

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207695Orig1s000

OTHER REVIEW(S)

Under Section 2 of the Pediatric Research Equity Act (PREA) the applicant is required to submit adequate safety and efficacy data for pediatric subjects. There is no clinical pharmacology and safety data for subjects with atopic dermatitis age 3 months to < 2 years to support labeling.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct an open-label safety trial in up to 100 evaluable pediatric subjects with mild to moderate atopic dermatitis ages 3 months to < 2 years and at least 5% treatable percent body surface area (%BSA). Evaluate the pharmacokinetics of crisaborole under maximal use conditions in 16 evaluable subjects with moderate atopic dermatitis and at least 35% treatable percent body surface area (%BSA).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

X Other (provide explanation)

PREA-required trial in pediatric population to assess efficacy and safety

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
- Are the objectives clear from the description of the PMR/PMC? Yes
- Has the applicant adequately justified the choice of schedule milestone dates? Yes
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

OMOLARA R LAIYEMO
12/05/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207695

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Eucrisa® (crisaborole) ointment, 2%

Applicant: Anacor Pharmaceuticals, Inc.

Receipt Date: January 7, 2016

Goal Date: January 6, 2017

1. Regulatory History and Applicant's Main Proposals

The following is the regulatory history for this product:

- 10/08/2015 Meeting Minutes for Type B (Pre-NDA) meeting
- 10/06/2014 Agreed Upon iPSP
- 03/06/2014 Meeting Minutes for Type B (End-of-Phase 2) meeting
- 01/09/2012 Special Protocol Agreement (Clinical)
- 07/06/2011 Special Protocol Agreement (Carcinogenicity)

The applicant proposes a new molecular entity (NME) for the treatment of mild to moderate atopic dermatitis.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI were conveyed to the applicant during labeling discussions.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment: *Extended the horizontal line over the entire width of the page*

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required

Selected Requirements of Prescribing Information

• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A

Selected Requirements of Prescribing Information

14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

Selected Requirements of Prescribing Information

(insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:
-

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use “ Labor and Delivery ”)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use “ Nursing Mothers ”)
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment:

N/A

Selected Requirements of Prescribing Information

33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

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

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *PENDING*

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

-----RECENT MAJOR CHANGES-----

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

-----INDICATIONS AND USAGE-----

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

-----DOSAGE AND ADMINISTRATION-----

- Text (2.x)
- Text (2.x)

-----DOSAGE FORMS AND STRENGTHS-----

Dosage form(s): strength(s) (3)

-----CONTRAINDICATIONS-----

- Text (4)
- Text (4)

-----WARNINGS AND PRECAUTIONS-----

- Text (5.x)
- Text (5.x)

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Text (7.x)
- Text (7.x)

-----USE IN SPECIFIC POPULATIONS-----

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

BELAINESH ROBNETT
12/01/2016
On behalf of O. Laiyemo

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 207695	NDA Supplement #: S- N/A	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: EUCRISA Established/Proper Name: crisaborole Dosage Form: Ointment Strengths: 2%		
Applicant: Anacor Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: 1/6/2016 Date of Receipt: 1/7/2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: 1/7/2017		Action Goal Date (if different): 12/14/2016
Filing Date: 3/7/2016		Date of Filing Meeting: 2/19/2016
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

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Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
Review Classification: <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher

Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <ul style="list-style-type: none"> <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): 077537

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				N/A
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		N/A
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		1.1.3
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2)	YES	NO	NA	Comment

(NDAs/NDA Efficacy Supplements only)				
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		<input type="checkbox"/>	<input type="checkbox"/>	
If yes , please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes , # years requested:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.3.5.3

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		1.1.2
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.1.2
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.3.5.1
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		1.3.4
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		1.2
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

²

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.9.6
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Separate submission dated 2/4/2016
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		1.14.1.3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		1.14.1.3
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> QT/iRT consult- sent 2/23/2016 DPP consult- sent 5/26/2016	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): [REDACTED] (b) (4) 02/26/2014: End-of-Phase 2 meeting (atopic dermatitis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 09/23/2015: Pre-NDA meeting	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): 07/06/2011: Non-Clinical SPA agreement letter 01/09/2012: Clinical SPA agreement letter	<input checked="" type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/19/2016

BACKGROUND: NDA is being submitted for Crisaborole Topical Ointment, 2% for the treatment of mild to moderate atopic dermatitis in patients 2 years and older, and comprises data from all studies supportive of the intended claim. However, studies in healthy volunteers and in subjects with psoriasis, as well as nonclinical studies using crisaborole (b)(4) and/or other ointment formulations conducted under either IND (b)(4) or IND 77,537 are also included in this NDA as they contribute to support the safety of crisaborole.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lydia Springs	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	Snezana Trajkovic		Y
Division Director/Deputy	Kendall Marcus		Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Melinda McCord	Y
	TL:	Snezana Trajkovic	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		N/A
	TL:		N/A
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		N/A
	TL:		N/A
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		N/A
	TL:		N/A
Clinical Pharmacology	Reviewer:	Chinmay Shukla	Y
	TL:	Doanh Tran	Y
• Genomics	Reviewer:		N/A

• Pharmacometrics	Reviewer:		N/A
Biostatistics	Reviewer:	Matthew Guerra	Y
	TL:	Mohamed Alesh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kumar Mainigi	Y
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:		N/A
	TL:		N/A
Product Quality (CMC) Review Team:	ATL:	Yichun Sun	Y
	RBPM:	Grafton Adams	N
• Drug Substance	Reviewer:	Joseph Leginus	Y
• Drug Product	Reviewer:	Bhavishya Mittal	Y
• Process	Reviewer:	Chidambaram Nallaperumal/ Kejun Cheng	Y
• Microbiology	Reviewer:	Bryan Riley/Samata Tiwari	Y
• Facility	Reviewer:	Grace McNally/Vipul Dholaki	Y
• Biopharmaceutics	Reviewer:	Tapash Ghosh	Y
• Immunogenicity	Reviewer:		N/A
• Labeling (BLAs only)	Reviewer:		N/A
• Other (e.g., Branch Chiefs, EA Reviewer)			N/A
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		N/A
	TL:		N/A
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Mishale Mistry	N
OSE/DRISK (REMS)	Reviewer:		N/A
	TL:		N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:	Jamie Wilkins Parker	Y

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		N/A
	TL:		N/A
Other reviewers/disciplines			
<ul style="list-style-type: none"> Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		N/A
	TL:		N/A
Other attendees			
*For additional lines, right click here and select "insert rows below"			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505 b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <i>the application did not raise significant safety or efficacy issues</i>
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>10/8/15 –PreNDA Meeting – Updated drug product stability data for 100-g tubes (12-month data for 3 primary stability lots) within 30 calendar days of the original NDA submission.</p> <p>1.2 Reviewers Guide - Anacor is including 12-month long term stability data for three primary stability lots of Crisaborole Topical Ointment. 2% in 100 g, 60 g, and physician sample presentations manufactured at (b)(4) in Module 3.2.P.8 of this NDA. Therefore, the previous agreement with the Agency to submit 12-month long term stability data for the 100 g presentation 30 days after the original NDA submission is no longer applicable (pre-NDA Meeting Minutes dated 08 OCT 2015; Reference ID: 3830997).</p>

