CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-107

Korlym™ (Mifepristone) Tablets

Corcept Therapeutics

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

(Clinical Review Division: DMEP)

Table of Contents

Comment [Note1]:
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To automatically have MSWord update the Table of Contents with the correct pagination, Click once anywhere in the Table of Contents (the Table of Contents should now be shaded) and then press either the F9 key or Alt+Shift+U

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. **NDA:** 202-107

2. **REVIEW #:** 2

3. **REVIEW DATE:** 17-Jan-2012

4. **REVIEWER:** Xavier Ysern

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
--	--

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	15-Apr-2011
Amendment (Proprietary name)	19-Apr-2011
Amendment (Labeling/ Package Insert and Container-Carton)	25-Apr-2011

7. **NAME & ADDRESS OF APPLICANT**

Name: Corcept Therapeutics
Address: 149 Commonwealth Dr., Menlo Park, CA 94025
Representative: Luana Staiger
Telephone: 650 678 7230 (email: lstaiger@corcep.com)

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Korlym™ (mifepristone) Tablets
b) Non-Proprietary Name (USAN): Mifepristone
c) Code Name/# --
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: Type 5 – New Formulation
- Submission Priority:

(b) (4)

9. **LEGAL BASIS FOR SUBMISSION:** 505(b)(2)

10. **PHARMACOL. CATEGORY** Synthetic steroid, Progesterone receptor antagonist
[To reduce the effects of hypercortisolism in patients with endogenous Cushing's Syndrome.]

Comment [Note2]:
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Comment [Note16]:
Refer to FDA Form 356h or available references.

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11. **DOSAGE FORM**: Tablet

12. **STRENGTH/POTENCY**: 300 mg

13. **ROUTE OF ADMINISTRATION**: Oral

14. **Rx/OTC DISPENSED**: Rx

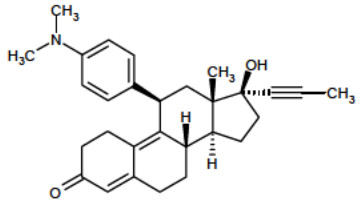
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)** Not a SPOTS product

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT**:

Mifepristone
Roussel Uclaf company name: RU486
Formula: $C_{29}H_{35}NO_7$

MW: 429.60 g/mol

CAS #: 84371-65-3



11β-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (IUPAC name)

17. **RELATED/SUPPORTING DOCUMENTS**

A. DMFs:

DMF #	Holder	Item Referenced	Code[1]	Status[2]	Review Completed	LOA d
(b) (4)			1	Adequate	29-Dec-2011	11-Mar-2
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Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION #	DESCRIPTION
IND	(b) (4)	Mifepristone
IND	76,480	Corcept Therapeutics' Corlux (mifepristone) Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable	12-Jan-2012	
Pharm/Tox	--		
Biopharm	--		
DMEPA	Tradename "Korlym" acceptable	21-Oct-2011	Carol Holquist, RPh
Methods Validation	Revalidation by Agency laboratories is not recommended		
EA	Acceptable		Part of this review
Microbiology	N.A.		

DMEPA: Division of Medication Error Prevention and Risk Management.

Comment [Note26]:

The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

The Chemistry Review for NDA 202-107

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC point of view this application is recommended for APPROVAL. All pending issues have been satisfactorily resolved.

Based on the stability data submitted, an expiry of 24 months for drug product packaged in HDPE bottles (b) (4) is granted under the recommended storage conditions: Store at 25 C (77 F); excursions permitted to 15-30 C (59-86 F) [see USP Controlled Room Temperature]. Protect from moisture.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- **Drug Substance** Mifepristone

Mifepristone, chemical name 11β-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (IUPAC name), molecular formula $C_{29}H_{35}NO_7$ and molecular weight 429.60 g/mol, is the drug substance of the drug product Korlym™ Tablets. Mifepristone is a synthetic steroid belonging to the class of compounds/medications known as antiprogestational steroids. It is a progesterone and cortisol antagonist, and exerts its physiological action by blocking the activity of progesterone and glucocorticoid (GR-II) receptors. Mifepristone, formerly known as RU486 9 (code name given by Ruussel-Ucraf), is the active ingredient of the widely used and approved oral tablets for medical abortion. In this application, mefipristone is proposed to reduce the effects of hypercortisolism in patients with endogenous Cushing's Syndrome.

