goal Date: November 30, 2014	Action Goal Date (if different): November 16, 2014	
Filing Date: March 31, 2014	Date of Filing Meeting: March 12, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NA		
Proposed indication(s)/Proposed change(s): introduction of 3.75% benzoyl peroxide strength in addition to already approved 2.5% benzoyl peroxide in Acanya Gel.		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 041733

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		Acanya is already approved for 1.25/2.5% strength. New proposed proprietary name for the 1.2%/3.75% strength- Onexton
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☒	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	No Form 3542, but Patent certification letter included
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☒	☐	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☒	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☒	☐	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Proposed name: Onexton
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** October 6, 2003 ***If yes, distribute minutes before filing meeting***	☒	☐		Reference IND 41733
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Pre-NDA meeting: November 27, 2007 Type C Guidance meeting (written responses): January 15, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		Reference IND 41733
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 12, 2014

BLA/NDA/Supp #: NDA 050819/ S-012

PROPRIETARY NAME: Onexton gel

ESTABLISHED/PROPER NAME: (clindamycin phosphate and benzoyl peroxide)

DOSAGE FORM/STRENGTH: gel, 1.2%/3.75%

APPLICANT: Dow Pharmaceutical Sciences

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): introduction of 3.75% benzoyl peroxide strength in addition to already approved 2.5% benzoyl peroxide in Acanya gel.

BACKGROUND: The Agency approved NDA 050819 Acanya gel on October 23, 2008. The applicant requested a meeting to discuss the development of the increased benzoyl peroxide strength and was provided with written responses on January 15, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Dao	Y
	CPMS/TL:	Barbara Gould	N
Clinical	Reviewer:	Dr. Gary Chiang	Y
	TL:	Dr. David Kettl	Y

Clinical Pharmacology	Reviewer:	An-Chi Lu	Y
	TL:	Donny Tran	Y
Biostatistics	Reviewer:	Matthew Guerra	Y
	TL:	Mohamed Alosh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jiaqin Yao	Y
	TL:	Barbara Hill	Y
Product Quality (CMC)	Reviewer:	Yubing Tang	N
	TL:	Shulin Ding	Y
OSE/DMEPA (proprietary name)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Lubna Merchant	N

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	N
	TL:	Janice Pohlman	N
OMP/DPDP	Reviewer:	Puja Shah	Y
		Morgan Walker	Y
OSE/DPVI	Reviewer:	Jessica Weintraub	Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO Bridge to NDA 050741 Duac gel in original approval.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO ☐ To be determined

If no, for an NME NDA or original BLA , include the reason. For example: ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Comments:	

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☒ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Stanka Kukich, MD	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): June 16, 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)

☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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

/s/

JENNIFER M DAO
03/27/2014

STROTHER D DIXON
03/27/2014
Signed on behalf of Barbara Gould

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 25, 2014
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 050819/S-012
Product Name and Strength:	Onexton (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Dow Pharmaceutical Sciences
Submission Date:	January 30, 2014
OSE RCM #:	2014-307
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

This review responds to a request from DDDP to evaluate the proposed container labels and carton labeling for Onexton for areas of vulnerability that could lead to medication errors. The applicant already markets a lower strength clindamycin phosphate and benzoyl peroxide gel 1.2%/2.5% under the proprietary name Acanya. However, they are pursuing a separate proprietary name, Onexton, for the higher strength 1.2%/3.75% in supplement S-012 currently under review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	n/a
ISMP Newsletters	n/a
Other	n/a
Labels and Labeling	D

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market Onexton in 50 g pump dispensers, which is the same size of the currently marketed product Acanya. Therefore, this package size seems reasonable. In addition, a 3.5 g tube will be available for physician samples. We note that the sample tubes will not be packaged in a carton.

We reviewed the proposed Onexton container labels and carton labeling and noted that with the exception of a few minor differences, the content and placement of information follows that of the Acanya labels. However, the established name is not commensurate in prominence to the proprietary name as per CFR 201.10(g)(2).

4 RECOMMENDATIONS FOR THE APPLICANT

DMEPA recommends the following be implemented prior to approval of this Application.