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES 2.3.S.2.1 <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Amy Egan, MD	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): June 21, 2016	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

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/s/

OMOLARA R LAIYEMO
12/01/2016

Clinical Inspection Summary

Date	October 3, 2016
From	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To	DTOP\Team Leader\William Boyd DTOP\Medical Officer\Lucious Lim DTOP\Project Manager\Judit Milstein/June Germain
NDA/BLA #	NDA 207695
Applicant	Anacor Pharmaceuticals, Inc.
Drug	Eucrisa (crisaborole)
NME (Yes/No)	Yes
Therapeutic Classification	Standard Review
Proposed Indication(s)	Treatment of mild to moderate atopic dermatitis in patients 2 years and older
Consultation Request Date	February 24, 2016
Summary Goal Date	October 21, 2016
Action Goal Date	December 14, 2016
PDUFA Date	January 6, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Gower, Rees, Shepard, and Williams, were inspected in support of this NDA. The final classification of the inspections of Drs. Gower, Rees, and Shepard was No Action Indicated (NAI). The final classification of the inspection of Dr. Williams was Voluntary Action Indicated (VAI).

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

The Applicant submitted this NDA to support the use of Eucrisa for the treatment of mild to moderate atopic dermatitis in patients 2 years and older.

Protocols AN2728-AD-301 and AN2728-AD-302, both entitled "A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis" were inspected in support of this application.

Study AN2728-AD-301 was conducted at 48 sites in the U.S. with a projected enrollment of 750 subjects.

Study AN2728-AD-302 was conducted at 42 sites in the U.S with a projected enrollment of 750 subjects.

Protocols AN2728-AD-301 and AN2728-AD-302

The primary objective of these identical protocols was to determine the safety and efficacy of AN2728 Topical Ointment, 2% applied twice daily (BID) compared to AN2728 Topical Ointment, Vehicle in children (ages 2 years and older), adolescents, and adults with mild-to-moderate atopic dermatitis (AD).

These were multicenter, randomized, double-blind, vehicle-controlled studies. Following screening, subjects were randomized at baseline in a 2:1 ratio to either AN2728 Topical Ointment, 2%, BID or AN2728 Topical Ointment, Vehicle, BID.

The primary efficacy endpoint for these studies was the proportion of subjects achieving success in ISGA at Day 29 in the AN2728-treated group compared to the vehicle-treated group.

The sites of Drs. Williams, Gower, Rees, and Shepard were selected because they were high treatment responders and represented relatively large enrollments for the studies.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
138/ Joe Lynn Williams, Jr, MD IMMUNOe International Research Center 3240 E 104th Ave Thornton, CO 80233	AN2728-AD-301/ 39	20-28 Apr 16	VAI
150/ Richard G. Gower, MD Marycliff Allergy Specialists PS 324 S Sherman St, A2 Spokane, WA 99202	AN2728-AD-301/ 30	10-13 May 16	NAI
211/ William C. Rees, MD PI-Coor Clinical Research, LLC 8982 Fern Park Dr Burke, VA 22015	AN2728-AD-302/ 46	26 Apr 16	NAI
240/ Julie Shepard, MD Ohio Pediatric Research Association 7200 Poe Avenue, Suite 200 Dayton, OH 45414	AN2728-AD-302/ 33	4-11 May 16	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Joe Lynn Williams, Jr, M.D.

At this site for Protocol AN2728-AD-301, 51 subjects were screened, 39 subjects were enrolled, seven subjects withdrew consent, and 32 subjects completed the study.

Review of the study records included, but was not limited to, delegation logs, IRB and CRO communications, source documents, adverse events, financial disclosure forms, personnel training, and study drug accountability and storage.

Appropriate informed consent for all 51 subjects was obtained and documented prior to any study-related testing. The source data for 26 of the 39 subjects were compared with line listings.

The assignment noted “missing” data for six subjects. These subjects discontinued early in the study and their disposition is described in the table below.

Subject #	Treatment Arm	Reason for discontinuation
029	Vehicle	Schedule conflicts
034	Active	Lost to follow up
039	Active	Schedule conflicts
041	Active	Withdrew consent
045	Active	Lack of efficacy
049	Active	Lack of efficacy

A Form FDA 483 was issued at the conclusion of the inspection for two instances of failure to follow the protocol. Subject 021 used hydroxyzine on a PRN basis despite the protocol’s exclusion of subjects using systemic antihistamines on a non-stable basis. Subject 013 used Mupirocin, a topical antibacterial medication, despite the protocol’s exclusion of subjects using topical antibacterial agents (except on the hands).

Dr. Williams, in his written response dated, May 12, 2016, acknowledged the above protocol deviations and has implemented study practices and staff training to prevent such deviations in future studies.

The isolated protocol deviations noted above would not appear to have a significant impact on safety or efficacy considerations. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Richard G. Gower, M.D.

At this site for Protocol AN2728-AD-301, 32 subjects were screened, 30 subjects were enrolled, three subjects discontinued early for lack of efficacy, and 27 subjects completed the study.

The records for the 30 enrolled subjects were reviewed. Source data were compared with line listings.

All 32 consent forms (including two screen failures) were completed prior to any study-related testing. Review of these records included, but was not limited to, financial disclosure, IRB, sponsor, and monitor correspondence, personnel training, inclusion/exclusion criteria, blinding and randomization, primary and secondary efficacy endpoints, adverse events, subject discontinuations, concomitant medications, protocol deviations, and drug accountability and storage.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. William C. Rees, M.D.

At this site for Protocol AN2728-AD-302, 49 subjects were screened, 46 subjects were randomized, and 42 subjects completed the study.

The records for all 49 subjects, including informed consent documents, were reviewed. Source data were compared with line listings.

All consent forms were completed prior to any study-related testing. Review of other records included, but was not limited to, staff training, financial disclosure, IRB, sponsor, and CRO communications, laboratory reports, subject eligibility, subject diaries and questionnaires, primary and secondary endpoints, concomitant medications, adverse events, and test article accountability and storage.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Julie Shepard, M.D.

At this site for Protocol AN2728-AD-302, 36 subjects were screened, three subjects were screen failures, and 33 subjects were enrolled and completed the study.