Mifepristone drug substance is synthesized for Corcept (b) (4) has submitted DMF (b) (4) for (b) (4) (mifepristone) and has authorized that their DMF may be referenced for this application (letter of authorization (LOA) dated 11-Mar-2011). The drug substance (DS) is (b) (4) for Corcept (b) (4). Details of the synthesis and manufacturing process for Mifepristone are referred to (b) (4) confidential information under DMF (b) (4). Its structure and physicochemical properties, well described in DMF (b) (4), are well known in the scientific literature. The aqueous solubility is pH dependent, with a sharp decline in solubility between pH 1.5 – 2.0. At pH values above 2.5, the solubility of mifepristone is less than 0.5 mg/mL. According to the Bipharmaceutics Classification System (BCS), mifepristone is a class 2 compound (high permeability, low solubility).

Mifepristone employed for the manufacture of Korlym™ (mifepristone) Tablets has an appearance of a (b) (4) powder (visual). The DS complies with IR and HPLC based identity tests, specific optical rotation and melting point criteria, with (b) (4) w/w content. Regarding purity, estimated by HPLC, the content of the known impurity (b) (4) of mifepriostone is not more than (NMT) (b) (4) individual unspecified impurities are requred to be below (b) (4) the amount of total unspecified impurities cannot exceed (b) (b), and the total amount of impurities ((b) (4) is NMT (b) (4) (b) (4) Residua (b) (4) requirements are NMT (b) (4) and NMT (b) (4) respectively. Particle size distribution complies with (b) (4) NMT (b) (4)

Comment [Note27]:
The primary reviewer should write the Chemistry Executive Summary with the following objectives in mind:
1 To meet the needs of a multiple audience of internal Chemistry management, Team Leaders, Reviewers, Clinical Division Directors, ODE Directors, Office Directors, or others with signatory responsibility This will be especially important when looking back historically on a review decision It can also serve to communicate Chemistry concerns to other CDER disciplines
2 To provide a brief account (1-2 pages) of the important aspects of quality of the drug substance and drug product
3 To discuss any unique scientific and regulatory issues that had a significant effect on the review decision (e g , concerns surrounding a stability issue, an acceptance criteria, dissolution testing, special dosage forms, impurity, stereochemistry)
4 To describe the attributes of the drug product that can affect safety ... [18]

Comment [Note28]:
You should state whether your recommendation is approval, approvable or not approvable from a chemistry review perspective.

Comment [Note29]:
This summary is intended to pull together all the assessments and conclusions made during the chemistry review(s) This summary serves as both an orientation to the review and a stand-alone document communicating the important findings without reiterating the assessment The summary should be a *bottom-line* document without equivocation and should be written in plain language appropriate for educated lay as well as technical audiences The information requested below should be included since the reviewer is expected to be ab ... [19]

Comment [Note30]:
•Describe the drug product (name(s), strength(s)/potency, dosage form, sterile, indication, and how it is packaged)
•Describe the drug substance(s) (e g , USAN, retest date) Identify and describe key physicochemical (e g , particle size distribution, solubility, morphic form) and biological properties that can influence batch reproducibility, product performance and/or drug product quality The type and extent of issues will vary with the uniqueness and complexity of the drug substance
•Describe the formulation and d ... [20]

(b) (4) mifepristone is packaged in (b) (4) bags, each bag individually sealed and placed within secondary packaging (b) (4).

Over the 24 months of the stability completed to date, no significant changes to appearance, assay, impurities, particle size, or moisture content were seen during storage at either the accelerated or room temperature storage conditions. (b) (4) mifepristone which is intended for commercial mifepristone tablet production will be retested (b) (4). No additional stability studies will be conducted on (b) (4) mifepristone.

[During the review of original DMF (b) (4), a request for additional information was send to the Holder of DMF (b) (4). All Agency requests were answered satisfactory by the Holder of the DMF in their Amendment dated 27-Dec-2011 (details referred to DMF (b) (4) CMC Reviews 1 and 2, dated 06-Oct-2011 and 29-Dec-2011 respectively).]

- **Drug Product** Korlym™ (mifepristone) Tablets

Korlym™ (Mifepristone) Tablets are immediate release tablets containing 300 mg of the active component mifepristone. Korlym™ Tablets are light yellow to yellow, oval, film coated tablets debossed with "CORCEPT" on one side and "300" on the other.

