

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021951Orig1s000

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: 21951
Supporting document/s: 33, 39 and 41
Applicant's letter date: 11/29/2011, 2/22/2012 and 3/16/2012
CDER stamp date: 11/29/2011, 2/22/2012 and 3/16/2012
Product: CIP Isotretinoin Capsules
Indication: Severe Recalcitrant Nodular Acne
Applicant: Cipher Pharmaceuticals
Review Division: Dermatology and Dental Products
Reviewer: Jiaqin Yao, PhD
Supervisor/Team Leader: Barbara Hill, PhD
Division Director: Susan Walker, MD
Project Manager: Matthew White

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21951 are owned by Cipher Pharmaceuticals or are data for which Cipher Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 21951 that Cipher Pharmaceuticals 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 21951.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	3
1.1	INTRODUCTION	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	3
1.3	RECOMMENDATIONS	3
2	DRUG INFORMATION	5
2.1	DRUG	5
2.2	RELEVANT INDs, NDAs, BLAs AND DMFs	5
2.3	DRUG FORMULATION	6
2.4	COMMENTS ON NOVEL EXCIPIENTS	6
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	6
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	6
2.7	REGULATORY BACKGROUND	6
3	STUDIES SUBMITTED	6
3.1	STUDIES REVIEWED	6
3.2	STUDIES NOT REVIEWED	7
3.3	PREVIOUS REVIEWS REFERENCED	7
11	INTEGRATED SUMMARY AND SAFETY EVALUATION	7
12	APPENDIX/ATTACHMENTS	7

1 Executive Summary

1.1 Introduction

Accutane (isotretinoin) was approved in the US for the treatment of severe recalcitrant nodular acne in 1982 and was discontinued in the US in 2009. Isotretinoin is currently available in the US under the generic brand names Amnesteem and Claravis. The sponsor is developing their Isotretinoin capsule formulation for the treatment of recalcitrant nodular acne under a 505(b)(2) regulatory pathway with Accutane as the listed drug.

1.2 Brief Discussion of Nonclinical Findings

The original submission and this resubmission did not contain any nonclinical studies. It has been determined by the clinical review team that an adequate clinical bridge has been generated to Accutane. This NDA relies on published data for isotretinoin as well as the Agency's findings of safety for the listed drug Accutane® (isotretinoin).

1.3 Recommendations

1.3.1 Approvability

This NDA is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The following wording is recommended for the nonclinical sections of the label:

HIGHLIGHTS

INDICATION AND USAGE

Trade Name is a retinoid indicated for the treatment of severe recalcitrant nodular acne (1).

8.1 Pregnancy

Pregnancy Category X. See *Contraindications* (4).

10 Overdosage

In humans, overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. These symptoms quickly resolve without apparent residual effects.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1 mg/kg/day, inhibits sebaceous gland function and keratinization. The exact mechanism of action of isotretinoin is unknown.

13 NONCLINICAL TOXICOLOGY

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 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.

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.

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. In studies of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving isotretinoin therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

13.2 Animal Toxicology

In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1.0 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 1.0 mg/kg/day, respectively, after normalization for total body surface area).

2 Drug Information

2.1 Drug

CAS Registry Number

4759-48-2

Generic Name

Isotretinoin

Code Name

CIP Isotretinoin

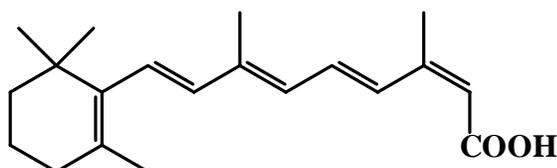
Chemical Name

13-*cis* retinoic acid, (2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid

Molecular Formula/Molecular Weight

C₂₀H₂₈O₂ / 300.44

Structure or Biochemical Description



Pharmacologic Class

Retinoid

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 64,927, NDA 18-662 (Accutane™, Hoffman-La Roche)

2.3 Drug Formulation

Ingredient	Amount per capsule (mg)			
	Strength 10 mg	Strength 20 mg	Strength 30 mg	Strength 40 mg
Isotretinoin, USP	10	20	30	40
Stearoyl macroglycerides (b) (4)	(b) (4)			
Soybean oil, USP				
Sorbitan monooleate, NF (Span 80)				
Propyl gallate, NF				
Total fill weight				

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

The recommended dosage range for Trade Name (CIP Isotretinoin) capsules is 0.5 to 1.0 mg/kg/day given orally in two divided doses without regard to meals for 15 to 20 weeks. Patients may require dose adjustments up to 2 mg/kg/day as tolerated.

