CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211913Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

Date: September 23, 2019
To: NDA 211913
Regulatory Pathway: 505(b)(2) of the Public Health Service Act
From: Roselyn E. Epps, M.D., Medical Officer DDDP

THROUGH: David Kettl, M.D., Clinical Team Leader DDDP
SUBJECT: Unireview Completion Memorandum
Submission type: New Drug Application
Submission date: August 17, 2018
Drug: Absorica LD capsules
Indication: For the treatment of severe recalcitrant nodular acne in patients 12 years of age and older
Route: Oral
Applicant: Sun Pharmaceutical Industries, Inc.

Background
Sun Pharmaceutical Industries, Inc. submitted a New Drug Application (NDA) dated August 17, 2018 under section 505(b)(2) of the Public Health Service Act for ABSORICA LD capsules 8 mg, 16 mg, 20 mg, 24 mg, 28 mg and 32 mg, for oral use. An isotretinoin product, this application compares the new drug to approved drug ABSORICA; Sun Pharmaceuticals is the holder of the approved drug NDA 021951. ABSORICA was used to bridge the new drug to Accutane, the listed drug (LD) for this application.

The approved oral dosing regimen is 0.5 to 1.0 mg/kg/day given in two divided doses without regard to meals for 15 to 20 weeks. The applicant proposed the following ABSORICA LD dosing regimen: "recommended dosage of 0.4 to 0.8 mg/kg/day given in two divided doses without regard to meals for 15 to 20 weeks" .

The applicant submitted bioavailability and bioequivalence pharmacokinetics data to compare the new drug to the approved drug. The clinical pharmacology data support the updated dosing regimen, based on weight.

No pharmacology/toxicology studies and phase 3 clinical trial for efficacy and safety were conducted to support this NDA. Isotretinoin has been approved since 1982, and the safety profile is well-known. ABSORICA LD is proposed to participate in the established Risk Evaluation and Mitigation Strategy (REMS) program, iPLEDGE. The Agency and the applicant agreed upon combined labeling for ABSORICA LD and ABSORICA.

Approval is supported by the clinical bridge data established and included in this submission.

Recommendation:
The clinical team recommends approval of ABSORICA LD (isotretinoin) capsules, for the treatment of nodular acne in patients 12 years and older with a new dosing regimen (0.4 to 0.8 mg/kg/day) for all patients.

The clinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for the details.

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

/s/

ROSELYN E EPPS
10/16/2019 02:28:33 PM

DAVID L KETTL
10/16/2019 04:17:57 PM

New Drug Application Multi-disciplinary Review and Evaluation for Absorica LD (Isotretinoin Capsules) for Treatment of Recalcitrant Nodular Acne

Application Type	NDA
Application Number(s)	211913
Priority or Standard	Standard
Submit Date(s)	August 17, 2018
Received Date(s)	August 17, 2018
PDUFA Goal Date	September 17, 2019
Division/Office	Division of Dermatology and Dental Products Office of Drug Evaluation III
Review Completion Date	October 07, 2019
Established Name	Isotretinoin capsules
(Proposed) Trade Name	Absorica LD
Pharmacologic Class	Retinoid
Code name	Isotretinoin
Applicant	Sun Pharmaceutical Industries Limited
Dosage form and strengths	Capsules, 8 mg, 16 mg, 20 mg, 24 mg, 28 mg and 32 mg
Applicant proposed Dosing Regimen	0.4 to 0.8 mg/kg/day given in two divided doses without regard to meals for 15 to 20 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of severe recalcitrant nodular acne in patients 12 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	403359004 Acne nodule (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of severe recalcitrant nodular acne in patients 12 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	403359004 Acne nodule (disorder)
Recommended Dosing Regimen	0.4 to 0.8 mg/kg/day given in two divided doses without regard to meals for 15 weeks to 20 weeks

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Barbara Gould
Nonclinical Reviewer	Carmen Booker, PhD
Nonclinical Supervisor	Barbara Hill, PhD
Office of Clinical Pharmacology Reviewer(s)	Soo Hyeon Shin, PharmD, PhD
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, PhD
Clinical Reviewer	Roselyn E. Epps, MD
Clinical Team Leader	David Kettl, MD
Associate Director for Labeling	Nancy Xu, MD
Cross-Disciplinary Team Leader	David Kettl, MD
Office Director (or designated signatory authority)	Jill A. Lindstrom, MD

Additional Reviewers of Application

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Product Quality QAL	Hamid Shafiei, PhD	DNDP II, NDPB V	Sections: 4.2	Select one: _X__ Authored __X_ Approved
	Signature: See DARRTS			
Nonclinical Reviewer	Carmen Booker, PhD	ODE 3/DDDP	Sections: 5 and 15.3	Select one: _X__ Authored ___ Approved
	Signature: See DARRTS			
Nonclinical Supervisor	Barbara Hill, PhD	ODE 3/DDDP	Sections: 5 and 15.3	Select one: ___ Authored _X__ Approved
	Signature: See DARRTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Soo Hyeon Shin, PharmD, PhD	OCP/ DCP III	Section: 6 and 15.4	Select one: _X_ Authored ___ Approved
	Signature: See DARRTS			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DCP III	Section: 6 and 15.4	Select one: ___ Authored _X_ Approved
	Signature: See DARRTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Roselyn E. Epps, MD	OND/Division of Dermatology and Dental Products	Sections: 1; 2; 3; 4.1; 7; 9; 10; 19.1; 19.2	Select one: _X_ Authored ___ Approved
	Signature:			
Clinical Team Leader	David Kettl, MD	OND/Division of Dermatology and Dental Products	Sections: All	Select one: ___ Authored __X_ Approved
	Signature:			
Associate Director for Labeling	Nancy Xu, MD	OND/Division of Dermatology and Dental Products	Sections: 11	Select one: __x_ Authored ___ Approved
	Signature: See DARRTS			
Deputy Division Director (Clinical)	Jill A Lindstrom, MD	OND/Division of Dermatology and Dental Products	Sections: all	Select one: ___ Authored __x_ Approved
	Signature: See DARRTS			

Glossary

API	active pharmaceutical ingredient
AUC	area under the curve
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
DDDP	Division of Dermatology and Dental Products
DPMH	Division of Pediatric and Maternal Health
FDA	Food and Drug Administration
FPI	full prescribing information
LDT	Labeling Development Team
NDA	new drug application
PI	prescribing information
PK	pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy

1 Executive Summary

1.1. Product Introduction

Isotretinoin (13-cis-retinoic acid) is a systemic retinoid whose effects include normalizing keratinization, and reducing sebaceous cell number and sebum synthesis. Isotretinoin was initially approved and marketed as Accutane® on May 7, 1982, for the treatment of severe, recalcitrant, nodular acne, where the patient is unresponsive to conventional therapy including systemic antibiotics. Subsequently, multiple isotretinoin products and generics have been approved.

In this marketing application, Sun Pharmaceuticals has submitted an isotretinoin product with the proposed proprietary name "Absorica LD", a different formulation of the currently marketed drug Absorica® (isotretinoin capsules). The new formulation is intended to increase the bioavailability of isotretinoin thus enabling a reduced dose. The proposed indication for Absorica LD is identical to the indication for Absorica: for the treatment of severe recalcitrant nodular acne in patients 12 years and older. The recommended, weight-based dosing of Absorica LD is 0.4 to 0.8 mg/kg/day in two divided doses for 15 to 20 weeks. Absorica LD may be taken without regard to meals.

1.2. Conclusions on the Substantial Evidence of Effectiveness

To support this application, the Applicant needed to establish a clinical bridge between the study drug and the approved drug, Absorica. The Applicant provided substantial evidence of effectiveness from a bioavailability study that compared Absorica LD 32 mg capsules to Absorica 40 mg capsules in healthy adult volunteers. Additionally, the Applicant evaluated the bioavailability of Absorica LD 32 mg under fasting and fed conditions and Absorica 40 mg under fed conditions in healthy adult volunteers. The study data support establishment of the clinical bridge between Absorica LD and Absorica.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Isotretinoin (13-cis-retinoic acid) is a systemic retinoid whose effects include normalizing keratinization, and reducing sebaceous cell number and sebum synthesis. Isotretinoin is approved and marketed for the treatment of severe, recalcitrant, nodular acne, where the patient is unresponsive to conventional therapy including systemic antibiotics.

Acne vulgaris is a common dermatological condition. The disease manifestations include open and closed comedones and inflammatory papules. In severe cases, nodules develop, which can cause scarring. Acne affects an estimated 85% of young people aged 12 to 24 years ; 20% have moderate to severe disease.

The Applicant provided substantial evidence of effectiveness from a bioavailability study that compared Absorica LD 32 mg capsules to Absorica 40 mg capsules in healthy adult volunteers. Additionally, the Applicant evaluated the bioavailability of Absorica LD 32 mg under fasting and fed conditions and Absorica 40 mg under fed conditions in healthy adult volunteers. The clinical bridge was established.