All subject records were reviewed for informed consent, the primary efficacy endpoint, and adverse event reporting. The records of 17 enrolled subjects were reviewed in depth for protocol compliance, inclusion/exclusion criteria, concomitant medications protocol deviations vital signs, electrocardiograms, and laboratory test results. Source data were compared with line listings. Review of other records included financial disclosure, informed consent, and drug accountability.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

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Central Doc. Rm.\NDA 207695
DDDP\Division Director\Kendall Marcus
DDDP\Team Leader\Snezana Trajkovic
DDDP\Medical Officer\Melinda McCord
DDDP\Project Manager\Lydia Springs
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Janice Pohlman
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
10/06/2016

JANICE K POHLMAN
10/06/2016

KASSA AYALEW
10/06/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health,
Office of New Drugs

Through: Mona Khurana, M.D., Acting Pediatric Team Leader,
John J. Alexander, M.D., M.P.H., Deputy Director,
Division of Pediatric and Maternal Health,
Office of New Drugs

To: Division of Dermatology and Dental Products (DDDP)

Drug: Eucrisa (crisaborole) Ointment, 2%

Application Number: NDA 207695 (IND 77537)

Sponsor: Anacor Pharmaceuticals, Inc.

Proposed Indication: For the topical treatment of mild to moderate atopic dermatitis (AD) in patients 2 years and older

Proposed Dosage Form: 2% Ointment

Route of Administration: For topical administration

Proposed Dosing Regimen: Apply twice daily to affected areas

Consult Request:

DDDP requested the Division of Pediatric and Maternal Health (DPMH) to provide recommendations regarding how to assess weight loss in the pediatric patients evaluated in the clinical program for this product and to provide feedback regarding the following specific questions:

- “Can we draw a conclusion about the presence of a safety signal for weight loss with exposure to crisaborole?”
- “If the data is inadequate to determine if there is a safety signal, how could the study design for a post marketing trial be optimized to assess weight loss?”

Materials Reviewed:

- July 13, 2016 DPMH consult request (DARRTS Reference ID 3958593)
- Current Otezla (apremilast) labeling at Drugs@FDA (September 23, 2014)
- Current Daliresp (roflumilast) labeling at Drugs@FDA (November 24, 2015)
- Module 2.5 Clinical Overview in Eucrisa (crisaborole) NDA 207695

Background and Regulatory History:

Anacor Pharmaceuticals, Inc. submitted an NDA for Eucrisa (crisaborole) 2% ointment, NDA 207695, on January 7, 2016, for the topical treatment of mild to moderate atopic AD in patients 2 years and older. Crisaborole is a novel topical benzoxaborole phosphodiesterase-4 (PDE-4) inhibitor. PDE-4 deactivates cyclic adenosine monophosphate (cAMP), thus, PDE-4 inhibition results in increased intracellular cAMP levels. Although the specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined, the applicant proposes that crisaborole penetrates into the skin to sites of inflammation and reduces the production of several inflammatory cytokines implicated in the pathophysiology of atopic dermatitis (AD).¹ Crisaborole is also being evaluated in clinical trials in adults for plaque psoriasis. Other PDE-4 inhibitors, which are orally administered, include:

- Otezla (apremilast), NDA 205437/206088, which is approved in the US in adults for active psoriatic arthritis and for moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy.^{2,3}
- Daliresp (roflumilast), NDA 22522, which is approved in the US in adults for chronic obstructive pulmonary disease.⁴
- (b) (4).

Weight loss is a noted adverse event associated with PDE-4 inhibitors and is included in the Warning and Precautions and Adverse Reactions sections of labeling for both apremilast and roflumilast. Consequently, DDDP evaluated weight loss associated with crisaborole and noted a potential signal in the pediatric population. Accordingly, they consulted DPMH to provide recommendations regarding how to assess weight loss in the pediatric patients included in the crisaborole clinical development program and how to optimize the design of a post-marketing study to assess weight loss.

¹ Clinical Overview of Eucrisa (crisaborole) NDA 207695 (January 7, 2016)

² March 21, 2014 Approval Letter for NDA 205437:

http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/205437Orig1s000ltr.pdf; accessed 9/15/16.

³ September 23, 3104 Approval Letter for NDA 206088:

http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/206088Orig1s000ltr.pdf; accessed 9/15/16.

⁴ February 28, 2011 Approval Letter for NDA 22522:

http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/022522s000ltr.pdf; accessed 9/15/16.

Pediatric Assessment:

The following studies were conducted to support pediatric approval:

- Study AD-301: A Multicenter (48 sites), Randomized, Double Blind, Vehicle-Controlled 28-Day Study of the Safety and Efficacy of Crisaborole Topical Ointment, 2% given BID in Children, Adolescents, and Adults (Ages 2 Years and Older) With AD involving $\geq 5\%$ of BSA (n=759)
- Study AD-302: A Multicenter (42 sites) , Randomized, Double-Blind, Vehicle-Controlled 28-Day Study of the Safety and Efficacy of AN2728 Topical Ointment, 2% given BID in Children, Adolescents, and Adults (Ages 2 Years and Older) With AD involving $\geq 5\%$ of BSA (n=763)
- Study AD-303: A Multicenter (40-60 sites), Open-Label 48-Week Study of the Long-Term Safety of AN2728 Topical Ointment, 2% given on an as needed basis in the Treatment of Children, Adolescents, and Adults (Ages 2 Years and Older) With Mild to Moderate AD who completed Study AD-301 or AD-302 without drug-related safety issues that precluded use of crisaborole 2% ointment (n=517)

In the two pivotal 28-day phase 3 studies (Study AD-301 and 302), weight was obtained only at baseline. For patients in both studies who went on to enrollment into the long-term open-label safety study (Study AD-303), additional weights were obtained at Week 24 and Week 48. The data were examined according to the following age groups 2-6, 7-11, 12-17 and 18+ years of age. However, weight data were not provided for all patients in Study AD-303. Of the 517 patients enrolled in Study AD-303, 385 patients had their weights taken at Week 24 and 271 patients had their weight taken at Week 48. Patients in Study AD-301 and 302 were randomized in a 2:1 ratio to receive crisaborole ointment or vehicle ointment. Of note, treatment in the long term safety study (Study AD-303) was given as needed and not continuously; therefore, drug exposure is not equivalent to study duration. Table 1 summarizes the results of the findings.