A. Proposed Container Label and Carton Labeling (all package sizes)

1. The established name is not commensurate to the prominence of the proprietary name as per CFR 201.10(g)(2). Revise the presentation of the proprietary name to use title case (i.e. Onexton) and ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Onexton that Dow Pharmaceuticals submitted on January 30, 2014. In addition, we are including relevant product information for Acanya, since Onexton is a dual trade name/different strength to the marketed product Acanya.

Table 2. Relevant Product Information for Onexton and Acanya

Product Name	Onexton	Acanya
Active Ingredient	Clindamycin phosphate and Benzoyl peroxide	Clindamycin phosphate and Benzoyl peroxide
Indication	Acne vulgaris in patients 12 years of age and older	Acne vulgaris in patients 12 years of age and older
Route of Administration	Topical	Topical
Dosage Form	Gel	Gel
Strength	1.2%/2.5%	1.2%/3.75%
Dose and Frequency	Apply to affected area once daily	Apply to affected area once daily
How Supplied	50 g pump 3.5 g sample tube	50 g pump
Storage	PHARMACIST: Prior to dispensing, store in a refrigerator, 2°C to 8°C (36°F to 46°F). PATIENT: Store at room temperature at or below 25°C (77°F).	PHARMACIST: Prior to Dispensing Store in a refrigerator, 2°C to 8°C (36°F to 46°F). PATIENT: Store at room temperature at or below 25°C (77°F)
Container Closure	Packaged in a 50 mL [redacted] (b) (4)	Packaged in a 50 mL [redacted] (b) (4)

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 20, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	March 20, 2014
Drug Names	Acanya [product name]
MedDRA Search Strategy	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues NEC [HLT]

B.2 Results

Our search identified 3 cases, all 3 cases were excluded because they did not describe a medication error associated with the product labeling; off-label use (n=1), expired drug (n=1), and drug substitution error (n=1).

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases retrieved for this review.

Case No.	Case version	Manufacturer Control No.
7532954	1	n/a
7825703	1	2010VX001111
8576765	1	n/a

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

Since Onexton is a dual trade name for a different strength to the marketed product Acanya, we searched the L: drive on March 19, 2014 using the term Acanya to identify reviews previously performed by DMEPA.

C.2 Results

DMEPA reviewed Acanya labels and labeling in OSE review 2010-1251, dated July 28, 2010. The AERS search performed for this reviews did not retrieve any cases.

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Onexton labels and labeling submitted by Dow Pharmaceuticals on January 30, 2014. In addition, we reviewed the currently marketed labels and labeling for Acanya.

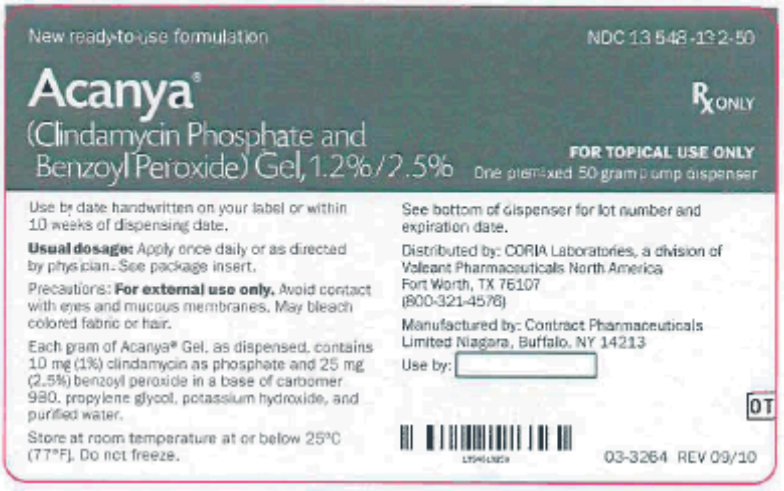
- Container label
- Carton labeling

D.2 Label and Labeling Images (not to scale)

Proposed Container labels

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Currently Marketed Acanya label



Proposed Carton labeling

(b) (4)

Currently marketed Acanya carton labeling

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

/s/

CARLOS M MENA-GRILLASCA
03/25/2014

LUBNA A MERCHANT
03/25/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-819/S-12