The safety profile of isotretinoin is well known, as the drug was initially approved in 1982. No clinical safety and efficacy trials were conducted for this application. The new drug formulation has established a clinical bridge to an approved isotretinoin product with a reviewed safety profile, and is therefore expected to demonstrate similar safety. Isotretinoin is a known teratogen and should not to be taken by pregnant patients; therefore, this drug will participate in the iPLEDGE program intended to prevent pregnancy exposure. The labeling for Absorica LD and Absorica will be combined to differentiate the weight-based dosing regimens while acknowledging the identical intended population and indication, and comparable expected safety profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acne is a common dermatologic condition in adolescents as well as adults. Severe, nodular acne presents treatment challenges.	Patients seek and prescribers recommend treatment of severe acne to prevent complications such as cysts, pain, and permanent scarring.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Multiple oral isotretinoin products are available for severe, nodular acne. Almost all approved oral isotretinoin products are taken with meals; currently marketed Absorica has improved absorption and is taken without regard to meals. The proposed isotretinoin drug demonstrated, at lower doses, similar exposure to Absorica dosed as labeled.	Absorica LD adds to the therapeutic options for treatment of severe nodular acne.
Benefit	• According to the bioavailability studies, the new formulation of isotretinoin provides comparable exposure at lower doses to an available, US-approved isotretinoin.	The new formulation provides increased bioavailability enabling reduced dose.
Risk and Risk Management	• No clinical trials were conducted. Isotretinoin is a known teratogen, so pregnancy exposure is contraindicated. • The unified risk evaluation and mitigation strategy (REMS) program established for marketed oral isotretinoin products is known as iPLEDGE. The manufacturer of Absorica LD participates in this program with an approved isotretinoin product.	The new dose formulation will provide a comparable exposure and is expected to result in a similar adverse event profile. The established REMS program enrolls all stakeholders with the intent to provide safety measures to prevent pregnancy exposure. Combined labeling with Absorica intends to emphasize difference in dosing.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	The patient experience data that were submitted as part of the application include:			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Acne vulgaris is a common dermatological condition that affects an estimated 85% of people aged 12 to 24 years and approximately one-quarter of women in their 30s.(Perkins et al. 2012; Bhate and Williams 2013) The disease manifestations include open and closed comedones and inflammatory papules. In severe cases, nodules and cysts develop. Scarring may be a consequence of acne lesions, even in mild cases. Acne vulgaris usually occurs on the face, and may be seen in sebaceous areas including the neck, chest, back, and upper arms. While the pathogenesis is not completely understood, contributing factors to acne development are follicular hyperkeratinization, *Cutibacterium acnes* colonization, sebum production, genetic and other immune factors. Acne may be exacerbated by or a consequence of certain medications, such as systemic corticosteroids and androgen products.

Many cases of acne are mild and respond well to basic hygiene, lifestyle changes, and over-the-counter products. A smaller group of patients present with severe, nodular acne requiring intervention to treat inflammatory lesions and prevent scarring; such patients may benefit from oral retinoids. Prior to approval of Accutane in 1982, there were no adequate and approved treatments specifically for severe, nodular acne. Multiple oral retinoid formulations have been approved since the approval of Accutane, which is no longer marketed.

2.2. Analysis of Current Treatment Options

Acne treatment uses multiple modalities; therapeutic options include over-the counter and prescription keratolytic products, topical and oral antibiotics, and topical and oral retinoids that may be used alone or in combination.(Zaenglein et al. 2016) In 2018, a microparticle topical product for use as an accessory to 1,064 nm laser therapy was cleared for treatment of mild to moderate inflammatory acne.

For severe, nodular acne, the Agency has approved oral isotretinoin. Specific formulations of minocycline and doxycycline, and sarecycline are approved for the treatment of non-nodular moderate to severe acne. The formulations differ by the age of indicated patients and whether the drug is taken with or without food. For details, see the table below.

Table 1: FDA-Approved Treatments for Severe Acne

Product Name	Relevant Indication	Year Approved	Dosing/ Administration	Efficacy	Important Safety and Tolerability Issues	Comments
Retinoids						
Isotretinoin [Accutane][1] (TE: Clavaris, Amnesteen, Myorisan, Zenatane)	Nodular acne	1982	Oral; 0.5 to 2 mg/kg/ day ÷2 doses w/ food. May repeat course after 8 weeks	Course 15-20 weeks. 13/14 patients clear. Prolonged remission up to 20 months.(Peck et al. 1979)	Oral isotretinoin is teratogenic; Possibly reversible AE: psych disorder; pseudotumor cerebri; ↑lipids; pancreatitis; IBD; ↑LFTs; ↓hearing; ↓/no WBC; vision changes hypersensitivity. Other AE: hyperostosis; premature epiphysis closure; eye changes.	Contraindicated in pregnancy. REMS program established for stakeholders. Do not take with vitamin A. In 2009, Accutane was discontinued.
Absorica (Isotretinoin)	Severe recalcitrant nodular acne	2012	1mg/kg/day ÷2 doses. Oral; ≥12 yrs; May take w/o food	925 subjects R, DB, parallel group study, 1:1 Absorica vs Accutane, 0.5 initially then 1 mg/kg/ day	>5 %: dry lips, dry skin, back pain, dry eye, arthralgia, epistaxis, headache, nasopharyngitis chapped lips, dermatitis, ↑blood creatine kinase, cheilitis, musculoskeletal discomfort, URI, ↓visual acuity.	Cannot be substituted for other forms of isotretinoin. Contraindicated in pregnancy. REMS program to established for stakeholders. Do not take with Vitamin A, tetracycline.
Oral Antibiotics						
Solodyn Tablet, extended release (minocycline hydrochloride	Inflammatory lesions, non-nodular mod to severe acne vulgaris	2006	Oral; ≥ 12 yrs	924 subjects R, DB, PC non-nodular mod-severe acne IP vs placebo 2:1. Dose: 1mg/kg/day for 12 weeks With or w/o food	Class: anaphylaxis, photosensitivity, CNS Sx, discolored teeth/bone, scars, SJS, autoimmune syndromes. C diff colitis, liver injury. Possible drug interactions: OCP, anticoagulant, PCN some antacids, Fe, methoxyflurane. False ↑ level urine catecholamines	Class: Not taken w/OCPs ↓ effectiveness. Rec. not taken by anyone attempting to conceive. Excreted in human milk.

[1] Accutane was the first approved isotretinoin; it is no longer marketed.

Product Name	Relevant Indication	Year Ap-proved	Dosing/ Admini-stration	Efficacy	Important Safety and Tolerability Issues	Comments
Ximino (Minocycline hydrochloride)	Inflammatory lesions, non-nodular mod to severe acne vulgaris	2012	Oral; ≥ 12 yrs	See clinical minocycline trial above. Given by weight, rec 1mg/kg/d for 12 weeks, with or w/o food	Class: anaphylaxis, photosensitivity, CNS Sx,, discolored teeth, bone, scars, SJS, autoimmune syndromes. C diff colitis, liver injury Possible drug Interactions: OCP, anticoagulant, PCN some antacids, Fe, methoxyflurane. False ↑ level urine catecholamines	Class: Not taken w/OCPs ↓ effectiveness. Rec. not taken by anyone attempting to conceive. Excreted in human milk.
Minolira, extended release tablet (minocycline hydrochloride	Inflammatory lesions, non-nodular mod to severe acne vulgaris	2017	Oral; ≥ 12 yrs	See clinical minocycline trial above. Given by wt, rec 1mg/kg/d for 12 weeks with or w/o food	Class: anaphylaxis, photosensitivity, CNS Sx,, discolored teeth, bone, scars, SJS, autoimmune syndromes. C diff colitis, liver injury Possible drug Interactions: OCP, anticoagulant, PCN some antacids, Fe, methoxyflurane. False ↑ level urine catecholamines	Class: Not taken w/OCPs ↓ effectiveness. Rec. not taken by anyone attempting to conceive. Excreted in human milk.
Acticlate tablets & CAP (Doxycycline Hyclate) capsules	Severe acne adjunctive therapy	2016	Oral	200 mg on day 1 (100 mg q 12 hours) then maintenance dose=100 mg daily.	W & P: tooth dvlpt; C diff diarrhea; photosensitivity; intracranial HTN; skeletal dvpt delay; antianabolic action; drug-resistant bacteria. Monitoring recommended.	Case-control study: (18,515 mothers of infants w/congenital anomalies; 32,804 controls) marginally statistically significant assoc w/ total malformations and use of doxy anytime during pregnancy.
Seysara tablets (Sarecycline)	Inflammatory lesions, non-nodular mod to severe acne	2018	Oral; ≥ 9 yrs	Given by wt--33 to 54 kg: 60 mg; 55 to 84 kg: 100 mg; 85 to 136 kg: 150 mg	Tetracycline-like AEs: teratogenic effects; tooth color, ↓bone growth; C diff colitis; CNS; intracranial HTN; photosensitivity; drug-resistant bacteria; superinfection.	Toxicity in animal studies. TCNs cross BBB. Excreted in human milk. Avoid in M and F trying to conceive

REMS = risk evaluation and mitigation strategy, TE = therapeutic equivalent
Source: Clinical Reviewer's Table.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Isotretinoin is a systemic retinoid first approved May 7, 1982 under the name Accutane for the treatment of severe, recalcitrant, nodular acne, when the patient is unresponsive to conventional therapy including systemic antibiotics. Since initial approval, additional isotretinoin formulations have been approved in varying strengths. Six generic isotretinoin drug products have been approved in the US for severe recalcitrant nodular acne. Accutane was discontinued from the market for reasons unrelated to safety and efficacy. The applicant constructed a clinical bridge to Absorica, for which the applicant previously relied upon Accutane (as a listed drug) for approval; hence Accutane is the listed drug for this application as well.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Agency provided presubmission advice and held meetings with the Applicant regarding this drug development program for the severe acne indication.