Table 1: Categorized Weight (lbs) Change (Lost, No Change and Gained) at Week 24 and Week 48 by Age in Study AD-303⁵

	Age				Overall
	2 - 6	7 - 11	12 - 17	18+	
Week 24	N=129	N=94	N=112	N=50	N=385
Lost	7 (5.4%)	4 (4.3%)	23 (20.5%)	24 (48.0%)	58 (15.1%)
No Change	4 (3.1%)	1 (1.1%)	3 (2.7%)	2 (4.0%)	10 (2.6%)
Gained	118 (91.5%)	89 (94.7%)	86 (76.8%)	24 (48.0%)	317 (82.3%)
Week 48	N=81	N=71	N=79	N=40	N=271
Lost	1 (1.2%)	1 (1.4%)	19 (24.1%)	20 (50.0%)	41 (15.1%)
No Change	1 (1.2%)	2 (2.8%)	1 (1.3%)	1 (2.5%)	5 (1.9%)
Gained	79 (97.5%)	68 (95.8%)	59 (74.7%)	19 (47.5%)	225 (83.0%)

⁵ Statistics review of growth in the pediatric population with Eucrisa (crisaborole)

DDDP noted that the greatest percent of pediatric patients with any weight loss were noted in the 12 to 17-year-old age group with 20.5% and 24.1% of patients with weight loss reported at 24 weeks and 48 weeks, respectively. Of note, a much larger percentage of weight loss was reported in adults with 48.0% and 50.0% at 24 weeks and 48 weeks, respectively. However, given the low drug exposure and small numbers of adult patients (14% of the total patients), the relevance of this finding appears small. The interpretation of the data is confounded by the lack of a vehicle control after day 28, intermittent dosing in the open label extension, and uncertainty regarding the quality/standardization of the collected data. Additionally, prior steroid use and psychosocial factors associated with increased risk of affective disorders⁶ and obesity⁷ in patients with AD could also confound an assessment of weight changes. Accordingly, weight loss or normalization of weight in a patient with baseline obesity may not be very concerning. Moreover, a regression analysis did not demonstrate a significant correlation between weight (or height) change and drug exposure in any age group (see Table 2 below).

Table 2: Correlation Between Weight Change from Baseline to Week 48 and Total Amount of EUCRISA Ointment Used by Age Groups⁸

Age	N	Correlation	p-Value
2-6	78	-0.044	0.7043
7-11	65	0.036	0.7780
12-17	77	0.026	0.8221
18+	39	-0.190	0.2479
Overall	259	0.063	
2-9	114	0.023	

Discussion:

The pediatric assessment for crisaborole was discussed with the Pediatric Review Committee (PeRC) on August 10, 2016. DPMH also participated in this discussion. PeRC noted a low concern for the risk of weight loss for this topical product due to the decreased exposure compared to oral products and the likely temporary duration of use. PeRC noted that a formal evaluation of growth would be difficult to assess in a long-term extension trial which typically does not include a control/comparator group and was likely unnecessary given the low concern. However, current data could be evaluated to determine if any significant decrease in weight based on percentiles is noted. Furthermore, due to variability with growth following puberty, data should be evaluated in pre-pubertal patients (2- 9 years of age) separately from post-pubertal patients (10-17 years of age). PeRC provided the following recommendations to DDDP:

- Evaluate the current weight and height data based on the Centers for Disease Control and Prevention (CDC) clinical growth charts and assess for any changes

⁶ Cheng CM, Hsu JW, Huang KL, Bai YM, Su TP, Li CT, Yang AC, Chang WH, Chen TJ, Tsai SJ, Chen MH. Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: a nationwide longitudinal study. *J Affect Disord.* 2015 Jun 1;178:60-5.

⁷ Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. *J Am Acad Dermatol.* 2015 Apr;72(4):606-16.

⁸ Adapted from the Statistics review of growth in the pediatric population with Eucrisa (crisaborole)

in weight and height percentiles for age and sex according to the following age groups: 2-9 years of age and 10-17 years of age.

- If findings suggest a signal of weight loss, consider conducting a more formalized growth study designed to mitigate the confounding factors noted with the current data (e.g., lack of control group, limited duration of evaluation, and limited number and standardization of measurements).
- Include standardized growth measurements in the planned post-approval long-term safety study in patients 3 months- 2 years of age that will be issued as a pediatric post-marketing study requirement (PMR) under the Pediatric Research Equity Act (PREA).

Accordingly, the statistics reviewer evaluated weight and height data for patients 2-9 years of age based on CDC growth charts. The statistics reviewer also compared the weight data to drug exposure. No significant trends or correlation between drug exposure and weight loss were noted.

For the observed growth data, the statistics reviewer flagged patients that did not increase weight or height by at least the amount of weight increase expected for a child at the 5th percentile based on the CDC's growth chart data for weight and height. Patients were unflagged if they reached the expected weight or height increase for child at the 5th percentile by Week 48. In clinical practice, however, further evaluation is typically initiated for secondary causes of weight loss when a decrease in percentile of two or more standard deviations is seen (e.g., a change in the weight curve from the 75th percentile to the 25th percentile). Therefore, the approach to the re-analysis appears to be conservative. Additionally, for the re-analysis of height, the statistics reviewer unflagged subjects if they had a decrease in height of 6 inches or more, which was assumed to be a measurement error. However, negative growth of any magnitude (not just 6 inches or more) highly suggests measurement error, and therefore, patients with any negative growth reported could reasonably have been excluded in the re-analysis. Furthermore, given the fact that there are many measurements with loss of height in each age group, the reliability of the height data is questionable. Additionally, there were several patients that were overweight at baseline. Therefore, this reviewer examined changes in percentiles of weight data alone, paying particular attention to patients who were not overweight or obese (i.e., in the 85th percentile or more) at baseline. None of the patients appear to have a decrease in percentile for weight of at least two standard deviations. (See Appendix 1: Weight Growth Data based on CDC's Percentile Curves.)

Conclusions:

The growth data obtained from Studies AD-301, 302, and 303 do not suggest the presence of a clear safety signal for weight loss in pediatric patients. Furthermore, these studies show no correlation between the observed weight loss and cumulative exposure to crisaborole. Conservative re-analysis of the growth data using age- and sex-based reference values from the CDC clinical growth charts also failed to show a clear safety signal for weight loss, reduction in height velocity, or both in patients 2 years to 19 years of age. Therefore, a more formalized growth study does not appear to be warranted for

the pediatric population that has already been studied in the clinical development program for crisaborole.

Standardized growth measurements should be included in the planned post-approval long-term safety study in patients 3 months to 2 years of age that will be issued as a PREA PMR. The study protocol must specify how height and weight measurements will be standardized and performed and what steps will be taken to reduce measurement errors. The study protocol should incorporate recommendations from the March 2007 Guidance for Industry on Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children⁹. This guidance provides general recommendations for designing growth studies in children in order to minimize variability in results and to improve the interpretability of the findings.