(b) (4)

The coated tablets are packaged into one of two packaging configurations, a 28-count bottle with (b) (4) child resistant closure, or a 280-count bottle with (b) (4) child resistant closure.

Tablets are formulated to contain 300 mg of (b) (4) mifepristone (active ingredient), (b) (4) sodium starch glycolate NF (b) (4) hydroxypropylcellulose NF (b) (4) silicified microcrystalline cellulose (b) (4) sodium lauryl sulfate (b) (4) magnesium stearate (b) (4), and (b) (4) film coating, (b) (4). All excipients, (b) (4) meet compendial requirements. *[Notice that the content of mifepristone, the active component, is almost (b) (4) % of the weight of the tablets.]*

Drug product specifications include appearance (visual examination), identification (HPLC), assay (HPLC), impurities (HPLC), dissolution, content uniformity, water content and microbial limits. Regarding impurities, the acceptance criteria require that individual impurities to be not more than (NMT (b) (4) each, and that the total impurity content not to exceed (b) (4)

Included in the submission are 9 months of data on the primary stability batches as well as up to 24 months long-term data available on supportive batches. Only occasional unidentified impurities were noted during all thermal studies. None of these were reported at levels higher than the proposed commercial acceptance criterion of ≤ (b) (4)

The drug product has been shown to be stable to light and UV exposure without any packaging and, therefore, the primary packaging configurations (28-count and 280-count bottles) are appropriate for the product. No secondary packaging is required for light protection and the product does not require labeling to indicate light protection is required.

The primary impurity found in the drug product is (b) (4) . This impurity did not increase under accelerated conditions of 40 C/75 % RH, at 25 C/60 % RH, or in the photostability study. This demonstrates that this impurity is not a degradation product and a specification for it in the drug product is not required.

Based on the overall assessment of the results for real time and accelerated conditions for the thermal stability studies for the primary stability batches and for the supportive stability batches, as well as the photostability study, a shelf life of 2 years is proposed for Korlym™ Tablets.

[During the review of the drug product section, a request for additional information was send to the holder of DMF (b) (4). After Amendment dated 27-Dec-2011, the information pertaining (b) (4) was deemed acceptable (details referred to DMF (b) (4) CMC Review 1, dated 05-Jan-2012).]

B. Description of How the Drug Product is Intended to be Used

The drug Product, Korlym™ Tablets, which contains the active component mifepristone, an active cortisol receptor blocker, is indicated to treat the clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome. The drug product is intended to be used orally as a single daily dose. Based on assessment of clinical response and tolerability, the starting dose of 300 mg once daily, may be increased to 600 mg once daily. Further escalation in 300-mg increments to a maximum of 1200 mg once daily may be appropriate in some patients, with increased monitoring for risk factors associated with the drug (see patient package insert). (b) (4) tablets should always be taken with a meal.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent DMFs amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf life.

Comment [Note31]:

Describe the relationship of the recommended dose to the amount of drug product supplied (e g , multiple-dose container, pharmacy bulk package) Describe any unusual preparation of dose prior to administration and indicate any incompatibilities of the drug product with reconstitution diluents or dosage devices List the dosing schedule, proposed strength(s), and maximum daily dose Identify the expiration dating period and recommended storage conditions

Comment [Note32]:

State the reasons for the recommendation If the application is not approval, cite the major chemistry issues and include a discussion of their relationship to the safety and quality of the drug product Include any risk management steps taken

Executive Summary Section

III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 17-Jan-2012

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief, ONDQA/ DNDQA III/ Branch VII Date: 17-Jan-2012

C. CC Block

Jena M. Weber Project Manager, OND/ ODE II/ DMEP

Comment [Note33]:
For ONDC, the signatures are captured electronicly in DFS

Comment [Note34]:
•ONDC: In DFS
•OGD:
ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

Comment [Note35]:

•ONDC: Each chemistry team can decide who should be copied in DFS
•OGD:
cc:
Original ANDA ##-###
HFD-###/Division File/NDA ##-###

10 PAGES 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/

XAVIER J YSERN
01/17/2012
All CMC pending issues have been satisfactorily resolved