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 050819 BLA #	NDA Supplement # 012 BLA Supplement #	If NDA, Efficacy Supplement Type: SE-2 *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Onexton gel Established/Proper Name: (clindamycin phosphate and benzoyl peroxide), 1.2%, 3.75% Dosage Form: gel		Applicant: Dow Pharmaceutical Sciences Agent for Applicant (if applicable):
RPM: Strother D. Dixon		Division: Division of Dermatology and Dental Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☒ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: November 24, 2014

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is November 30, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☒ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval: November 24, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	4/24/14 – Letter 4/22/14 - Review
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 3/28/14 & 11/03/14 DMEPA: ☐ None 3/25/14 DMPP/PLT (DRISK): ☐ None 9/24/14 OPDP: ☐ None 9/24/14 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	3/27/14 ☐ Not a (b)(2) 10/24/14
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC NA If PeRC review not necessary, explain: Increase in strength and is not a new formulation	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	n=3
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	n=2
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11/21/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	10/21/14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	p. 14, Clinical review 10/21/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 10/3/14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 9/26/14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 8/28/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 9/30/14
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	P. 18 and 19 of the CMC Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 7/21/14 P. 20 and 21 of the CMC Review ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done NA
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done NA
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

STROTHER D DIXON
11/24/2014

EXCLUSIVITY SUMMARY

NDA # 050819 SUPPL # 012 HFD # 540

Trade Name Onexton

Generic Name (clindamycin phosphate and benzoyl peroxide) topical gel, 1.2%/3.75%

Applicant Name Dow Pharmaceutical Sciences

Approval Date, If Known November 24, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(2) SE-2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 50819	Acanya (clindamycin phosphate and benzoyl peroxide) topical gel, 1.2%/2.5%
NDA# 50741	Duac (clindamycin phosphate and benzoyl peroxide) topical gel, 1.2%/5%
NDA# 50756	Benzaclin (clindamycin phosphate and benzoyl peroxide) topical gel, 1%/5%

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability

studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could

independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol: V01-ACYC-301 titled "A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of ACYC and ACYC Vehicle Gel in the Treatment of Acne Vulgaris"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 Protocol: V01-ACYC-301 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 Protocol: V01-ACYC-301 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol: V01-ACYC-301 titled "A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of ACYC and ACYC Vehicle Gel in the Treatment of Acne Vulgaris"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Protocol: V01-ACYC-301	!
	!	
IND # 041733	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Strother D. Dixon
Title: Regulatory Project Manager
Date: October 24, 2014

Name of Division Director signing form: Tatiana Oussova, MD, MPH
Title: Deputy Director for Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

STROTHER D DIXON
11/24/2014

TATIANA OUSSOVA
11/24/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 16, 2014

Application Number: NDA 050819 S-012
Product Name: NDA 050819 S-012 Onexton (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%
Sponsor Name: Dow Pharmaceutical Sciences

Subject: Request for [redacted] (b) (4) and 5 year environmental forecast.

FDA Participants
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Thomas Oliver, PhD, Branch Chief, DNDQA II, Branch VI
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Yubing Tang, PhD, Product Quality Reviewer, DNDQA II, Branch VI
Jennifer Dao, Regulatory Health Project Manager, DDDP
Strother D. Dixon, Regulatory Health Project Manager, DDDP

Sponsor Participants:
Arturo Angel, Associate Director, Formulation and Process Development
Sean Humphrey, Manager, Regulatory Affairs
Steve Knapp, Dermatology/Aesthetics Head, Regulatory Affairs
Kwame Obeng, Executive Director, Regulatory Affairs-CMC
RK Pillai, Head Dermatology Development
Shruti Sahay, Senior Manager, Analytical Sciences, Laboratory and Stability Operations
Shankar Swaminathan, Associate Director, Regulatory Affairs-CMC
Simon Yeh, Director, Analytical Sciences

DISCUSSION:
The Agency inquired about the [redacted] (b) (4)

The Agency informed the sponsor that the environmental assessment to should include af of their products that contain the active pharmaceutical ingredient (e.g., Onexton and Acanya).

ACTION ITEM:
The sponsor agreed to submit the information requested by the Agency to the NDA.