For the current application, the following regulatory actions and meetings occurred.

- On February 23, 2015, a Type B, Pre-IND meeting was held to discuss the drug development plan.
- The Agency agreed on the 505(b)(2) regulatory pathway, and that the regulatory requirements should apply to each listed drug upon which an applicant relies.

> *If you intend to rely on the Agency's findings of safety for a listed drug to support the safety of your drug product, you must establish that such reliance is scientifically appropriate and you need to establish an adequate clinical bridge to the listed drug. You must clearly specify which findings of safety you intend to rely on for a listed drug. You may not reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries of a listed drug for support of safety and/or efficacy of your proposed drug product. A 505(b)(2) applicant that seeks to rely upon FDA's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug.*

  - The Agency advised that dose proportionality studies may not be required if stated conditions were met.
  - The Applicant and the Agency agreed that the study design was acceptable, and that subjects enrolled in the bioequivalence/food effect study should be representative of the US population, i.e., male and female.

- On October 15, 2015, the Applicant opened an Investigational New Drug Application (IND 125118) for isotretinoin capsules 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, 32 mg.
- On February 15, 2017, a Type B, Pre-NDA teleconference was held to discuss the Applicant's plan for New Drug Application (NDA) submission.
  Highlights included:
  - The Agency did not agree to qualify the additional active pharmaceutical ingredient (API) source ((b) (4) site) in the original NDA. The proposed change, i.e., qualifying the additional API source, involves both a site change as well as a significant change in the specification of the API. From the API perspective, in addition to manufacture of drug product, a side-by-side comparison of the APIs manufactured at the two different sites will need to be provided in the NDA.
  - The Agency agreed that the drug substance specifications, test parameters and acceptance criteria from both sources (b) (4) look reasonable to support filing of an NDA. However, the final determination was considered an NDA review issue.
  - The Agency recommended the Applicant add a uniformity test to the final bulk suspension specification, and include a test for particle size analysis of the API in the drug product specification and include such a test in the stability protocols.
  - The proposed specifications of packaging components appear reasonable to support filing of the NDA.
  - Regarding acceptability of foreign data, the Applicant was referred to the guidance for industry *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data*.
  - The Agency agreed with Applicant's plans to market, promote, offer for sale, sell and/or distribute the product in accordance with the iPLEDGE program following receipt of final approval from the Agency for the subject NDA.
  - The proposed 20 mg strength overlaps with currently marketed isotretinoin products. The new formulation increases bioavailability; the overlap in strength may be a source of confusion to prescribers, pharmacists, and patients. The Agency requested that the Applicant clarify methods to mitigate the risk of wrong strength errors for patients who switch between Absorica LD and Absorica or generic isotretinoin.
  - The application must submit prescribing information conforming to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57, including the Pregnancy and Lactation Labeling Rule (PLLR).

Correspondence from the Agency to the Applicant:

- October 30, 2015: An Information Request was sent to the Applicant regarding timing of pregnancy tests prior, during, and after administering study drug.
- February 26, 2016: An Advice Letter was sent to the Applicant. Advice regarding changes to enrollment criteria included the following:
  - The Agency stated that the proposal to assess relative bioavailability in normal healthy postmenopausal females appeared reasonable.

- The Agency did not agree with a revised proposal to enroll a minimum of 10% of subjects of any one gender, and recommended enrolling both male and female subjects in an approximately equal ratio.

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

4.1. Office of Scientific Investigations (OSI)

Study 11440306
On December 17, 2018, the Division of Dermatology and Dental Products (DDDP) consulted the Office of Study Integrity and Surveillance (OSIS) for biopharmaceutical inspection, requesting routine inspections for the (b) (4) The Division of New Drug Bioequivalence Evaluation within OSIS determined that inspections in (b) (4) had been conducted within the specified time interval, and additional inspections were not warranted. Additionally, the (b) (4) site was inspected (b) (4). The final classification for the inspection consult was No Action Indicated.

4.2. Product Quality

Sun Pharmaceutical Industries Limited has submitted this (505)(b)(2) application for ABSORICA™ LD (isotretinoin) Capsules for the treatment of severe recalcitrant nodular acne in patients 12 years of age or older. Sun Pharmaceutical Industries Limited currently is the holder of the approved application, NDA 21951 for ABSORICA™ (isotretinoin) Capsules for the same indication. ABSORICA™ has been used to bridge to Accutane, the listed drug for this application.

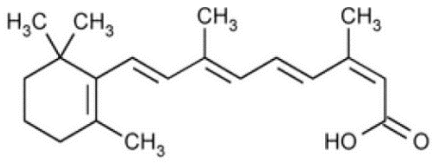
- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance and drug product.
- All labels/labeling issues have been satisfactorily resolved.
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for approval with the drug product expiration dating period of 24 months.

Drug Substance

ABSORICA™ LD (isotretinoin) Capsules contains micronized isotretinoin (b) (4) this API. Isotretinoin was first approved on May 7, 1982 as the active ingredients of ACCUTANE capsules marketed by Hoffmann La Roche for the treatment of severe recalcitrant nodular acne. Although marketing of ACCUTANE has been discontinued, the discontinuation of ACCUTANE was not due to any safety or efficacy reasons. Since the original approval, multiple brand name and generic versions for isotretinoin capsules have been approved for marketing in the United States.

Isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A). This API is a compendial drug substance with an existing USP monograph. Isotretinoin has a molecular formula of $C_{20}H_{28}O_2$, molecular weight of 300.44g/mol, and molecular structure below:



Isotretinoin for this application is manufactured by (b) (4) in accordance to the cGMP requirements and also in compliance with the USP. . The drug substance (b) (4) into the capsule dosage form. It is tested against an adequate specification that assures identity, strength, purity and quality of drug substance at release and throughout its proposed retest date of (b) (4). Information regarding the manufacture of isotretinoin produced by (b) (4).

(b) (4) is provided in DMF (b) (4) which has been reviewed and found to be adequate to support this new drug application.

Drug Product

The drug product ABSORICA™ LD (isotretinoin) capsules are manufactured in 8mg, 16mg, 20mg, 24mg, 28mg, 32mg strengths. The drug product is manufactured, packaged, and tested for release and stability in accordance to the cGMP by M W Encap Ltd.

Each capsule contains 8mg, 16mg, 20mg, 24mg, 28mg, or 32mg of isotretinoin as the active ingredient and butylated hydroxy anisole, gelatin, polysorbate 80, soybean oil, and hard gelatin capsule shells as inactive ingredients. All components used in the composition of the drug product including the drug substance, capsule shells, and inks are all compendial materials, composed of compendial materials, or materials that comply to the applicable 21 CFR requirements.

The to-be-marketed drug product capsules are packaged in blisters consisting of white (b) (4) and child resistant peelable aluminum lid foil configured in blister cards containing 10 capsules. Blister card is further packaged into a blister wallet. Three blister wallets each containing 10 capsules are packaged in an outer carton (30 capsules per carton).

The drug product is tested and released according to a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant is proposing a new micronized formulation of isotretinoin capsules with reduced dosages. The new formulations come in 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, and 32 mg capsules but it is bioequivalent to the previous formulation strength under fed condition. The Applicant claims that the new formulation is similar to the previous formation in that it has no significant food effect and may be taken without regard to meals. No pharmacology and/or toxicology studies have been conducted by the Applicant. The nonclinical safety profile is being demonstrated based on FDA's previous findings of safety and efficacy for the listed drug (Accutane), as well as published literature. The Applicant has generated a clinical bridge to Absorica (which previously relied for approval upon Accutane as a listed drug) through conduct of a clinical comparative bioavailability pharmacokinetic study.

There are no nonclinical safety issues; therefore, this NDA is approvable from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

NDA 21951 (Absorica), DMF (b) (4)

5.3. Pharmacology

Isotretinoin is related to retinoic acid, which regulates epithelial cell growth and differentiation by binding to nuclear hormone receptors. Its efficacy appears to be due to its effect on abnormal keratinization of the hair follicle, sebum production, follicular inflammation and colonization with *Propionibacterium acnes*. In several in vitro studies, tretinoin was shown to decrease the production of keratin by inhibiting cellular differentiation. In cultured human sebocytes, isotretinoin inhibited the proliferation of cells and decreased synthesis of triglycerides, wax/sterylesters and free fatty acids. Isotretinoin has been shown to have anti-inflammatory properties. In vitro, isotretinoin has been shown to inhibit the function of neutrophils, monocytes and lymphocytes. Isotretinoin has also shown potential efficacy in rat

models of experimental autoimmune encephalomyelitis and arthritis. 13-cis-retinoic acid suppresses T cell proliferation and mitogen-induced DNA synthesis.