Recommendations:

1. DPMH does not recommend a formal study to evaluate growth in the pediatric population that has already been studied in the clinical development program for crisaborole.
2. With regards to the planned post-approval long-term safety study in patients 3 months to 2 years of age which will be issued as a PREA PMR, the lack of a long-term comparator and the amount of variability of growth typically seen in patients less than 3 years of age, will likely limit a reliable growth assessment in this age group. However, DPMH recommends DDDP consider including growth measurements in this study and in any future pediatric studies of this product (e.g., for psoriasis). The study protocol should specify how height (or length in patients <2 years of age) and weight measurements will be replicated (at least 3), standardized and performed. The steps that will be taken to reduce measurement errors should also be outlined. The study protocol should incorporate recommendations from the March 2007 Guidance for Industry on Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. DPMH recommends the sponsor submit the study protocol for review by the Agency before initiating the study. Consider the following general recommendations:
 - All weights should be measured on a calibrated scale.
 - Length should be measured for patients < 2 years of age using a fixed headboard.
 - Standing height should be measured in patients 2 years and older using stadiometer.

⁹ March 2007 Guidance for Industry on Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071968.pdf>

- Measurements should be obtained for a long enough interval to detect changes (e.g., 1 year).
- Changes in growth are best detected during the period of linear growth, between 3 years of age and prior to puberty. Thus, growth studies in this population are deemed most clinically relevant and Tanner staging should also be performed, when applicable.

DPMH reviewed the data and provided the above feedback regarding the assessment of the weight data and further evaluations of weight in the pediatric population for future studies of crisaborole involving pediatric patients.

Appendix 1: Weight Growth Data based on CDC's Percentile Curves⁸

Figure 1: Weight Growth Data with CDC's Percentile Curves for Males 2-19 years of Age at Baseline

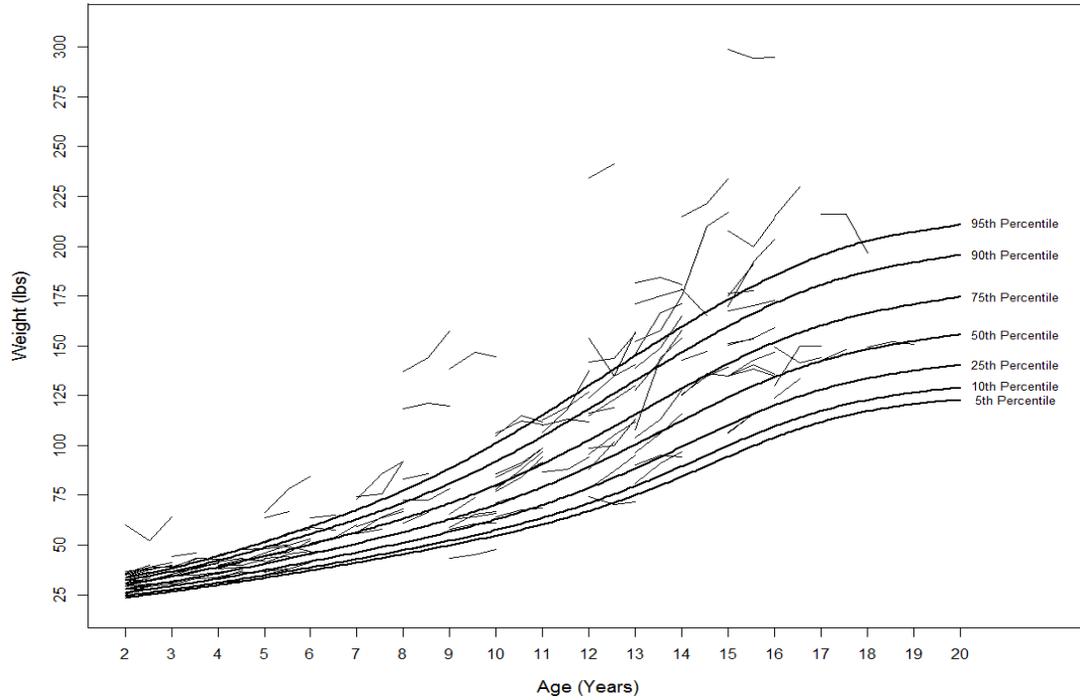


Figure 2: Weight Growth Data with CDC's Percentile Curves for Females 2-19 years of Age at Baseline

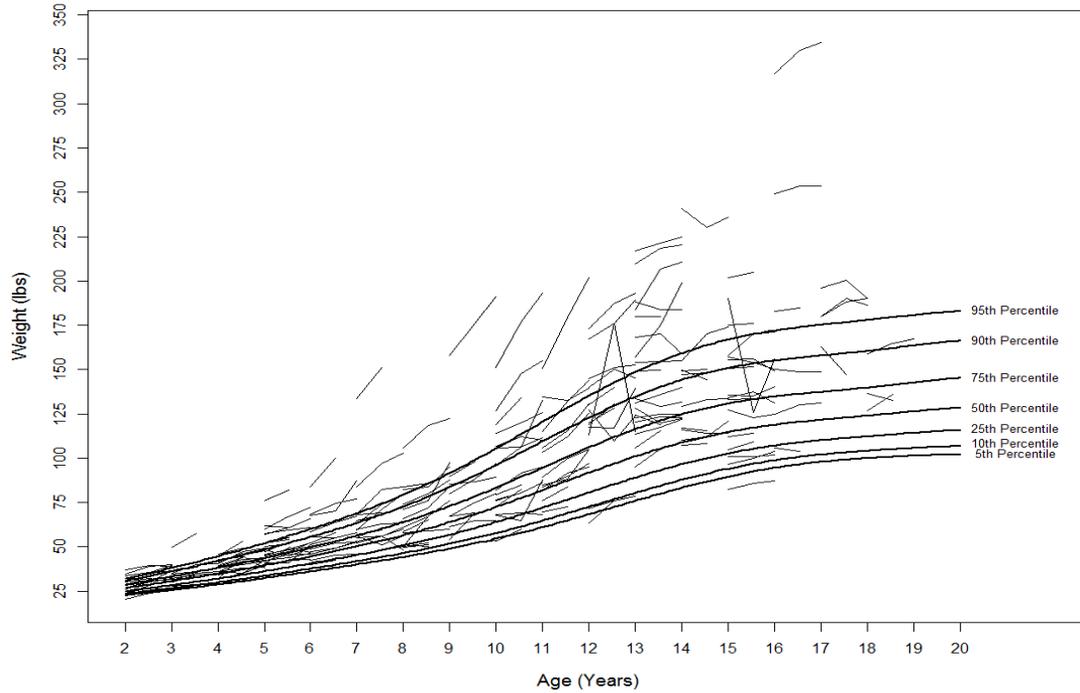


Figure 3: Weight Growth Data with CDC's Percentile Curves for Males 2-9 years of Age at Baseline