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/s/

STROTHER D DIXON
10/28/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 27, 2014

Application Number: NDA 050819 S-012
Product Name: NDA 050819 S-012 Onexton (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%
Sponsor Name: Dow Pharmaceutical Sciences

Subject: Acceptance criteria proposed for the [redacted] (b) (4)

FDA Participants
Tatiana Oussova, MD, MPH, Acting Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Thomas Oliver, PhD, Branch Chief, DNDQA II, Branch VI
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Yubing Tang, PhD, Product Quality Reviewer, DNDQA II, Branch VI
Strother D. Dixon, Regulatory Health Project Manager, DDDP

Sponsor Participants:
Kwame Obeng, CMC-Regulatory Affairs
[redacted] (b) (4) CMC-Regulatory Affairs
Steven Knapp, Regulatory Affairs
Sean Humphrey, Regulatory Affairs
RK Pillai, Dermatology Development
Arturo Angel, Formulation Process Development
Simon Yeh, Analytical Sciences
Shruti Sahay, Analytical Sciences

DISCUSSION:
The Agency asked the sponsor to [redacted] (b) (4)

[redacted] (b) (4)

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/s/

STROTHER D DIXON
10/24/2014

From:	Dixon, Strother
To:	Humphrey, Sean (SHumphrey@dowpharmsci.com)
Cc:	Gould, Barbara; Williams, Dawn
Subject:	Agency Proposed Labeling: NDA 050819 S-012 (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%
Date:	Wednesday, October 22, 2014 2:33:00 PM
Attachments:	NDA 050819 S-012 Label 20141022.docx

Greetings. Attached, please find the Agency proposed labeling for NDA 050819 S-012 (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%. Below, please find the recommended changes for the physician and 50 g sizes of the carton and container labeling.

1. The established name is not commensurate to the prominence of the proprietary name as per CFR 201.10(g)(2). Revise the presentation of the proprietary name to use title case (i.e. Onexton) and ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).

2. For the expression of "… **10mg (1%) clindamycin as phosphate…**" change to read"… **12mg clindamycin phosphate equivalent to 10mg (1%) clindamycin**..."

3. Change "**for external use only**" to "**for topical use only**".

Please submit agreed upon labeling to the NDA and provide a courtesy copy of the submission (e.g., labels, 356h and cover letter) to me via email by Wednesday, October 29, 2014. If you have additional edits, please convey those in track changes.

Please confirm receipt of this email.

If you require additional information or have questions, please do not hesitate to contact me directly.

Regards,
Strother

Strother D. Dixon
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: strother.dixon@fda.hhs.gov
Phone: 301.796.1015
Fax: 301.796.9895

14 page(s) has been Withheld in Full as draft labeling (CCI/TS) immediately following this page

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/s/

STROTHER D DIXON
10/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 050819/S-012

INFORMATION REQUEST

Dow Pharmaceutical Sciences
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75%.

We also refer to your July 3, 2014 submission, containing Chemistry, Manufacturing and Controls (CMC) information pertaining to (b) (4) and proposal, and revised environmental analysis.

We are reviewing your submission and have the following information requests:

(b) (4)

(b) (4)

We request a prompt written response by August 15, 2014, in order to continue our evaluation of your supplemental application.

If you have any questions, please contact Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

TATIANA OUSSOVA
08/07/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 050819/S-12

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Dow Pharmaceutical Sciences
1330 Redwood Way
Petaluma, CA 94954

ATTENTION: Sean Humphrey
Manager, Regulatory Affairs

Dear Mr. Humphrey:

Please refer to your Supplemental New Drug Application (NDA) dated and received, January 30, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Clindamycin Phosphate and Benzoyl Peroxide Gel, 1.2%/3.75%.

We also refer to:

- Our email, dated March 03, 2014, requesting you to submit the independent assessment of the proposed proprietary name, Onexton, as an amendment
- Your sNDA amendment, dated and received March 06, 2014, submitting the independent assessment of the proprietary name
- Your correspondence, dated and received January 31, 2014, requesting review of your proposed proprietary name, Onexton

We have completed our review of the proposed proprietary name, Onexton, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your January 31, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application, contact Strother Dixon, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
04/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 050819/S-012

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Dow Pharmaceutical Sciences, Inc.
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your Supplemental New Drug Application (sNDA) dated and received January 30, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75%.