5.4. ADME/PK

The pharmacokinetics (PK) of isotretinoin has been evaluated in many species including mouse, rat, hamster, rabbit, dog and monkey with significant species variation. The pharmacokinetics in the mouse and rat are similar, but different from the hamster, rabbit, dog and monkey. The monkey mostly resembles the pharmacokinetic profile in humans. Isotretinoin is metabolized by CYP2C8 and CYP3A4. In human plasma, isotretinoin is 99.9% bound to albumin.

5.5. Toxicology

5.5.1. General Toxicology

The animal toxicology information contained in the listed drug (Accutane®) label is provided below.

In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day (30 to 60 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area).

5.5.2. Genetic Toxicology

The genotoxicity information contained in the listed drug (Accutane) label is provided below.

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6 x background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D7 assay, in vitro clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

5.5.3. Carcinogenicity

The carcinogenicity information contained in the listed drug (Accutane) label is provided below.

In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The fertility and early embryonic development information contained in the listed drug (Accutane) label is provided below.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of spermatogenesis, but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen.

(b) (4)

No animal data concerning prenatal and postnatal development is provided in the listed drug label.

6 Clinical Pharmacology

6.1. Executive Summary

Isotretinoin (13-cis-retinoic acid) is a non-aromatic retinoid that was approved by the FDA as an oral capsule formulation in 1982 for the treatment of severe recalcitrant nodular acne. The initially approved product, which was marketed as Accutane, is discontinued but generic drugs are available. Also approved is another formulation of isotretinoin under the tradename Absorica, which was approved via 505(b)(2) regulatory pathway using Accutane as a listed drug.

The Applicant for this NDA is pursuing a 505(b)(2) application and has identified Accutane as the listed drug. It should be noted that the Applicant for this NDA and Absorica is the same. The proposed proprietary name for the product under this NDA is Absorica LD.

Absorica LD, is a new capsule formulation intended to increase bioavailability and thereby reducing the strength of isotretinoin by 20% compared to the corresponding strength of Absorica.

- Proposed indication: for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older (identical to the approved indication of Absorica)
- Proposed dosing regimen: 0.4 to 0.8 mg/kg/day given in two divided doses without regard to meals for 15 weeks to 20 weeks
- Proposed dosage form and strengths: oral capsules with 6 strengths (8, 16, 20, 24, 28 and 32 mg)

In this NDA, to support a clinical bridge, the Applicant evaluated the relative bioavailability of 32 mg dose of Absorica LD compared to 40 mg Absorica under fed conditions in healthy adult subjects (Study 11440306). In addition, the Applicant evaluated the effect of food on the bioavailability on 32 mg dose of Absorica LD. The Applicant submitted a biowaiver of lower strengths based on dissolution data and the biowaiver is deemed to be acceptable by the Biopharmaceutics review team.

The key review findings with specific recommendations and comments are summarized below in Table 2.

Table 2: Summary of Clinical Pharmacology Review

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy was not evaluated as this application provided a clinical bridge to Absorica and is a 505(b)(2) application . The efficacy results from the Absorica label will be included in the combined label.
General dosing instruction	The proposed weight-based dosing regimen of 0.4 to 0.8 mg/kg/day given in two divided doses without regard to meals for 15 weeks to 20 weeks is acceptable.
Pharmacokinetics (PK)	PK of isotretinoin following a single dose of 32 mg of the proposed new formulation, Absorica LD, under fasted and fed conditions and 40 mg Absorica under fed conditions were evaluated.
Food effect	Food effect on Absorica LD was evaluated following a single dose of 32 mg capsule under fasted and fed conditions in healthy subjects.
Clinical Bridge between Absorica LD and Absorica	The relative bioavailability (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) between 32 mg dose of Absorica LD and 40 mg Absorica capsules under fed conditions were within the no effect boundary of 80% to 125% under fed conditions. The clinical bridge between Absorica LD and Absorica is considered as established.
Pediatric subjects	Pediatric subjects were not studied in this NDA. The Applicant requested for a partial waiver in pediatric population below 12 years of age and relied on the existing data in adults to support approval in pediatric subjects aged 12 to 17 years.
Formulations used in clinical trial	To-be-marketed formulation of Absorica LD and approved formulation of Absorica were used.

Abbreviations: PK = pharmacokinetic, AUC = area under the curve, NDA = New Drug Application

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable.

6.1.2. Post-Marketing Requirement(s) and Commitment(s)

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

<table>
<tr><td>Mechanism of Action</td><td>The exact mechanism of action of isotretinoin in treating nodular acne is unknown. The inhibition of sebaceous gland differentiation resulting in reduced sebum secretion appears to be related to the efficacy of isotretinoin.</td></tr>
<tr><td>PK Parameters</td><td>Isotretinoin is an endogenous substance. The table below summarizes baseline corrected PK parameters of isotretinoin following a single dose of 32 mg Absorica LD under fasted and fed conditions and 40 mg Absorica under fed conditions.
<table>
<tr><th></th><th>32 mg Absorica LD – Fasted</th><th>32 mg Absorica LD – Fed</th><th>40 mg Absorica - Fed</th></tr>
<tr><td>Mean C_{max} (SD) (ng/mL)</td><td>611 (285)</td><td>646 (275)</td><td>596 (184)</td></tr>
<tr><td>Mean AUC_{0-t} (SD) (h*ng/mL)</td><td>8466 (2458)</td><td>10209 (1967)</td><td>10693 (2247)</td></tr>
<tr><td>Mean $AUC_{0-\infty}$ (SD) (h*ng/mL)</td><td>9219 (2782)</td><td>10922 (2176)</td><td>11677 (2851)</td></tr>
<tr><td>Median T_{max} (h)</td><td>3.5</td><td>5.0</td><td>6.0</td></tr>
</table></td></tr>
<tr><td>Food Effect</td><td>Following administration of Absorica LD with a high fat high calorie meal, the median T_{max} was delayed by 1.5 h and median area under the curve (AUC) was increased by approximately 20%. The food effect on C_{max} was negligible.</td></tr>
<tr><td>Relative Bioavailability</td><td>Under fed conditions, 32 mg of Absorica LD and 40 mg Absorica, the 90% confidence interval of the ratio of the geometric mean of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} fell within the no effect boundary of 80% to 125%.</td></tr>
<tr><td>Pharmacodynamics (PD)</td><td>The PD of isotretinoin are unknown. The Applicant did not evaluate the PD of isotretinoin.</td></tr>
<tr><td>Bioanalytical Method</td><td>A high-performance liquid chromatography tandem mass spectrometric method (LC-MS/MS) was used to estimate isotretinoin concentration in plasma. Full validation report was submitted and bioanalytical method was adequately validated. See Section 15.4 for additional details.</td></tr>
</table>

Abbreviations: PK = pharmacokinetic, PD = pharmacodynamic, AUC = area under the curve

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosing regimen is 0.4 to 0.8 mg/kg/day given in two divided doses without regard to meals for 15 weeks to 20 weeks. The proposed dose strength is 20% lower

than the approved dose of Absorica. This regimen is supported by results from the relative bioavailability Study 11440306, which demonstrated that the relative bioavailability of 32 mg dose of Absorica LD and 40 mg of Absorica capsules is within the no effect boundary of 80% to 125%.

Therapeutic Individualization

Therapeutic individualization was not evaluated in this NDA.

6.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of from a Clinical Pharmacology perspective.

6.2.4. Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following recommendation and comments:

Section 12.3 Pharmacokinetics: remove speculative text regarding (b) (4) .

Reviewer's comment: For additional edits, see the labeling section of this review.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The PK characteristics of isotretinoin from Absorica LD was addressed in Study 11440306. This was an open-label, multiple-center, balanced, randomized, single-dose, three-treatment, three-period, six-sequence, crossover study to compare the bioavailability of the 32 mg dose Absorica LD and the 40 mg dose Absorica capsules under fed conditions and to evaluate the food effect of the 32 mg dose Absorica LD in healthy adult subjects.

The three treatments were:

- Test Treatment A: Absorica LD isotretinoin capsule 32 mg, administered following an overnight fast of at least 10 hours.
- Test Treatment B: Absorica LD isotretinoin capsule 32 mg, administered following a standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours.
- Reference Treatment C: Absorica isotretinoin capsule 40 mg, administered following a standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours.

Reviewer's comment: A standardized high-fat, high-calorie breakfast in Treatment B and Treatment C consisted of 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, 2 slices of toast with butter, and 8 oz of whole milk, containing about 150 protein calories, 250 carbohydrate calories and 500 fat calories.

Subjects received treatments according to a six-sequence randomization schedule. A washout period of at least 21 days was ensured between treatments.

A total of 71 subjects were enrolled in the study, 64 subjects completed at least two periods of the study including Test Treatment B, and 61 subjects completed all three periods of the study. The reasons for dropouts were failure to complete the standardized high-fat, high-calorie breakfast, voluntary withdrawal, a positive substance abuse screen result and non-compliance. Data from 65 subjects were included in the fed bioequivalence (Test Treatment B vs. Reference Treatment C). Data from 63 subjects were included for each comparison (Test Treatment B vs. Reference Treatment C and Test Treatment B vs Test Treatment A). Demographic characteristics from PK population are summarized in Table 3.