SUONG T TRAN
01/17/2012
For Ali Al Hakim, Branch Chief

NDA 202-107

Korlym™ (Mifepristone) Tablets

Corcept Therapeutics

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

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2. **REVIEW #:** 1

3. **REVIEW DATE:** 10-Jan-2012

4. **REVIEWER:** Xavier Ysern

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
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Amendment (Labeling/ Package Insert and Container-Carton)	25-Apr-2011

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Name: Corcept Therapeutics
Address: 149 Commonwealth Dr., Menlo Park, CA 94025
Representative: Luana Staiger
Telephone: 650 678 7230 (email: lstaiger@corcep.com)

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a) Proprietary Name: Korlym™ (mifepristone) Tablets
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c) Code Name/# --
d) Chem. Type/Submission Priority (ONDC only):
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- Submission Priority:

(b) (4)

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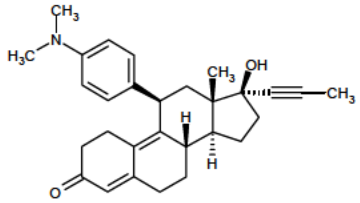

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EES	Pending		
Pharm/Tox	--		
Biopharm	--		
DMEPA	Tradename "Korlym" acceptable	21-Oct-2011	Carol Holquist, RPh
Methods Validation	Revalidation by Agency laboratories is not recommended		
EA	Acceptable		Part of this review
Microbiology	N.A.		

DMEPA: Division of Medication Error Prevention and Risk Management.

Comment [Note26]:

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The Executive Summary

I. Recommendations

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B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

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A. Description of the Drug Product(s) and Drug Substance(s)

- **Drug Substance** Mifepristone

Mifepristone, chemical name 11β-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (IUPAC name), molecular formula $C_{29}H_{35}NO_7$ and molecular weight 429.60 g/mol, is the drug substance of the drug product Korlym™ Tablets. Mifepristone is a synthetic steroid belonging to the class of compounds/medications known as antiprogestational steroids. It is a progesterone and cortisol antagonist, and exerts its physiological action by blocking the activity of progesterone and glucocorticoid (GR-II) receptors. Mifepristone, formerly known as RU486 9 (code name given by Ruussel-Ucraf), is the active ingredient of the widely used and approved oral tablets for medical abortion. In this application, mefipristone is proposed to reduce the effects of hypercortisolism in patients with endogenous Cushing's Syndrome.

Mifepristone drug substance is synthesized for Corcept (b) (4) has submitted DMF # (b) (4) for (b) (4) (mifepristone) and has authorized that their DMF may be referenced for this application (letter of authorization (LOA) dated 11-Mar-2011). The drug substance (DS) is (b) (4) for Corcept (b) (4). Details of the synthesis and manufacturing process for Mifepristone are referred to (b) (4) confidential information under DMF (b) (4). Its structure and physicochemical properties, well described in DMF (b) (4), are well known in the scientific literature. The aqueous solubility is pH dependent, with a sharp decline in solubility between pH 1.5 – 2.0. At pH values above 2.5, the solubility of mifepristone is less than 0.5 mg/mL. According to the Bipharmaceutics Classification System (BCS), mefipristone is a class 2 compound (high permeability, low solubility).

Mifepristone employed for the manufacture of Korlym™ (mifepristone) Tablets has an appearance of a (b) (4) (visual). The DS complies with IR and HPLC based identity tests, specific optical rotation and melting point criteria, with (b) (4) w/w content. Regarding purity, estimated by HPLC, the content of the known impurity (b) (4) of mifepriostone is not more than (NMT (b) (4) individual unspecified impurities are requred to be below (b) (4) the amount of total unspecified impurities cannot exceed (b) (4) and the total amount of impurities (b) (4) is NMT (b) (4) (b) (4). Residual (b) (4)) requirements are NMT (b) (4) and NMT (b) (4) respectively. Particle size distribution complies with (b) (4)) NMT (b) (4)

Comment [Note27]:
The primary reviewer should write the Chemistry Executive Summary with the following objectives in mind:
1 To meet the needs of a multiple audience of internal Chemistry management, Team Leaders, Reviewers, Clinical Division Directors, ODE Directors, Office Directors, or others with signatory responsibility This will be especially important when looking back historically on a review decision It can also serve to communicate Chemistry concerns to other CDER disciplines
2 To provide a brief account (1-2 pages) of the important aspects of quality of the drug substance and drug product
3 To discuss any unique scientific and regulatory issues that had a significant effect on the review decision (e g , concerns surrounding a stability issue, an acceptance criteria, dissolution testing, special dosage forms, impurity, stereochemistry)
4 To describe the attributes of the drug product that can affect safety ... [18]

Comment [Note28]:
You should state whether your recommendation is approval, approvable or not approvable from a chemistry review perspective.