We also refer to your amendment dated February 19, 2014.

This supplemental application proposes the following change(s): introduction of 3.75% benzoyl peroxide strength in combination with clindamycin phosphate 1.2% for the treatment of acne vulgaris in addition to the already approved 1.2% clindamycin phosphate/2.5% benzoyl peroxide in Acanya Gel.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is November 30, 2014.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 6, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by April 30, 2014:

Chemistry, Manufacturing and Controls

1. Representative samples for the trade size and physician sample.
2. (b) (4)
3.
4. Information/data supporting the proposed (b) (4) for benzoyl peroxide should be added to Module 3. Additionally, indicate the proposed (b) (4) in the Formulation Composition table in Section 3.2.P.1.

Clinical Pharmacology

5. We acknowledge that you request a waiver for conduct of pharmacokinetic trial with ACYC Gel and state that plasma levels of clindamycin would be bracketed by levels determined for Acanya Gel and BenzaClin Gel. However, we note that although the (b) (4) ACYC Gel is (b) (4) to Acanya Gel (b) (4) of difference in concentration of benzoyl peroxide), it is (b) (4) of BenzaClin Gel. Provide rationale on how the plasma levels of clindamycin would be bracketed between Acanya Gel (containing 2.5% benzoyl peroxide) and BenzaClin Gel (containing 5% benzoyl peroxide) when the (b) (4)

6. Provide a summary of product composition for Acanya Gel, 1.2%/2.5%, BenzaClin Gel, and (b) (4) (product used in bioequivalent trial with BenzaClin Gel).

Biostatistics

7. In Table 11-4 (page 56 of the study report), you presented the efficacy results for the three co-primary endpoints at Week 12. It is not clear how you obtained the presented response rates for the 2-grade reduction from baseline in EGSS. Submit the SAS code used to generate these rates.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

8. In the Highlights (HL), increase the margins to a minimum of ½ inch on all sides and between columns.

9. In the HL, center all headings in the horizontal line.

10. In the HL, format the horizontal line preceding ADVERSE REACTIONS to be consistent with the other horizontal lines throughout Highlights section.

11. In the HL, place Product Title (i.e. proposed trade name, established name, dosage form, and strength) on the same line.

12. Add a period at the end of the statement in Adverse Reactions in Highlights. The following statement below should precede the presentation of adverse reactions:

    "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch."

13. The following statement should be verbatim when postmarking adverse reaction data are included:

    "The following adverse reactions have been identified from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

In addition we have the following comments regarding your proposed container label and carton labeling (all package sizes):

14. The established name is not commensurate to the prominence of the proprietary name as per CFR 201.10(g)(2). Revise the presentation of the proprietary name to use title case (i.e. Onexton) and ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 25, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Jennifer Dao, Regulatory Project Manager, at (301) 796-8189.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

STANKA KUKICH
04/14/2014

Thomas, Teena

From: Humphrey, Sean <SHumphrey@dowpharmsci.com>
Sent: Monday, March 03, 2014 5:18 PM
To: Thomas, Teena
Cc: Anderson, Janet; Mena-Grillasca, Carlos
Subject: RE: NDA 050819 Onexton
Attachments: emfalert.txt

Dear Ms. Thomas,

I am confirming receipt of your request. I will send the below referenced report via email ASAP as well submit the report as an amendment to the Proprietary Name Review Request (Sequence 0086).

Best regards,
Sean

Sean Humphrey
Manager, Regulatory Affairs
Dow Pharmaceutical Sciences, a division of
Valeant Pharmaceuticals North America LLC
1330 Redwood Way
Petaluma, CA 94954
Phone: 707-796-7222
Email: shumphrey@dowpharmsci.com

From: Thomas, Teena [mailto:Teena.Thomas@fda.hhs.gov]
Sent: Monday, March 03, 2014 8:08 AM
To: Humphrey, Sean
Cc: Thomas, Teena; Anderson, Janet; Mena-Grillasca, Carlos
Subject: NDA 050819 Onexton

Hi Sean,

This is in reference to NDA 050819, Onexton. The Review Division is requesting you to submit the independent assessment of the proposed proprietary name Onexton that you mentioned in your proprietary name request. Please submit it as soon as possible and send it in email to me first concurrently as an amendment to the proprietary name request submission. Let me know if you have any questions.