Table 3: Demographic Characteristics (PK Population)

		Treatment Groups		
		Test A Absorica LD 32 mg Fasted (n=63)	**Test B Absorica LD 32 mg Fed (n=65)**	**Reference C Absorica 40 mg Fed (n=63)**
Gender	Male	47 (74.60%)	49 (75.38%)	47 (74.60%)
	Female	16 (25.40%)	16 (24.62%)	16 (25.40%)
Race	Asian	2 (3.17%)	2 (3.08%)	2 (3.17%)
	Black	34 (53.97%)	35 (53.85%)	34 (53.97%)
	Caucasian	20 (31.75%)	20 (30.77%)	19 (30.16%)
	Hispanic	4 (6.35%)	5 (7.69%)	5 (7.94%)
	Other	3 (4.76%)	3 (4.62%)	3 (4.76%)
Age (years)	Mean ± SD	44.24 ± 14.75	44.20 ± 14.58	44.30 ± 14.35
	Median	38.00	38.00	38.00
	Range	21 - 68	21 - 68	21 - 68
Age group	< 18	0 (0.00%)	0 (0.00%)	0 (0.00%)
	18 - 40	33 (52.38%)	34 (52.31%)	33 (52.38%)
	41 - 64	25 (39.68%)	26 (40.00%)	25 (39.68%)
	65 - 75	5 (7.94%)	5 (7.69%)	5 (7.94%)
	> 75	0 (0.00%)	0 (0.00%)	0 (0.00%)
Weight (lbs)	Mean ± SD	169.44 ± 26.98	169.54 ± 27.22	169.90 ± 27.57
	Median	165.00	165.00	166.00
	Range	90 - 225	90 - 225	90 - 225
BMI (kg/m^2)	Mean ± SD	25.45 ± 2.91	25.44 ± 2.97	25.53 ± 2.97
	Median	26.10	26.10	26.10
	Range	18.2 - 30.0	18.2 - 30.0	18.2 - 30.0
Tobacco user	Yes	20 (31.75%)	21 (32.31%)	20 (31.75%)
	No	43 (68.25%)	44 (67.69%)	43 (68.25%)

Abbreviations: BMI = body mass index
Source: Adapted from Table 11.2.1 in CSR for Study 11440306.

Pre-dose samples for measurement of baseline endogenous isotretinoin concentrations were collected at 12, 10, 2 and 0 hours prior to dosing. The mean of the four pre-dose concentration values was subtracted from all post-dose concentrations to calculate baseline-adjusted concentrations. The baseline sampling times and baseline correction method are similar to those used in Absorica NDA and are deemed adequate (see Clinical Pharmacology review dated April 12, 2012 by Dr. Chinmay Shukla under NDA 021951). Baseline correction was applied specific to each subject and period and any plasma concentration that resulted in a negative baseline corrected value was set to zero for PK analysis. Any subject with baseline-corrected pre-dose concentrations greater than 5% of the measured maximum plasma concentration (C_{max}) value for that specific study period was excluded from the statistical analysis for that specific study period (None of the subjects were excluded using this criterion). Baseline-uncorrected data was submitted only as supportive information.

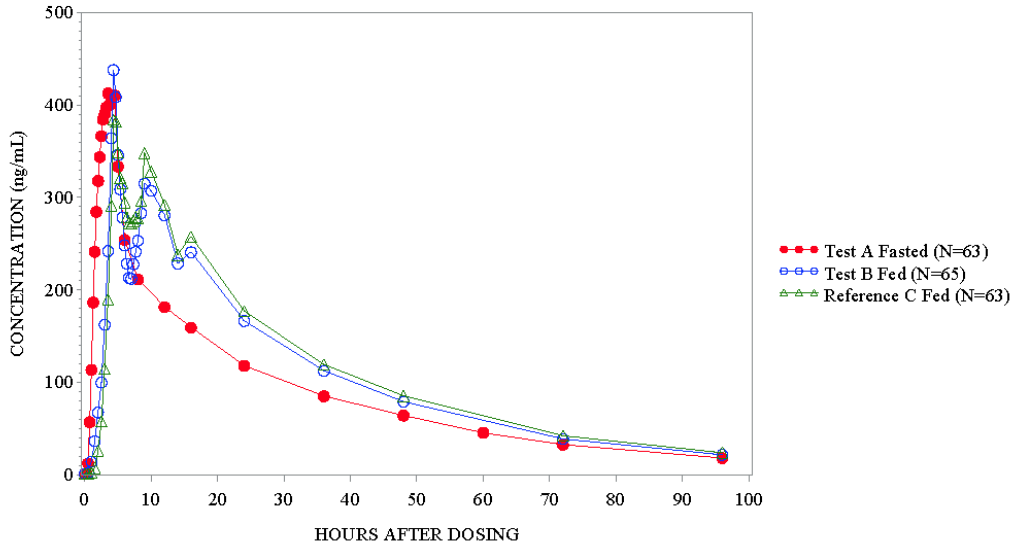
Post-dose samples were collected at following times:

- Fasted treatment (Test Treatment A): 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00 72.00, and 96.00 hours post-dose
- Fed treatments (Test Treatment B and Reference Treatment C): 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 6.33, 6.67, 7.00, 7.33, 7.67, 8.00, 8.50, 9.00, 10.00, 12.00, 14.00, 16.00, 24.00, 36.00, 48.00, 72.00, and 96.00 hours post-dose

The PK profiles following a single dose of 32 mg Absorica LD and 40 mg Absorica under fed conditions were very similar to each other as shown in Figure 1. When a single dose of 32 mg Absorica LD capsule was taken under fasted conditions, the absorption of isotretinoin was faster and the systemic exposure was lower compared to when the same product was taken under fed conditions. The graphical analysis can also be confirmed by PK parameters summarized in Table 4. Mean T_{max} from Treatment Groups A, B and C were 3.7, 7.8 and 7.8 h, respectively. Mean $AUC_{0-\infty}$ from Treatment Groups A, B and C were 9219, 10922 and 11677 ng·hr/mL, respectively. Mean C_{max} from Treatment Groups A, B and C were 611, 646 and 596 ng/mL respectively.

Reviewer's comment: A high-fat, high-calorie meal appears to significantly delay and increase absorption of isotretinoin from both Absorica LD and Absorica, but has no significant impact on C_{max} and K_{el}. The mean AUC_{0-t}, mean $AUC_{0-\infty}$ and mean T_{max} from Treatment Group A were significantly lower than those from Treatment Groups B and C based on this reviewer's statistical analysis (one-way ANOVA followed by Tukey's post-hoc analysis). The mean of these three PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, and T_{max}) from Treatment Groups B and C were comparable. Mean C_{max} and mean K_{el} from the three treatment groups were comparable (one-way ANOVA).

Figure 1: Mean Plasma Concentrations of Isotretinoin (Baseline-Corrected)



Source: Adapted from Figure 14.2.1 in CSR for Study 11440306.

Table 4: Pharmacokinetic Parameters (Baseline-Corrected)

Parameter	Treatment	# Datasets	Arithmetic mean ± SD (%CV)	Min.	Median	Max.
AUC_{0-t} (ng·hr/mL)	Test A	63	8466.2596 ± 2458.2219 (29.0355)	3639.2919	8338.2692	14668.9617
	Test B	65	10209.1108 ± 1967.4847 (19.2719)	6894.4413	10148.3488	15655.7855
	Reference C	61	10692.9997 ± 2247.2590 (21.0162)	6696.6914	10626.4035	15142.0067
$AUC_{0-\infty}$ (ng·hr/mL)	Test A	63	9219.0567 ± 2782.0992 (30.1777)	4229.9224	9111.0681	15342.9700
	Test B	64	10921.9038 ± 2176.0965 (19.9241)	6976.6973	10640.2613	16932.2070
	Reference C	62	11676.6069 ± 2850.9600 (24.4160)	7422.8905	11328.2065	18435.4636
AUC % Extrapolated	Test A	63	7.7536 ± 5.2719 (67.9930)	0.6602	6.6408	26.6981
	Test B	64	6.9325 ± 4.8978 (70.6502)	0.4169	5.0890	19.3749
	Reference C	62	7.4743 ± 5.8985 (78.9173)	0.6781	4.9141	28.0793
C_{max} (ng/mL)	Test A	63	611.3302 ± 285.1527 (46.6446)	108.2935	584.6323	1364.6313
	Test B	65	645.7434 ± 275.1842 (42.6151)	223.8988	630.2910	1402.7030
	Reference C	63	595.7336 ± 183.8075 (30.8540)	220.0583	578.1430	1202.8365
T_{max} (hr)	Test A	63	3.6757 ± 1.9236 (52.3347)	1.2500	3.5000	12.0000
	Test B	65	7.7777 ± 4.6046 (59.2027)	1.5000	5.0000	24.0000
	Reference C	63	7.8386 ± 4.3766 (55.8343)	3.5000	6.0000	24.0000

Parameter	Treatment	# Datasets	Arithmetic mean ± SD (%CV)	Min.	Median	Max.
K_{el} (hr^{-1})	Test A	63	0.0293 ± 0.0083 (28.3312)	0.0141	0.0277	0.0555
	Test B	64	0.0319 ± 0.0092 (28.8688)	0.0172	0.0312	0.0594
	Reference C	62	0.0312 ± 0.0085 (27.1455)	0.0154	0.0318	0.0574
$T_{1/2}$ (hr)	Test A	63	25.4964 ± 7.0735 (27.7431)	12.4827	25.0523	49.0607
	Test B	64	23.5219 ± 6.5954 (28.0396)	11.6696	22.2008	40.3430
	Reference C	62	24.0362 ± 7.0850 (29.4764)	12.0798	21.8092	45.1380

Abbreviations: AUC = area under the curve, SD = standard deviation
Source: Adapted from Table 11.4.1.1 in CSR for Study 11440306.