Comment [Note29]:
This summary is intended to pull together all the assessments and conclusions made during the chemistry review(s) This summary serves as both an orientation to the review and a stand-alone document communicating the important findings without reiterating the assessment The summary should be a *bottom-line* document without equivocation and should be written in plain language appropriate for educated lay as well as technical audiences The information requested below should be included since the reviewer is expected to be ab ... [19]

Comment [Note30]:
•Describe the drug product (name(s), strength(s)/potency, dosage form, sterile, indication, and how it is packaged)
•Describe the drug substance(s) (e g , USAN, retest date) Identify and describe key physicochemical (e g , particle size distribution, solubility, morphic form) and biological properties that can influence batch reproducibility, product performance and/or drug product quality The type and extent of issues will vary with the uniqueness and complexity of the drug substance
•Describe the formulation and d ... [20]

(b) (4) mifepristone is packaged in food grade double polyethylene bags, each bag individually sealed and placed within secondary packaging (b) (4)

Over the 24 months of the stability completed to date, no significant changes to appearance, assay, impurities, particle size, or moisture content were seen during storage at either the accelerated or room temperature storage conditions. (b) (4) mifepristone which is intended for commercial mifepristone tablet production will be retested (b) (4). No additional stability studies will be conducted on (b) (4) mifepristone.

[During the review of original DMF (b) (4), a request for additional information was send to the Holder of DMF (b) (4). All Agency requests were answered satisfactory by the Holder of the DMF in their Amendment dated 27-Dec-2011 (details referred to DMF (b) (4) CMC Reviews 1 and 2, dated 06-Oct-2011 and 29-Dec-2011 respectively).]

- **Drug Product** Korlym™ (mifepristone) Tablets

Korlym™ (Mifepristone) Tablets are immediate release tablets containing 300 mg of the active component mifepristone. Korlym™ Tablets are light yellow to yellow, oval, film coated tablets debossed with "CORCEPT" on one side and "300" on the other.

(b) (4)

The coated tablets are packaged into one of two packaging configurations, a 28-count bottle with (b) (4) child resistant closure, or a 280-count bottle with (b) (4) child resistant closure.

Tablets are formulated to contain 300 mg of (b) (4) mifepristone (active ingredient), (b) (4) sodium starch glycolate NF (b) (4) hydroxypropylcellulose NF (b) (4) silicified microcrystalline cellulose (b) (4) sodium lauryl sulfate (b) (4) magnesium stearate (b) (4) and (b) (4) film coating, (b) (4) All excipients, (b) (4) meet compendial requirements. *[Notice that the content of mifepristone, the active component, is almost (b) (4) % of the weight of the tablets.]*

Drug product specifications include appearance (visual examination), identification (HPLC), assay (HPLC), impurities (HPLC), dissolution, content uniformity, water content and microbial limits. Regarding impurities, the acceptance criteria require that individual impurities to be not more than (NMT) (b) (4) each, and that the total impurity content not to exceed (b) (4)

Included in the submission are 9 months of data on the primary stability batches as well as up to 24 months long-term data available on supportive batches. Only occasional unidentified impurities were noted during all thermal studies. None of these were reported at levels higher than the proposed commercial acceptance criterion of ≤ (b) (4)

The drug product has been shown to be stable to light and UV exposure without any packaging and, therefore, the primary packaging configurations (28-count and 280-count bottles) are appropriate for the product. No secondary packaging is required for light protection and the product does not require labeling to indicate light protection is required.

The primary impurity found in the drug product is (b) (4) . This impurity did not increase under accelerated conditions of 40 C/75 % RH, at 25 C/60 % RH, or in the photostability study. This demonstrates that this impurity is not a degradation product and a specification for it in the drug product is not required.

Based on the overall assessment of the results for real time and accelerated conditions for the thermal stability studies for the primary stability batches and for the supportive stability batches, as well as the photostability study, a shelf life of 2 years is proposed for (b) (4) Tablets.

[During the review of the drug product section, a request for additional information was send to the holder of DMF (b) (4). After Amendment dated 27-Dec-2011, the information pertaining the (b) (4) was deemed acceptable (details referred to DMF (b) (4) CMC Review 1, dated 05-Jan-2012).]