2.7 Regulatory Background

The original NDA submission did not receive approval. The original NDA submission and the current NDA resubmission did not contain any nonclinical studies. This NDA relies on published data for isotretinoin as well as the Agency's findings of safety for the listed drug Accutane® (isotretinoin).

3 Studies Submitted

3.1 Studies Reviewed

The sponsor has not conducted any nonclinical studies with the drug substance/product. No nonclinical studies have been submitted within this NDA.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

This NDA relies on published data for isotretinoin (mainly a review paper by Kamm, J. Am Acad Dermatol, 6:652-659, 1982) as well as the Agency's findings of safety for the listed drug Accutane® (NDA 18-662, Hoffman-La Roche).

11 Integrated Summary and Safety Evaluation

Isotretinoin has been used in the US for the treatment of severe recalcitrant nodular acne since 1982. The sponsor has developed their isotretinoin capsule formulation under a 505(b)(2) regulatory pathway with Accutane as the listed drug. This NDA relies on published data for isotretinoin as well as the Agency's findings of safety for the listed drug Accutane® (isotretinoin).

The recommended dosage range for Trade Name (CIP Isotretinoin) capsules is 0.5 to 1.0 mg/kg/day given orally in two divided doses without regard to meals for 15 to 20 weeks. Patients may require dose adjustments up to 2 mg/kg/day as tolerated. However, the listed drug Accutane or its generic drug products are recommended to be administered at the same dosages with food in patients. It was shown that under the fed condition the systemic exposure (AUC or C_{max}) after administration of CIP Isotretinoin was slightly less than that after administration of Accutane. The systemic exposure after fasting administration of CIP Isotretinoin was greater than that after fasting administration of Accutane. However, the systemic exposure after fasting administration was less than that after fed administration of Accutane or CIP Isotretinoin. Therefore, there are no nonclinical safety issues for oral administration of CIP Isotretinoin. It has been determined by the clinical review team that an adequate clinical bridge has been generated to Accutane. Therefore, the sponsor can rely on the Agency's findings of safety for Accutane to support the safety of CIP Isotretinoin capsules. This NDA is approvable from a pharmacology/toxicology perspective.

12 Appendix/Attachments

The following wording was proposed in the nonclinical sections of the label by the sponsor. However, the Trade Name (b) (4) has not been accepted by the Agency.

HIGHLIGHTS

INDICATION AND USAGE

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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

/s/

JIAQIN YAO
04/10/2012

BARBARA A HILL
04/10/2012
I concur



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: **21-951**
SERIAL NUMBER: **000AZ**
DATE RECEIVED BY CENTER: **10/27/2006**
DRUG NAME: **CIP Isotretinoin Capsules**
INDICATION: **Severe Recalcitrant Nodular Acne**
SPONSOR: **Cipher Pharmaceuticals**
REVIEW DIVISION: **Division of Dermatological and Dental
Products (DDDP)**
PHARM/TOX REVIEWER: **Jiaqin Yao, Ph.D**
PHARM/TOX SUPERVISOR: **Paul Brown, Ph.D.**
DIVISION DIRECTOR: **Susan Walker, M.D.**
PROJECT MANAGER: **Melinda Harris-Bauerlien**

Date of review submission to Division File System (DFS): 4-23-2007

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-951

Review number: 2

Sequence number/date/type of submission: 000 / 10-27-06 / AZ

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Cipher Pharmaceuticals

Manufacturer for drug substance: (b) (4)

Reviewer name: Jiaqin Yao

Division name: Division of Dermatological and Dental Products

HFD #: HFD-540

Review completion date: 4-23-2007

Drug:

Trade name: CIP-ISOTRETINOIN capsules, 10, 20, and 30 mg

Generic name: Isotretinoin

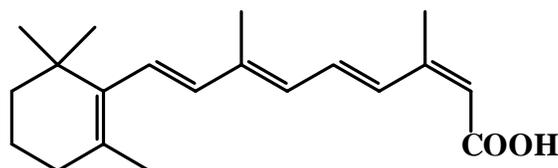
Code name: NA

Chemical name: 13-*cis* retinoic acid, (2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid

CAS registry number: 4759-48-2

Molecular formula/molecular weight: C₂₀H₂₈O₂ / 300.44

Structure:



Relevant INDs/NDAs/DMFs: IND 64,927, NDA 18-662 (Accutane™, Hoffman-La Roche)

Drug class: Retinoid

Indication: Severe recalcitrant nodular acne

Clinical formulation:

Ingredient	Amount per capsule (mg)		
	Strength 10 mg	Strength 20 mg	Strength 30 mg
Isotretinoin, USP	10	20	30
Stearoyl macrogolglycerides (b) (4)	(b) (4)		
Soybean oil, USP			
Sorbitan monooleate, NF (Span 80)			
Propyl gallate, NF			
Total fill weight			

Route of administration: Oral

Proposed use: The recommended dosage range for CIP-ISOTRETINOIN capsules is 0.5 to 1.0 mg/kg/day given orally in two divided doses with food for 15 to 20 weeks. Patients may require dose adjustments up to 2 mg/kg/day as tolerated.

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

Overall conclusions and recommendations

This NDA was originally not approved. The original submission and this resubmission did not contain any nonclinical studies. The NDA relies on published data for isotretinoin (mainly a review paper by Kamm, J. Am Acad Dermatol, 6:652-659, 1982) as well as the Agency's findings for the listed drug Accutane® (isotretinoin). The nonclinical information in the proposed labeling is taken entirely from the listed drug Accutane®. The sponsor's annotated labeling did not refer to the literature. The proposed labeling contains some information not found in the literature.

If the sponsor conducted an adequate clinical bridging study to the listed drug Accutane, then the Agency's findings of safety for Accutane would be adequate to support the nonclinical needs of this NDA since the relevant nonclinical studies would have been conducted at sufficiently high doses to cover the exposure from the new drug.

However, if it is determined that there was not a valid clinical bridging study to the listed drug Accutane then the sponsor can not refer to the Agency's finding of safety for Accutane and complete nonclinical information would need to be provided from other sources. The submitted literature information is summary in nature and does not alone provide sufficient detail to support the nonclinical informational needs of the NDA. In addition, in the absence of the clinical bridge, the proposed labeling is not supported because some of the information appears to only be available from the Accutane labeling.

It appears from the Clinical and the Clinical Pharmacology and Biopharmaceutics reviews that an adequate clinical bridge has not been established between the CIPHER

product and Accutane. Therefore, the Agency's finding of safety for Accutane can not be used in support of NDA 21-951.

Because of the lack of the clinical bridge and adequate literature, the NDA is not approvable from a pharm/tox perspective. For approval, the sponsor would have to:

- a. provide complete nonclinical data either from the literature or from studies conducted by themselves;
- b. provide a right of reference to the nonclinical data from the holder of the Accutane NDA; or
- c. establish an adequate clinical bridge to a listed product (e.g. Accutane).

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

cc: list:

- DDDP/CSO/BauerlienM
- DDDP/Pharm. Sup./BrownP
- OTS/OCP/DCP3/Clin. Biopharm/Bashaw
- DDDP/MO/CookD
- DDDP/TL/LukeM
- DDDP/DDD/KukichS
- DDDP/DD/WalkerSU

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

/s/

Jiaqin Yao
4/23/2007 08:14:52 PM
PHARMACOLOGIST

Paul Brown
4/24/2007 08:50:38 AM
PHARMACOLOGIST

Susan Walker
4/25/2007 11:27:29 AM
DIRECTOR



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: **21-951**
SERIAL NUMBER: **000**
DATE RECEIVED BY CENTER: **07/01/2005**
DRUG NAME: **CIP Isotretinoin Capsules**
INDICATION: **Severe Recalcitrant Nodular Acne**
SPONSOR: **Cipher Pharmaceuticals**
DOCUMENTS REVIEWED: **Vol. 1.1 - 1.5**
REVIEW DIVISION: **Division of Dermatological and Dental
Products (HFD-540)**
PHARM/TOX REVIEWER: **Jiaqin Yao, Ph.D**
PHARM/TOX SUPERVISOR: **Paul Brown, Ph.D.**
ACTING DIVISION DIRECTOR: **Stanka Kukich, M.D.**
PROJECT MANAGER: **Melinda Harris-Bauerlien**