The food effect on the PK of isotretinoin was evaluated following a single dose of 32 mg Absorica LD and the results are summarized in Table 5. The bioavailability of isotretinoin increased when administered with a high-fat, high-calorie meal. The effect on C_{max} was less compared to the effect on AUC. The % least square geometric mean (LSGM) ratio of fed-to-fasted was 125.04% for $AUC_{0-t,}$ 123.45% for $AUC_{0-\infty}$ and 110.31% for C_{max}.

Reviewer's comment: The magnitude of food effect on Absorica LD was less compared to that reported in the approved label for Absorica (Table 6). Since Absorica is approved to be administered regardless of meals and its magnitude of the food effect on systemic exposure was greater than that of Absorica LD, the available effect of food data on Absorica LD supports its administration regardless of meals.

Table 5: Food Effect Results (Test Treatment A vs. Test Treatment B) Based on Baseline-Corrected Data (With Inclusion of the Center-by-Treatment Interaction Term)

Parameter	Trt	LS Geometric Mean (# datasets)	Contrast (# subjects)	LSGM Ratio (%)	90% Confidence Interval (%)	ISCV (%)	p-value Center by Trt	p-value Sequence
AUC_{0-t} (ng·hr/mL)	A	8035 (66)	B vs A (n=63)	125.04	117.41-133.17	21.3	0.6025	0.0347
	B	10047 (67)						
$AUC_{0-\infty}$ (ng·hr/mL)	A	8704 (66)	B vs A (n=62)	123.45	116.04-131.34	20.7	0.6490	0.0595
	B	10745 (66)						
C_{max} (ng/mL)	A	534.3 (67)	B vs A (n=63)	110.31	96.97-125.48	45.1	0.0041	0.2835
	B	589.4 (67)						

Abbreviations: LS = least-squares, LSGM = least-square geometric means, ISCV = intra-subject coefficient of variation, Trt = treatment, AUC = area under the curve
Source: Adapted from Table 11.4.1.3.1 in CSR for Study 11440306.

Table 6: Comparison of Food Effect on Absorica and Absorica LD

	Mean AUC_{0-t} (ng·hr/mL)	Mean C_{max} (ng/mL)	Mean T_{max} (h)
Absorica 40 mg			
Fed	6095	395	6.4
Fasted	4055	314	2.9
Ratio (Fed/Fasted)	1.50	1.26	2.2
Absorica LD 32 mg			
Fed	10209	646	7.78
Fasted	8466	611	3.68
Ratio (Fed/Fasted)	1.21	1.06	2.1

Abbreviation: AUC = area under the curve
Source: Reviewer's table. Data for Absorica (n=14) and Absorica LD (n=65 for Fed and n=63 for Fasted) were obtained from the approved labelling and Table 11.4.1.1 in CSR for Study 11440306, respectively.

The relative bioavailability results between the 32 mg dose of Absorica LD and 40 mg dose of Absorica under fed conditions are summarized in Table 7. The 90% confidence interval for the ratio of least-squares geometric mean fell within the no effect boundary of 80%-125% for all three PK parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) demonstrating that a clinical bridge between Absorica LD and Absorica is established.

Reviewer's comment: The relative bioavailability study was conducted using only the highest proposed strength (32 mg) of the proposed product and the highest approved strength (40 mg) of the comparator drug product (Absorica). The Applicant requested biowaiver for the lower strengths (8, 16, 20, 24 and 28 mg) based on dissolution data. The biowaiver request is deemed to be acceptable by the Biopharmaceutics review team.

Table 7: Relative Bioavailability Results (Test Treatment B vs. Reference Treatment C) Under Fed Conditions Based on Baseline-Corrected Data (With Inclusion of the Center-by-Treatment Interaction Term)

Parameter	Trt	LS Geometric Mean (# datasets)	Contrast (# subjects)	LSGM Ratio (%)	90% Confidence Interval (%)	ISCV (%)	p-value Center by Trt	Relative BA Outcome
AUC_{0-t} (ng·hr/mL)	B	9959 (67)	B vs C (n=61)	95.89	92.97-98.90	10.1	0.0004	Pass
	C	10386 (62)						
$AUC_{0-\infty}$ (ng·hr/mL)	B	10702 (66)	B vs C (n=61)	95.54	92.61-98.57	10.2	0.0004	Pass
	C	11201 (63)						
C_{max} (ng/mL)	B	599.9 (67)	B vs C (n=63)	105.19	97.65-113.30	25.1	0.0078	Pass
	C	570.3 (64)						

Source: Adapted from Table 11.4.1.2.1 in CSR for Study 11440306.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The purpose of the pivotal Clinical Pharmacology relative bioavailability study was to establish a clinical bridge between the proposed new formulation, Absorica LD and drug Absorica. Through successful establishment of the clinical bridge, the Applicant intended to reference the efficacy and safety data from Absorica (owned by the applicant) and Accutane [through the 505(b)(2) regulatory pathway].

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen is appropriate based on the clinical bridge that is established between 32 mg Absorica LD and 40 mg Absorica capsules under fed conditions.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The effect of intrinsic and extrinsic factors was not evaluated in this NDA because it follows a 505(b)(2) regulatory pathway and the proposed indication is the same as the listed drug.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

A high-fat, high-calorie meal slowed absorption and increased bioavailability of isotretinoin. However, the magnitude of food effect on Absorica LD appears to be less compared to that of Absorica (Table 6). As Absorica was approved to be taken without regard to meals, Absorica LD could also be taken without regard to meals.

No drug-drug interaction studies were conducted with the proposed product because this NDA followed a 505(b)(2) regulatory pathway. The Drug Interactions section of the Applicant's proposed labeling text closely follows that of approved label of Absorica.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant conducted a single, open-label study 11440306 to support the Absorica LD development program by studying the bioavailability and food effects compared to Absorica. Study 11440306 was entitled, "A Study to Investigate the Food Effect of a Test Formulation of Isotretinoin Capsules, 32 mg (Sun Pharmaceutical Industries Limited) and to Evaluate the Relative Bioavailability of a Test Formulation of Isotretinoin Capsules, 32 mg (Sun Pharmaceutical Industries Limited) Compared to ABSORICA® (isotretinoin) Capsules, 40 mg (Ranbaxy) in Healthy Adult Subjects under Fed Conditions". There were three arms: Absorica LD 32 mg fasting; Absorica LD 32 mg after meal; Absorica 40 mg reference after meal. Other key elements of the study are summarized in the table below.

Table 8: Clinical Study 11440306 to Support Absorica LD

Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
11440306	Open-label, randomized, balanced, single-dose, three-treatment, three-period, six-sequence, crossover study	32 mg capsules Reference: Absorica capsules 40 mg Fasting and fed conditions Route: Oral	One dose study drug, and one dose Absorica/ 25 days	71 enrolled; 64 subjects completed at least 2 study periods, 61 subjects to complete all (3) study periods	Healthy	Two centers; USA

Source: Clinical Reviewer Table.

7.2. Review Strategy

A multidisciplinary team reviewed NDA 211913 Absorica LD capsules. This unified review document presents the reports and summaries from each discipline supporting the action.

The Clinical Pharmacology review team reviewed the primary clinical data submitted by the Applicant, a bioavailability and food effect study (Study 11440306). According to the analysis, the Applicant has generated a clinical bridge from Absorica LD to Absorica, and established that the Absorica LD may be taken with or without food.

No new pharmacology toxicology studies were conducted by the Applicant. The nonclinical safety profile submitted is based on FDA's previous findings of safety and efficacy for the listed drug (Accutane), and published literature.

The Applicant did not conduct a clinical trial for safety and efficacy to support this NDA. No statistical analysis or safety data reviews were conducted.

8 Statistical and Clinical and Evaluation

No clinical trial was submitted to support efficacy.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was held.

10 Pediatrics

Under the Pediatric Research Equity Act (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

The Applicant did not conduct assessments in the pediatric population or evaluate the effects on growth for this application. The Applicant requested a partial waiver in the pediatric population below 12 years of age, and relied on the existing data in adults to support approval for use in pediatric patients aged 12 to 17 years. Isotretinoin has been marketed for over 30 years. Additionally, the Division of Pediatric and Maternal Health (DPMH) consult review did not recommend testing in the pediatric population for ages 12 through 16 years, 11 months. According to DPMH, there is not a meaningful difference in the dosing regimen between Absorica LD and Absorica. Therefore, no pediatric study plan is needed for this application.