B. Description of How the Drug Product is Intended to be Used

The drug Product, (b) (4) Tablets, which contains the active component mifepristone, an active cortisol receptor blocker, is indicated to treat the clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome. The drug product is intended to be used orally as a single daily dose. Based on assessment of clinical response and tolerability, the starting dose of 300 mg once daily, may be increased to 600 mg once daily. Further escalation in 300-mg increments to a maximum of 1200 mg once daily may be appropriate in some patients, with increased monitoring for risk factors associated with the drug (see patient package insert). (b) (4) tablets should always be taken with a meal.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent DMFs amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf life.

Comment [Note31]:

Describe the relationship of the recommended dose to the amount of drug product supplied (e g , multiple-dose container, pharmacy bulk package) Describe any unusual preparation of dose prior to administration and indicate any incompatibilities of the drug product with reconstitution diluents or dosage devices List the dosing schedule, proposed strength(s), and maximum daily dose Identify the expiration dating period and recommended storage conditions

Comment [Note32]:

State the reasons for the recommendation If the application is not approval, cite the major chemistry issues and include a discussion of their relationship to the safety and quality of the drug product Include any risk management steps taken

Executive Summary Section

III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 10-Jan-2012

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief, ONDQA/ DNDQA III/ Branch VII Date: 10-Jan-2012

C. CC Block

Jena M. Weber Project Manager, OND/ ODE II/ DMEP

Comment [Note33]:
For ONDC, the signatures are captured electronicly in DFS

Comment [Note34]:
•ONDC: In DFS
•OGD:
ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

Comment [Note35]:

•ONDC: Each chemistry team can decide who should be copied in DFS
•OGD:
cc:
Original ANDA ##-###
HFD-###/Division File/NDA ##-###

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

/s/

XAVIER J YSERN
01/12/2012

ALI H AL HAKIM
01/12/2012
I concur

Initial Quality/CMC Assessment
ONDQA

Division of Metabolism and Endocrinology Products

NDA:	**202107**
Applicant:	Corcept Therapeutics
Stamp Date:	18-APR-2011
PDUFA Date:	**18-FEB-2012**
Proposed Proprietary Name:	(b) (4)
Established Name:	Mifepristone
Dosage form and strength:	Immediate release tablet 300 mg
Route of Administration:	Oral administration
Indications:	Treatment of hypercortisolism associated with Cushing's Syndrome
CMC Lead:	Su **(**Suong) Tran, ONDQA
ONDQA Fileability:	**Yes**

Are there comments for the 74-day letter? Yes.

- **Confirm that the formulations coded "E2" in the Clinical Summary (section 2.7.1) and "C2" in the Quality Summary (sec2.3.P.2) are the same and are the final formulation for the commercial product.**
- **Submit the master batch records for the drug product manufacture per 21 CFR 314.54(a)(1)(i).**

CONSULTS/ CMC RELATED REVIEWS	COMMENT
CBER	*Not applicable*
CDRH	*Not applicable*
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
Compliance (DMPQ)	EER was sent to Compliance by ONDQA PM (K. Sharma) *on 02-MAY-2011.*
Methods Validation	*Validation may be requested of FDA labs after test methods are finalized.*
Microbiology	*Not applicable.* The product is a solid oral dosage form.
OBP	*Not applicable*
ONDQA Biopharm	Review of all dissolution/drug release-related information. *(Reviewer: M. Hughes)*
OSE	*Labeling consult request will be sent as part of DMEP's request.*
Pharm/Tox	*Not applicable* (Impurities and degradants limits are within ICH qualification thresholds for the maximum daily dose.)
QbD	*Not applicable*

This is a paper NDA, filed as a 505(b)(2) application, with the listed drug (LD) being Mifeprex (mifepristone) Tablets (different applicant). The new NDA is relying on FDA's findings of safety for the LD.

Note to chemists: the reference to the RLD is for the reliance on FDA's findings of safety and/or effectiveness only, not for any CMC purpose.

Reference is made to the DMF (b) (4) for the CMC information on the drug substance.

The product will be packaged in 28-count and 280-count bottles with desiccant. The product is stored at room temperature.

Maximum daily dose is 1200 mg mifepristone.