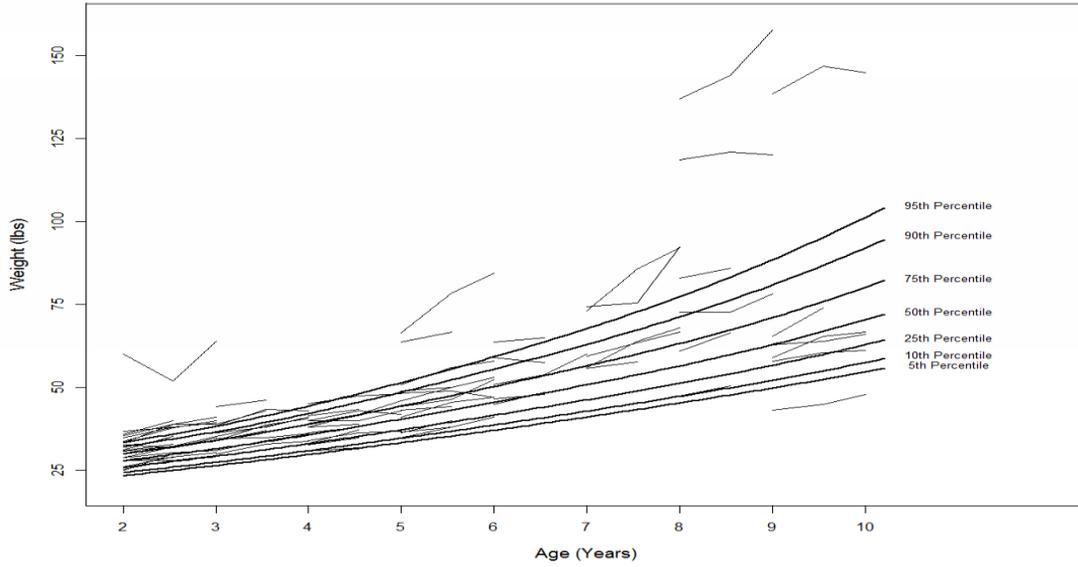
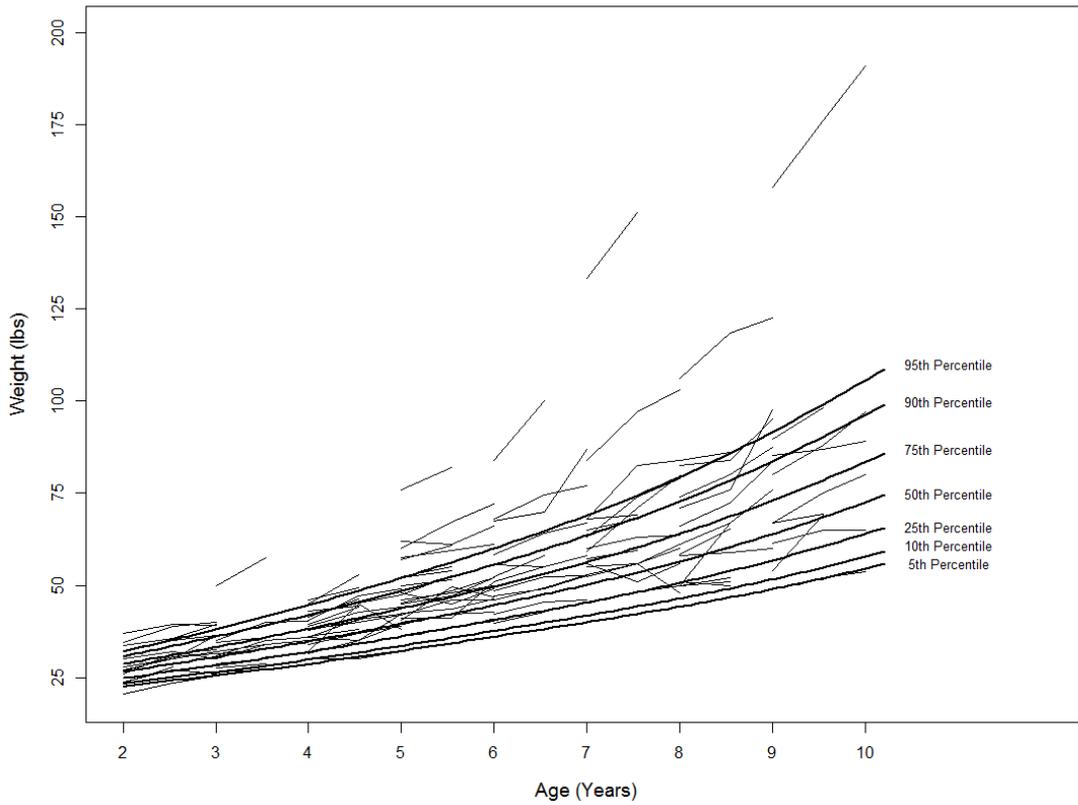


Figure 4: Weight Growth Data with CDC's Percentile Curves for Females 2-9 years of Age at Baseline



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/s/

ERICA D RADDEN
09/28/2016

MONA K KHURANA
09/28/2016

JOHN J ALEXANDER
09/29/2016

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

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

Memorandum

Date: August 15, 2016

To: Lydia Springs, MSHS
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

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

CC: Melinda McLawhorn, Pharm.D., BCPS, RAC, Team Leader, OPDP

Subject: **NDA 207695**
EUCRISA® (crisaborole) ointment, 2%, for topical use

On February 22, 2016, DDDP consulted OPDP to review the draft Package Insert (PI), Patient Package Insert (PPI), and carton and container labeling for EUCRISA® (crisaborole) ointment, 2%, for topical use (Eucrisa) for the original NDA submission.

OPDP reviewed the proposed substantially complete version of the PI provided by DDDP via e-mail on August 2, 2016. OPDP also reviewed the proposed PPI and carton and container labeling submitted to the electronic document room by the sponsor on January 7, 2016. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the PPI for Eucrisa under separate cover. OPDP's comments on the PI and carton and container labeling are provided below.

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

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/s/

TARA P TURNER
08/15/2016

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

PATIENT LABELING REVIEW

Date: August 10, 2016

To: Kendall Marcus, MD
Director
Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Tara Turner, PharmD, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): EUCRISA (crisaborole)

Dosage Form and Route: Ointment, 2%, for topical use

Application Type/Number: NDA 207695

Applicant Name: Anacor Pharmaceuticals, Inc.

1 INTRODUCTION

On January 7, 2016 Anacor Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 207695 for EUCRISA (crisaborole) ointment, 2%. The proposed indication for EUCRISA (crisaborole) ointment, 2% is for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on February 22, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EUCRISA (crisaborole) ointment, 2%.