11 Labeling Recommendations

11.1. Prescribing Information

This section summarizes the rationale for major changes to the prescribing information (PI) for Absorica LD as compared with the Applicant's draft PI dated May 6, 2019, and as compared with the currently approved PI (dated October 2018) for Absorica (also a product of the Applicant).

<u>Combining the PIs for Absorica LD and Absorica</u>
Given that Absorica and Absorica LD have the same active moiety (isotretinoin), health care provider audiences, application holder, safety profile(s), REMS with elements to assure safe use, and essentially the same conditions of use, DDDP, in consultation with the Labeling

Development Team (LDT), the Division of Medication Error Prevention and Analysis (DMEPA), and the Office of Regulatory Policy (ORP), believes that having the information in a single labeling document allows healthcare providers to directly compare the differences between the two products. Furthermore, having one labeling document will ensure consistency between the two PIs; two separate PIs would increase the chances of inappropriate divergent information being introduced with future labeling updates.

In the combined PI, revisions were made to:

- Ensure the information for accurate administration and dosing of the respective formulations is clearly presented throughout the labeling (both Highlights and Full Prescribing Information [FPI]):
    - Section 2 *Dosage and Administration* of the combined FPI presents the dosing information (different dosing regimens) for the respective formulations in separate and clearly demarcated tables.
    - Deleted the proposed (b) (4)
    - Section 3 *Dosage Forms and Strengths* organizes the characteristics of Absorica and Absorica LD and presents them in readily differentiable format.
    - Includes a dedicated subsection 5.3 entitled "*Absorica and Absorica LD are Not Substitutable*."
    - Section 3 *Dosage Forms and Strengths*, a dedicated subsection 5.3 of the Warnings and Precautions section, and Section 16 *How Supplied/Storage and Handling,* further highlight the information that although both Absorica and Absorica LD have a 20 mg strength, these strengths have different bioavailability are not substitutable, and that Absorica and Absorica LD have different dosage regimens. These sections cross-reference Section 2, as appropriate.
- Demarcate clearly the product-quality information (for example, the respective information for Absorica and Absorica LD in sections 3, 11, and 16 and the absorption and elimination characteristics for Absorica LD compared to the approved isotretinoin capsule product in the Pharmacokinetics subsection.
- Present side-by-side the identifying characteristics of the two formulations (in Section 11 Description and Section 16) to facilitate differentiation of each product.

The combined PI for Absorica LD and Absorica was shared with the Office of Generic Drugs (OGD) as the PI would have implications for generic isotretinoin product labeling.

Compliance with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[2]

DDDP worked closely with the Division of Pediatric and Maternal Health (DPMH), Division of Risk Management (DRISK), Labeling Development Team (LDT) to update labeling to be compliant with the Physician Labeling Rule (PLR) Pregnancy and Lactation Labeling Rule (PLLR) requirements.[2]

- Revised the Boxed Warning (BW) to be consistent with the recommendations in the guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format.* This guidance states that the BW *"provides a brief, concise summary of the information that is critical for a prescriber to consider, including any restriction on distribution or use*." A more detailed discussion of the risk elsewhere in the labeling (e.g., in CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections) is identified by cross-reference (21 CFR 201.57(c)(1). Therefore, we (b) (4) cross-referenced the labeling sections [e.g., Embryo-Fetal Toxicity warning and/or *Pregnancy* subsection]) where the information remains.
- Removed the phrase "(b) (4)" from the Contraindication statement throughout the labeling, because patients of child-bearing potential who use appropriate contraception can use this product. Although this phrase previously appeared in the PLR labeling regulations, it was removed from the regulations in December 2014 when the final PLLR rule was published.
- Edited subsection 5.2 iPLEDGE Program in labeling to provide a high-level summary of the responsibilities of each of the groups involved (prescribers, patients, pharmacies, wholesalers and distributors) while leaving the details in the Risk Evaluation and Mitigation Strategy (REMS) materials. The formatting changes are consistent with the recommendations from Medical Policy Council meeting.
- Moved the information in subsection 8.6 *Females of Reproductive Potential* to the new subsection *8.3 Patients of Reproductive Potential*. With the PLLR revised content and format requirements, this information should be placed under a subsection 8.3 (21 CFR 201.57(c)(9)(i) through (c)(9)(iii)).
- Moved information regarding micro-dosed progesterone as the unacceptable contraception from subsection 5.3 to subsection 8.3 *Patients of Reproductive Potential,* the subsection that discusses acceptable and unacceptable forms of contraception are when prescribing isotretinoin.

At the time of the review closure, a REMS modification is pending the Applicant's submission. Additional updates to the REMS simultaneous with labeling are anticipated for the contraception language.

<u>Formatting Edits to the Indications and Usage Section</u>

- We reformatted the *Indications and Usage* section to be consistent with CDER/OND best labeling practices and policies, to improve readability and succinctness, while not changing the condition of use (see below).

  From:
  ABSORICA LD (b) (4) for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older. (b) (4) inflammatory (b) (4) with a diameter of 5 mm or greater. (b) (4)

(b) (4)

Limitations of Use

(b) (4)

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To:
ABSORICA and ABSORICA LD are indicated for the treatment of severe recalcitrant nodular acne in non-pregnant patients 12 years of age and older with multiple inflammatory nodules with a diameter of 5 mm or greater. Because of significant adverse reactions associated with its use, ABSORICA and ABSORICA LD are reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics.

Limitations of Use

(b) (4) course of ABSORICA/ABSORICA LD therapy is not recommended before a two-month waiting period because the patient's acne may continue to improve following a 15 to 20-week course of therapy *[see Dosage and Administration (2.1)].*

According to the draft Guidance for Industry, *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products —Content and Format* (I&U section draft labeling guidance), indications should be concise and should not include prognostic information about disease (without drug treatment).

- We made additional edits for succinctness, to reduce redundancy between sections 1, 4, and the boxed warning.

Creation of Subsection 5.3 under *Warnings and Precautions* Section
5.3 ABSORICA and ABSORICA LD are Not Substitutable
Given that the bioavailability and the recommended dosage of ABSORICA and ABSORICA LD are different, ABSORICA and ABSORICA LD are not substitutable. For example, ABSORICA and ABSORICA LD have a 20 mg strength; however, these strengths have different bioavailability are not substitutable.

Edits to Improve Organization in the Adverse Reactions Section

In Section 6, we made edits to improve organization. Rather than repeating the source of the (*Clinical Trials Experience* versus *Postmarketing Experience*) with each adverse reaction heading, we put the source information in the beginning of the section, with the appropriate caveat statement.

We also deleted text that is inconsistent with the regulatory definition of adverse reactions (e.g., (b) (4)) and irrelevant text about the safety and effectiveness of (b) (4) (and not isotretinoin products).

Other Changes:

- Accepted the applicant's proposed addition of sexual dysfunction including erectile dysfunction and decreased libido to the ADVERSE REACTIONS section, as consultation with the Division of Bone, Reproductive and Urologic Products supported the addition to this section.
- In consultation with DPMH, added the information on isotretinoin's effect on ovarian reserve, submitted by the applicant, to subsection 8.3 Females and Males of Reproductive Potential, with the additional statement regarding the data limitations.
- Made content in HL consistent that of the FPI (e.g., for the Indications and Usage section), to be consistent with the I&U section draft labeling guidance.
- Placed information that appear between a section heading and a subsection heading (*floating* information that appeared in sections 2, 5, 6) to under a subsection heading. Floating information may be difficult to find when reviewing the labeling electronically. For example, for section 5, we moved the content of the floating information to subsections 5.1 and 5.14, to be also consistent with W&P section of labeling guidance, which indicates each "adverse reaction, syndrome, or group of reactions with a common pathogenesis (e.g., allergic contact dermatitis, maculopapular drug rash) included in the WARNINGS AND PRECAUTIONS section should have its own numbered subsection."
- Removed this subsection (b) (4) from the DRUG INTERACTION section because this section must contain clinically significant drug interactions with the subject drug (i.e., ABSORICA or ABSORICA LD) and not other drugs that are used concomitantly with the subject drug.
- Provide body weight (kg) in the weight tier-based dosing table using metric system alone, consistent with the recommendations by Institute for Safe Medication Practices and DMEPA. Using both "kg" and "pounds" for weight-based dosing has been associated with medication errors (the strength for the dosage form is already provided in the metric system).
- Reformatted the PEDIATRIC USE section to be consistent with the guidance for industry: *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling*.
- Used non-proprietary name "isotretinoin" when referring to isotretinoin products, as appropriate. Replaced (b) (4) with "another isotretinoin capsule product,"

(b) (4)

- Modified the PATIENT COUNSELING INFORMATION section to be consistent with the recommendations in the Patient Counseling Information section of labeling guidance (for example, to exclude intended for excluding information for healthcare providers but not patients from this section, include a concise and high-level elements of iPLEDGE that impact the patient and cross-referencing back to the W&P for more details.)
- Remove other redundancies from sections of the labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant is a member company in the Isotretinoin Products Manufacturers' Group and will market their product under the iPLEDGE REMS, the shared system REMS for isotretinoin. Sun is a member company in the iPLEDGE shared system REMS and submitted a full REMS proposal that includes a REMS document, Medication Guide, REMS supporting document, and all appended REMS materials

We recommend approval of the REMS for Absorica LD (NDA 211913), received on August 17, 2018, provided that the Patient Labeling Team in the Office of Medical Policy Initiatives determines the Medication Guide is adequate prior to the approval of the application.