Has all information requested during the IND phases, and at the pre-NDA meetings been included?
Yes. The primary reviewer will assess the information in the NDA and decide whether issues previously raised have been satisfactorily addressed. The reviewer will also confirm that information previously agreed upon by FDA and the sponsor has not been changed in its final version in the NDA (for example, specifications, packaging systems, etc.)

Drug substance:

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2.3.S.1.1 Nomenclature (Mifepristone, (b) (4))

Recommended International Non-Proprietary Name (INN): Mifepristone

Chemical name:

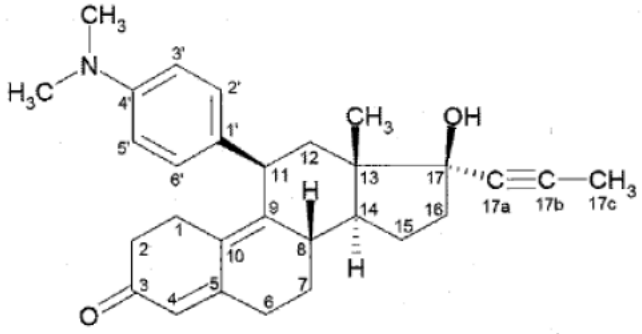
IUPAC: 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)estra-4,9-dien-3-one

Chemical Abstracts name: (11β, 17β)-11[(4-dimethylaminophenyl)]-17β-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one

CAS Number: 84371-65-3

Code names: (b) (4), C-1073, RU38486, EP10778

2.3.S.1.2 Structure (Mifepristone, (b) (4))



Molecular formula: $C_{29}H_{35}NO_2$

Molecular mass: 429.58

Review comments:

Reference is made to the DMF (b) (4) for all CMC information on the drug substance. The primary reviewer will review any new information in the DMF submitted after the most recent review.

Manufacturing site. One drug substance batch (53041S002) was manufactured at the commercial site (b) (4). This batch was used in the safety and efficacy study C-1073-400 and other clinical studies (C-1073-415, C-1073-425, C-1073-26, and C-1073-19).

(b) (4)

Specification. The drug substance specification is included in the NDA and copied on the next pages.

(b) (4)

- Chirality of the compound is controlled by Specific Rotation, which will be evaluated by the reviewer for its adequacy.
- There is only one major identified impurity, (b) (4) which would not be a qualification issue if it is indeed a metabolite as claimed by the applicant (This issue will be conveyed to the PharmTox and ClinPharm teams at the filing meeting).

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Drug product

(b) (4) Tablets are immediate release tablets containing 300 mg of the active ingredient mifepristone. (b) (4) Tablets are light yellow to yellow, oval, film coated tablets debossed with "CORCEPT" on one side and "300" on the other. The composition of mifepristone tablets is shown in Table 11.

Table 11. Composition of Mifepristone Tablets

Ingredient	Quality Standard	Amount per Tablet (mg)	Function
(b) (4)			
Mifepristone (b) (4)	In-house standard	300	Active ingredient
Sodium Starch Glycolate	NF	(b) (4)	
Hydroxypropylcellulose	NF		
Silicified Microcrystalline Cellulose	NF		
(b) (4)			
Sodium Lauryl Sulfate	NF	(b) (4)	
(b) (4)			
Sodium Starch Glycolate	NF	(b) (4)	
Magnesium Stearate	NF		
(b) (4) Tablet Weight (b) (4)			
(b) (4)			
Total Coated Tablet Weight		468	
(b) (4)			

Review comments:

- **Comparability of the product used in the clinical studies, stability studies, and commercial product**. There were several formulations used in the clinical studies. The final formulation for the commercial product is coded "E2" in the Clinical Summary (section 2.7.1) and "C2" in the Quality Summary (sec2.3.P.2); see the 74-day letter comment on the first page of this review. The

following product batches were produced with this final formulation and used in the pivotal clinical study C-1073-400 and extension study C-1073-415: batches 9J01, 9J11, 10A02, 10A02, 10A02, 10B13, 10B14, 10B15, and 10J13. Of these batches, 10B13, 10B14, 10B15 were packaged in both 28-count bottles and 280-count bottles as primary stability batches.