Thank you,

Teena

Teena Thomas, Pharm.D, CGP
Safety Regulatory Project Manager
FDA, CDER
Office of Surveillance and Epidemiology
Bldg.22, Room 3461

10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Tel: 301.796.0549
E-mail : teena.thomas@fda.hhs.gov

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/s/

TEENA THOMAS
03/04/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 050819/S-012

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Dow Pharmaceutical Sciences, Inc.
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 050819

SUPPLEMENT NUMBER: 12

PRODUCT NAME: (clindamycin phosphate and benzoyl peroxide) gel, 1.2%, 3.75%

DATE OF SUBMISSION: January 30, 2014

DATE OF RECEIPT: January 30, 2014

This supplemental application proposes the following change: introduction of a 3.75% benzoyl peroxide strength in addition to the already approved 2.5% benzoyl peroxide in Acanya Gel.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 31, 2014, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be November 30, 2014.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-796-8189.

Sincerely,

{See appended electronic signature page}

Jennifer Dao
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER M DAO
02/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Gary Chiang, MD, Medical Officer, DDDP, 301-796-5051 David Kettl, MD, Clinical Team Leader, DDDP, 301-796-2105 Jennifer Dao, Regulatory Project Manager, DDDP, 301-796-8189

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
February 14, 2014		050819	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75%	Standard	Topical Gel	September 9, 2014

NAME OF FIRM:	
Dow Pharmaceutical Sciences, Inc.	PDUFA Date: November 30, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☒ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission: \\CDSESUB1\evsprod\NDA050819\050819.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Filing Meeting: TBD
Mid-Cycle Meeting: TBD
Labeling Meetings: TBD
Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER
Jennifer Dao

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)
	☒ DARRTS ☐ eMAIL ☐ HAND

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/s/

JENNIFER M DAO
02/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Gary Chiang, MD, Medical Officer, DDDP, 301-796-5051
David Kettl, MD, Clinical Team Leader, DDDP, 301-796-2105
Jennifer Dao, Regulatory Project Manager, DDDP, 301-796-8189

REQUEST DATE:	NDA/BLA NO.:	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)
February 14, 2014	050819	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE
(clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75%	Standard	Topical Gel	September 9, 2014

SPONSOR:

Dow Pharmaceutical Sciences, Inc.

PDUFA Date: November 30, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA050819\050819.enx

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Filing/Planning Meeting: TBD

Mid-Cycle Meeting: TBD

Labeling Meetings: TBD

Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER
Jennifer Dao

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL (BLAs Only) ☒ DARRTS

Version: 12/9/2011

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/s/

JENNIFER M DAO
02/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Gary Chiang, MD, Medical Officer, DDDP, 301-796-5051
David Kettl, MD, Clinical Team Leader, DDDP, 301-796-2105
Jennifer Dao, DDDP, Regulatory Project Manager, 301-796-8189

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 14, 2014		050819	Efficacy/Labeling Supplement	2/14/14

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75%	Standard	Topical Gel	September 9, 2014

NAME OF FIRM: Dow Pharmaceutical Sciences, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review labeling and attend labeling meetings.
Filing Meeting: TBD
Mid-Cycle Meeting: TBD
Labeling Meetings: TBD
Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER Jennifer Dao	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☒ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

JENNIFER M DAO
02/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 050819/S-012

INFORMATION REQUEST

Dow Pharmaceutical Sciences
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/3.75%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following information requests. We request a prompt written response by February 19, 2014 in order to continue our evaluation of your supplemental application.

Provide the following:

1. Statement of readiness for inspection for each facility involved in the new strength;
2. Form 356h with establishment and DMF information;
3. Confirmation that the establishment and DMF information is identical to that provided in the original NDA;
4. Letter of Authorization of referenced Drug Master Files;
5. Fax number and email address for point of contacts for all four manufacturing and testing sites;
6. Master batch record;
7. Executed batch record.

If you have questions, call Jennifer Dao, Regulatory Project Manager, at (301) 796-8189.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
02/13/2014