13 Postmarketing Requirements and Commitment

No Postmarketing commitments or requirements are recommended at this time.

14 Division Director (Clinical) Comments

15 Appendices

15.1. References

Bhate, K and HC Williams, 2013, Epidemiology of acne vulgaris, Br J Dermatol, 168(3):474-485.
Peck, GL, TG Olsen, FW Yoder, JS Strauss, DT Downing, M Pandya, D Butkus, and J Arnaud-Battandier, 1979, Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid, N Engl J Med, 300(7):329-333.
Perkins, AC, J Maglione, GG Hillebrand, K Miyamoto, and AB Kimball, 2012, Acne vulgaris in women: prevalence across the life span, J Womens Health (Larchmt), 21(2):223-230.
Zaenglein, AL, AL Pathy, BJ Schlosser, A Alikhan, HE Baldwin, DS Berson, WP Bowe, EM Graber, JC Harper, and S Kang, 2016, Guidelines of care for the management of acne vulgaris, J Am Acad Dermatol, 74(5):945-973. e933.

15.2. Financial Disclosure

Financial disclosure forms were received from both principal investigators and the ten sub investigators. None of the investigators reported any proprietary or financial relationships with the Applicant.

Covered Clinical Study (Name and/or Number): 11440306

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not Applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S		

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

15.3. Nonclinical Pharmacology/Toxicology

Labeling Review

Recommended changes from the Applicant's proposed labeling are indicated below through use of strikeout (deletions) and underline (additions) fonts. The pharmacologic class for isotretinoin is retinoid. The human data concerning effects of isotretinoin on (b) (4) provided at the end of Section 13.1 should be moved to Section 8.3 to conform with the Pregnancy and Lactation Labeling Rule.

USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in patients exposed to isotretinoin during pregnancy. Any suspected fetal exposure during or 1 month after isotretinoin therapy (b) (4) immediately to the FDA via the MedWatch number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com).

(b) (4)

Risk Summary

ABSORICA LD (b) (4) contraindicated during pregnancy because isotretinoin can cause fetal harm when administered to a pregnant patient. There is an increased risk of major congenital malformations, spontaneous abortions, and premature births following isotretinoin exposure during pregnancy in humans. If (b) (4) drug is used during pregnancy, or if the patient becomes pregnant while taking (b) (4), the patient should be apprised of the potential hazard to a fetus.

(b) (4)

(b) (4)

If pregnancy (b) (4) occur during treatment of a patient who is taking ABSORICA LD, ABSORICA LD must be discontinued immediately and the patient should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Data

Human Data
Major congenital malformations that have been documented following isotretinoin exposure include malformations of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. External malformations include: skull; ear (including anotia, micropinna, small or absent external auditory canals); eye (including microphthalmia); facial dysmorphia and cleft palate. Internal abnormalities include: CNS (including cerebral and cerebellar malformations, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular; thymus gland; parathyroid hormone deficiency. In some cases death has occurred as a result of the malformations.

(b) (4)

Cases of IQ scores less than 85 with or without other abnormalities have been reported. An increased risk of spontaneous abortion and premature births have been (b) (4) with isotretinoin exposure during pregnancy.

(b) (4)

(b) (4)

Reviewer Note: (b) (4) *The remaining parts of 8.1 were reviewed by the clinical reviewer from DPMH.*

12.1 Mechanism of Action

(b) (4) ABSORICA/ABSORICA LD is a retinoid, which when administered at the recommended (b) (4) dosage (b) (4) *[see Dosage and Administration (2.1)]*, inhibits sebaceous gland function and keratinization. Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the dose and duration of treatment with isotretinoin capsules and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation. The exact mechanism of action of (b) (4) ABSORICA/ABSORICA LD in the treatment of severe recalcitrant nodular acne is unknown.

13 NONCLINICAL TOXICOLOGY

(b) (4)

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day [(1.3 (b) (4) or 5.3 times the recommended clinical ABSORICA dosage of 1 mg/kg/day (b) (4) or the recommended clinical ABSORICA LD dosage of 0.8 mg/kg/day (b) (4) respectively, after normalization for total body surface area]) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to (b) (4) humans (b) (4) is uncertain.

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative, while in the second laboratory, a weakly positive response (less than 1.6 ~~x~~times background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose response effect was seen, and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D7 assay, in vitro clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day [(0.3, 1.3, or 5.3 times the recommended clinical ABSORICA dosage of 1 mg/kg/day (b) (4) or the recommended clinical ABSORICA LD dosage of 0.8 mg/kg/day (b) (4)), respectively, after normalization for total body surface area]).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day [(10 or 30 times the recommended clinical ABSORICA dosage of 1 mg/kg/day (b) (4) or the recommended clinical ABSORICA LD dosage of 0.8 mg/kg/day (b) (4) respectively, after normalization for total body surface area]). In general, there was microscopic evidence for appreciable depression of spermatogenesis, but some sperm were observed in all testes examined, and in no instance were completely atrophic tubules seen.

(b) (4)

Reviewer's Comment: (b) (4)

13.2 Animal Toxicology

In rats given 8 or 32 mg/kg/day of isotretinoin [(1.3 (b) (4) or 5.3 times the recommended clinical ABSORICA dosage of 1 mg/kg/day or the recommended clinical ABSORICA LD dosage of (b) (4) 0.8 mg/kg/day, respectively, (b) (4) after normalization for total body surface area]) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day [(30 to 60 times the recommended clinical ABSORICA dosage of 1 mg/kg/day or the recommended clinical ABSORICA LD dosage of (b) (4)

(b) (4) 0.8 mg/kg/day (b) (4) respectively, after normalization for total body surface area]).

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Summary of Bioanalytical Method Validation and Performance
Isotretinoin in human plasma was quantified using a validated LC-MS/MS method. The method validation results are summarized in Table 9. The bioanalysis performance results are summarized in Table 10.

The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance. Incurred sample reanalysis for plasma samples were acceptable in terms of both sample size (at least 10% of the first 1000 samples and 5% of the remaining samples) and the results (>67% of the study samples evaluated within ± (b) (4)% of the original sample concentrations). All samples from Study 11440306 were analyzed within the established long-term stability window.

Table 9: Summary of LC-MS/MS Method Validation Results

Validation Report	NV 614/15
Matrix	Human plasma
Anticoagulant	Tripotassium Ethylene Diamine Tetra Acetic Acid (K_3EDTA)
Analyte	Isotretinoin
Internal standard (ISTD)	Isotretinoin D5
Linearity (calibration curve range)	0.996 ng/mL to 1503.934 ng/mL
LLOQ	0.996 ng/mL
Precision (% CV)	
Intra-day	0.73 to 14.19
Inter-day	1.06 to 11.98
Accuracy (% Nominal)	
Intra-day	93.23 to 97.00
Inter-day	93.91 to 97.30
Bench-top stability in human plasma	6.28 hours in ice cold water bath under red light condition
Bench-top stability during extraction	9.22 hours under red light condition
Sample collection process stability	2.57 hours in ice cold water bath under red light condition
In-injector stability	118.85 hours at 10.0 ± 1.0 °C
Stock solution stability	51 days (stored below -15°C protected from light) for both isotretinoin and isotretinoin d5

Short-term stability	Stable in ice cold water bath under red light condition for: • 9.23 hours (isotretinoin at LQC level) • 9.22 hours (isotretinoin at HQC level) • 9.22 hours (isotretinoin d5)
Long Term Storage Stability	214 days in human plasma stored below -50°C
Re-injection reproducibility	100.00 %

Abbreviations: LC-MS/MS = liquid chromatography tandem mass spectrometry, LLOQ = lower limit of quantification, LQC = low quality control, HQC = high quality control, ISTD = internal standard, RT = retention time

Table 10: Summary of Bioanalysis Performance Results

Relevant Clinical Trial	Study 11440306 (BE and Food Effect Study)
Bioanalytical method ID	NV 614/15
Matrix	Human plasma
Anticoagulant	Tripotassium Ethylene Diamine Tetra Acetic Acid (K_3EDTA)
Analyte	Isotretinoin
Internal standard	Isotretinoin D5
Linearity (calibration curve range)	0.997 ng/mL to 1498.192 ng/mL
Incurred Sample Reanalysis	
Total no. of incurred sample reanalysis	526 (7.85% of samples)
Total no. of sample whose % differences are within 20%	461
% of total no. of samples whose % differences are within 20 %	87.64
Duration from time sample was first drawn to date of last sample analysis including ISR	150 days
Actual sample storage temperature	• At clinical site: -80 ± 10 °C • At analytical sites: below -50 °C

Abbreviations: ISR = incurred sample reanalysis

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