Manufacturing process of the drug product

(b) (4)

Review comments:

- **Comparability of the product used in the clinical studies, stability studies, and commercial product**. The clinical and stability batches listed earlier in this review were manufactured at the commercial facility using a process claimed to be similar to the commercial process (to be verified by the reviewer) and at a scale of (b) (4) the commercial scale.
- **Master batch records.** These records are not included in the NDA for the commercial manufacturing process (to comply with 505(b)(2) regulations); see the 74-day letter comment on the first page of this review.

Drug product specification

The drug product specification is copied on the next page.

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Review comments:

- **Limits on degradation products.** The applicant states that no degradant has been found above the limit of (b) (4) and proposed this limit on an unknown degradant, which complies with ICH identification and qualification thresholds for the maximum daily exposure of 1200 mg mifepristone. The reviewer will evaluate the test method used in degradant testing to confirm that it is adequately stability-indicating.
- **Dissolution.** Review of all dissolution/drug release-related information will be conducted by the ONDQA Biopharm team.
- **Chirality and polymorphism**. The drug product specification does not include testing for polymorph (b) (4) . There is no testing for chirality. The omission will be evaluated by the reviewer, taking into account all available information in the drug substance DMF on the stability of the chiral configuration and (b) (4) of the drug substance. The reviewer will consult with the Biopharm reviewer (b) (4) .
- **Microbial limits**. Tests are per USP <61> and <62> and the proposed limits are consistent with those approved for other products that are solid oral dosage forms (b) (4) which is consistent with those approved for other products that are solid oral dosage forms with the same microbial limits. The reviewer may choose to confirm with the Microbiology team if needed.

Container closure systems for product distribution

The product will be packaged in 28-count and 280-count bottles (b) (4) .

Review comments:

- **Safety of the packaging components**. The reviewer will verify that all components comply with applicable U.S. indirect food additives regulations.
- **Suitability of the packaging components**. The applicant states that the 280-count stability batches were packaged in the proposed commercial bottles and closures, (b) (4) that is equivalent to the commercial one, and the 28-count stability batches were packaged with bottles,

closures, and (b) (4) that are equivalent to the commercial system. The information will be evaluated as part of the stability evaluation by the reviewer.

- **DMFs.** The reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for solid oral drug products.

Stability of the drug product

Review comments:

As discussed earlier in this review, product batches 10B13, 10B14, 10B15 were used in the pivotal efficacy study and each batch was packaged in both 28-count bottles and 280-count bottles as primary stability batches. They were manufactured at the commercial facility using a process claimed to be similar to the commercial process (to be verified by the reviewer) and at a scale of (b) (4) the commercial scale. The 280-count stability batches were packaged in the proposed commercial bottles and closures, (b) (4) that is equivalent to the commercial one, and the 28-count stability batches were packaged with bottles, closures, and (b) (4) that are equivalent to the commercial system (to be verified by the reviewer).

The applicant submitted 9-month data for the primary stability batches at 25 °C/60% RH and 6-month data at 40 °C/75% RH). Supportive data include 24-month data for clinical batches that have the commercial formulation and were produced with the same process, scale, and packaging as the primary stability batches. The supportive batches were manufactured at a different site (not commercial site). The Pre-NDA discussion included an agreement on the bracketing design for packaging sizes, but it does not appear that the stability data in the NDA has any bracketing (to be verified by the reviewer). The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data. Photostability data are provided per ICH to show that the product is not light-sensitive (to be evaluated by the reviewer).

Supporting NDA or IND: IND 76480 - same sponsor

Supporting DMFs:

Included here are letters authorizing Corcept Therapeutics to cross reference the following DMFs:

(b) (4)

GMP facilities: EER was sent to Compliance by ONDQA PM (K. Sharma) *on 02-MAY-2011.*

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 202107	**Established/Proper Name: Mifepristone**
Applicant: Corcept Therapeutics	**Stamp Date:** 18-APR-2011

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

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?			See Biopharm filing memo
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		Review issue: whether data and analysis are adequate to support expiry
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	No design space being proposed.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		
G. microbiology				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Non-sterile solid oral dosage form.
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		**See the first page of this review.**

{See appended electronic signature page}
Su (Suong) Tran
CMC Lead, Office of New Drug Quality Assessment
Date *{see appended electronic signature page}*

{See appended electronic signature page}
Ali Al Hakim
Branch Chief, Office of New Drug Quality Assessment
Date *{see appended electronic signature page}*

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

/s/

SUONG T TRAN
06/14/2011

ALI H AL HAKIM
06/14/2011