2 MATERIAL REVIEWED

- Draft EUCRISA (crisaborole) ointment, 2% PPI received on January 7, 2016, and received by DMPP and OPDP on February 22, 2016.
- Draft EUCRISA (crisaborole) ointment, 2% Prescribing Information (PI) received on January 7, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2016.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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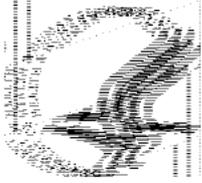
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/s/

MORGAN A WALKER
08/10/2016

TARA P TURNER
08/10/2016

LASHAWN M GRIFFITHS
08/10/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: August 4, 2016 **Date Consulted:** February 22, 2016

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Melinda McCord, M.D., Medical Officer
Division of Dermatology and Dental Products (DDDP)

Drug: Eucrisa (crisaborole) Ointment 2%

NDA: NDA 207695

Applicant: Anacor Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation labeling

Indication: Eucrisa is a benzoxaborole phosphodiesterase-4 (PDE-4) inhibitor indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

Materials Reviewed:

- Applicant's submitted background package for NDA 207695

Consult Question: "Please review Section 8 USE IN SPECIFIC POPULATIONS of labeling and provide comments regarding the adequacy of their proposal."

INTRODUCTION

On February 22, 2016, DDDP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of Eucrisa (crisaborole) Topical Ointment 2% labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

On January 7, 2015, Anacor Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 207695 for a new molecular entity (NME), Eucrisa, (crisaborole) Topical Ointment, 2%. Crisaborole is a phosphodiesterase 4 (PDE4) inhibitor, with the proposed indicated, “for the treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older.” Labeling to be consistent with the Pregnancy and Lactation Labeling Rule (PLLR) was included in the submission. The development program for Eucrisa for atopic dermatitis was conducted under IND 77537. Studies in healthy volunteers and in subjects with psoriasis, as well as nonclinical studies using crisaborole (b)(4) and/or other ointment formulations conducted under either IND (b)(4) or IND 77,537 were also included in the NDA as they contribute to support the safety of crisaborole.

BACKGROUND

Crisaborole and Drug Characteristics

Crisaborole is a (b)(4) (251.1 Dalton) (b)(4) PDE-4 inhibitor¹. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. While the specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined, crisaborole reduces the production of several inflammatory cytokines implicated in the pathophysiology of atopic dermatitis. Crisaborole is substantially metabolized into inactive metabolites once it crosses the skin barrier and reaches the bloodstream. In a clinical pharmacology trial of healthy adult male subjects who received a single topical dose of [14C] crisaborole 2% ointment, crisaborole oxidative or conjugated metabolites were shown to be excreted primarily in the urine.

The pharmacokinetics of crisaborole were investigated in 34 pediatric subjects aged 2 to 17 years of age with mild to moderate atopic dermatitis in a maximal use systemic exposure (MUSE) study. Crisaborole was rapidly absorbed, with a median T_{max} of 3.00 hours on day 1 (range 3–12 hours). Following twice daily topical application to treatable % body surface area (BSA) of 27% to 92%, steady state crisaborole plasma levels showed a mean C_{max} = 127 ng/mL, indicating minimal systemic exposure following topical application. The mean $t_{1/2}$ in adults in the MUSE trial was \approx 10 hours. The only adverse event reported in the pivotal trials that occurred in $\geq 1\%$ was application site pain, which occurred in 4.4% versus 1.2% in vehicle.

¹ Eucrisa proposed labeling

Atopic Dermatitis and Pregnancy

Atopic dermatitis (AD) is a chronic, pruritic inflammatory dermatosis that affects up to 25% of children and 2% to 3% of adults. Pregnancy does seem to have an effect on AD in most women with the condition. Approximately 25% of women with AD demonstrate improvement of their condition during pregnancy, and more than 50% of women with AD experience deterioration of their condition during pregnancy.² AD is the most common pregnancy dermatosis³. The effect of AD on pregnancy outcomes is unclear, with sparse literature and conflicting results.

Seeger JD, *et al.*⁴, reported on a cohort study among women with inflammatory skin diseases, including 3,261 women with AD (225 pregnancies) and did not demonstrate a significant difference from the comparator group in the age-adjusted incidence of pregnancy or spontaneous abortion.

Reviewer comment:

The study by Seeger, et al. was limited by the large number of unknown outcomes among the pregnancies identified.

In another study using the Norwegian national registry, Tronnes H *et al.*⁵, reported that “maternal atopic dermatitis was associated with decreased risk of preterm birth (RR 0.90, [95% CI 0.86, 0.93]), stillbirth (RR 0.70, [95% CI 0.62, 0.79]), and neonatal death (RR 0.76, [95% CI 0.65, 0.90]). Overall rates of preterm birth, stillbirth, and neonatal death were 6.0%, 0.6%, and 0.5%, respectively”.

In a Finnish study, reported by Savilahti E *et al.*, AD was associated with a lower risk of birth weight < 1000 gm (OR: 0.64, [95% CI 0.36, 1.15])⁶. Metzger, *et al.*⁷, assessed incidence of preterm birth, stillbirth, and neonatal death in a small sample of atopic mothers, and found lower rates than those reported for the general population.

Reviewer comment:

Limitations for the studies reported by Tronnes, Savilahti and Metzger include confounding by diagnosis (AD is associated with higher socioeconomic and education levels and poor

² Kemmett D, Tidman MJ. The influence of the menstrual cycle and pregnancy on atopic dermatitis. *Br J Dermatol* 1991; 125:59-61.

³ Kroutoulis I *et al.* Atopic Dermatitis in Pregnancy: Current Status and Challenges. *Obstetrical and Gynecological Survey*. 2011;66:654-663.

⁴ Seeger JD *et al.* Pregnancy and Pregnancy Outcome among Women with Inflammatory Skin Diseases. *Dermatology*. 2006;214; 32-39.

⁵ Tronnes H *et al.* Associations of Maternal Atopic Diseases with Adverse Pregnancy Outcomes: a National Cohort Study. *Paediatric and Perinatal Epidemiology*, 2014, 28, 489–497.

⁶ Savilahti E *et al.* Mothers of very low birth weight infants have less atopy than mothers of full-term infants. *Clinical and Experimental Allergy* 2004; 34:1851–1854.

⁷ Metzger WJ. *et al.* The safety of immunotherapy during pregnancy. *Journal of Allergy and Clinical Immunology* 1978; 61:268–272.

pregnancy outcomes with the reverse⁸), possible misclassification due to underreporting and the effect of disease treatments rather than the diseases themselves.

However, the effect of topical corticosteroids (by far the most common treatment used for AD during pregnancy) when used in large amounts over large body surface areas has been associated with poor pregnancy outcomes, specifically with low birth weight babies⁹.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹⁰ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹¹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical Experience

In animal reproduction studies, there were no teratogenic or embryo-fetal effects observed with oral administration of crisaborole in rats and rabbits during organogenesis at doses up to 7 and 4 times, respectively, the maximum recommended human dose (MRHD). In a perinatal/postnatal reproduction study, pregnant female rats were treated with crisaborole at doses of 150, 300 and 600 mg/kg/day by oral gavage during gestation and lactation (from gestation day 7 through day 7 of lactation). Due to reduced body weight gain and food consumption during the gestation and lactation periods, the maternal no-observed-adverse-effect-level (NOAEL) for crisaborole was 300 mg/kg/day (~7 times the MRHD). The reproductive NOAEL in the dams was 600 mg/kg/day (~25 times the MRHD).