Date of review submission to Division File System (DFS): 4-18-2006

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-951

Review number: 1

Sequence number/date/type of submission: 000 / 6-27-2005 / Original submission

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Cipher Pharmaceuticals

Manufacturer for drug substance: (b) (4)

Reviewer name: Jiaqin Yao

Division name: Division of Dermatological and Dental Products

HFD #: HFD-540

Review completion date: 4-18-2006

Drug:

Trade name: CIP-ISOTRETINOIN capsules, 10, 20, and 30 mg

Generic name: Isotretinoin

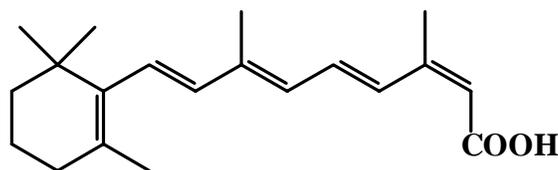
Code name: NA

Chemical name: 13-*cis* retinoic acid, (2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid

CAS registry number: 4759-48-2

Molecular formula/molecular weight: C₂₀H₂₈O₂ / 300.44

Structure:



Relevant INDs/NDAs/DMFs: IND 64,927, NDA 18-662 (Accutane™, Hoffman-La Roche)

Drug class: Retinoid

Indication: Severe recalcitrant nodular acne

Clinical formulation:

Ingredient	Amount per capsule (mg)		
	Strength 10 mg	Strength 20 mg	Strength 30 mg
Isotretinoin, USP	10	20	30
Stearoyl macrogolglycerides (b) (4)	(b) (4)		
Soybean oil, USP			
Sorbitan monooleate, NF (Span 80)			
Propyl gallate, NF			
Total fill weight			

Route of administration: Oral

Proposed use: The recommended dosage range for CIP-ISOTRETINOIN capsules is 0.5 to 1.0 mg/kg/day given orally in two divided doses with food for 15 to 20 weeks. Patients may require dose adjustments up to 2 mg/kg/day as tolerated.

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

Overall conclusions and recommendations

Cipher Pharmaceuticals has not conducted any nonclinical studies on CIP Isotretinoin Capsules and relies on published data for isotretinoin as well as the Agency’s findings for the listed drug Accutane® (isotretinoin). Both CIP Isotretinoin and Accutane are recommended to be administered with a meal. It was shown that under the fed condition the systemic exposure (AUC or C_{max}) after administration of CIP Isotretinoin was slightly less than that after administration of Accutane. Although under the fasted condition the systemic exposure after administration of CIP Isotretinoin was greater than that after administration of Accutane, the systemic exposure under the fasted condition was less than that under the fed condition after administration of Accutane or CIP Isotretinoin.

In addition, (b) (4) is one of the excipients in NORVIR (NDA 20-680). The daily dosage recommended of (b) (4) in NORVIR is 3.12 g [600 mg Ritonavir × 2/day ÷ 100 mg Ritonavir/capsule × 260 mg (b) (4) capsule], higher than the daily dosage from CIP Isotretinoin (2 mg/kg/day × 60 kg × 120 mg ÷ 10 mg = 1.44 g/day).

While there may be clinical issues around the safe use of this drug product due to its biopharmaceutical differences to Accutane, there are no nonclinical safety issues and so from a pharmacology/toxicology perspective, this NDA is approvable.

Suggested labeling: Refer to the labeling of the listed drug Accutane®.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

cc: list:

HFD-540/CSO/BauerlienM

HFD-540/Pharm. Sup./BrownP

HFD-540/MO/CookD

HFD-540/TL/LukeM

HFD-540/ADD/KukichS

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

/s/

Jiaqin Yao
4/18/2006 10:38:27 AM
PHARMACOLOGIST

Paul Brown
4/18/2006 11:11:14 AM
PHARMACOLOGIST