For further details, the reader is directed to the Nonclinical Review by Kumar Mainigi, MSc, PhD, MPH.

⁸ Mortensen LH et al. Socioeconomic differences in perinatal health and disease. *Scandinavian Journal of Public Health* 2011; 39:110–114.

⁹ Katz VL et al. Severe symmetric intrauterine growth retardation associated with the topical use of triamcinolone. *Am J Obstet Gynecol.* 1990; 162:396–397.

¹⁰ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹¹ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

Applicant's Review of Literature

The Applicant did not conduct a search of published literature.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms “crisaborole and pregnancy,” “crisaborole and pregnant women,” “crisaborole and pregnancy and birth defects,” “crisaborole and pregnancy and congenital malformations,” “crisaborole and pregnancy and stillbirth,” “crisaborole and spontaneous abortion” and “crisaborole and pregnancy and miscarriage.” No reports of adequate and well-controlled studies of crisaborole use in pregnant women were found. In fact, the only article found regarding crisaborole use was the publication by Zane *et. al.*,¹² sponsored by the applicant, which is a report on the findings from the MUSE trial.

Pharmacovigilance Database Summary

Four pregnancies occurred in the phase 3 trials for Eucrisa. One of these pregnant subjects was lost to follow-up five months prior to delivery. Two subjects had uneventful pregnancies and delivered healthy infants. One subject had a positive pregnancy test nine months after her treatment with crisaborole. That patient went on to have a spontaneous abortion that was attributed to her hypertension and not felt to be associated with the crisaborole.

Reviewer comment:

DPMH agrees with the investigator and the applicant that the nine month lag makes it very unlikely that the crisaborole treatment contributed to that event.

Summary

Human pregnancy outcome data for topical crisaborole were not found in the published literature. The limited numbers of cases from the applicant's files from the phase 3 trials are not sufficient to rule out a drug-associated risk to the fetus. However, pharmacokinetic data suggest systemic exposure with topical use is likely to be low and the animal data does not suggest a significant risk.

Lactation

Applicant's Review of Literature

The Applicant did not conduct a search of published literature.

¹² Zane et al. Crisaborole Topical Ointment, 2% in Patients Ages 2 to 17 Years with Atopic Dermatitis: A Phase 1b, Open-Label, Maximal-Use Systemic Exposure Study. *Pediatric Dermatology*. 2016;1-8.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*¹³, the Drugs and Lactation Database (LactMed),¹⁴ Micromedex¹⁵, and of published literature in PubMed and Embase using the search terms “crisaborole and lactation” and “crisaborole and breastfeeding.” No relevant information was found in the literature or in any of the databases regarding crisaborole and lactation. No mention of crisaborole was found in *Medications and Mother's Milk*, by Dr. Thomas Hale.

Summary

There are no data on the presence of crisaborole in human milk. Crisaborole has characteristics (molecular weight <800 Daltons), which may increase the presence of the drug in maternal circulation and may increase transfer of the drug into breastmilk. However, the MUSE study quoted above under the section entitled “Crisaborole and Drug Characteristics” revealed minimal systemic exposure following topical application, making significant transfer of the drug into breastmilk unlikely. Given the lack of severe adverse events in adults in clinical trials and minimal systemic exposure following topical administration, DPMH agrees with the applicant that the following risk/benefit statement be included in section 8.2 of labeling:

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

Use in Females and Males of Reproductive Potential

Nonclinical Experience

There were no effects on mating and fertility in male or female rats or Cesarean-sectioning and litter parameters of female rats dosed as high as 600 mg/kg/day at exposures ~25 times the MRHD.

In 2-year carcinogenicity studies, no evidence of crisaborole-induced tumors was observed in mice at dermal doses up to 2.1 times the MRHD (Crisaborole Ointment, 7%) or in rats at oral doses up to approximately 6.2 and 1.2 times the MRHD (300 mg/kg/day in males and 100 mg/kg/day in females, respectively). Benign granular cell tumors of the female reproductive tract (uterus with cervix and vagina) were observed in the rat carcinogenicity study at a dose

¹³ Hale, Thomas (2012) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing, pg. 422-423.

¹⁴ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 3/15/16.

of approximately 3 times the MRHD (300 mg/kg/day). Relevance of this finding in humans is unknown.

Crisaborole revealed no evidence of mutagenic or clastogenic potential.

For further details, the reader is directed to the Nonclinical Review by Kumar Mainigi, MSc, PhD, MPH.

Applicant's Review of Literature

The Applicant did not conduct a search of published literature.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding crisaborole and its effects on fertility and found no relevant literature.

Summary

Animal reproductive studies of administration of crisaborole did not show any adverse effects on fertility. Since there is no information available on the effect of crisaborole on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in crisaborole labeling.

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for Eucrisa (crisaborole) labeling:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of Eucrisa labeling was structured in the PLLR format to include the “Risk Summary” and “Data” sections.¹⁶
- **Lactation, Section 8.2**
 - The “Lactation” subsection of Eucrisa labeling was formatted in the PLLR format to include the “Risk Summary” section.¹⁷

¹⁶ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

¹⁷ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of Eucrisa (crisaborole) labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DDDP on 7/15/16. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Eucrisa (crisaborole) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are no available data with EUCRISA in pregnant women to inform the drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed with oral administration of crisaborole in rats and rabbits during organogenesis at doses up to (b)(4) times, respectively, the maximum recommended human dose (MRHD) [see Data].

The (b)(4) background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies (b)(4) risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, (b)(4) is 2-4% and 15-20%,

(b)(4)

Data

Animal Data

Rat and rabbit embryo-fetal development was assessed after oral administration. Crisaborole

(b)(4)

In a perinatal/postnatal reproduction study, pregnant (b)(4) rats were treated with crisaborole at doses of 150, 300 and 600 mg/kg/day by oral gavage during gestation and lactation (from gestation day 7 through day (b)(4) f lactation). (b)(4)

8.2 Lactation

Risk Summary

There is no information available on the presence of EUCRISA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production after topical application of EUCRISA to women who are breastfeeding. EUCRISA has low systemic absorption; ^{(b) (4)} the lack of clinical data during lactation precludes a clear determination of the risk of EUCRISA to an infant ^{(b) (4)}. Therefore the development and health benefits of breastfeeding should be considered along with the mother's clinical need for EUCRISA and any potential adverse effects on the breastfed infant from EUCRISA or from the underlying maternal condition.

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/s/

JANE E LIEDTKA
08/04/2016

MIRIAM C DINATALE
08/04/2016

LYNNE P YAO
08/04/2016



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 26, 2016

From: Jiang Liu, Ph.D., Scientific Lead, QT Interdisciplinary Review Team

Though: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Linda Springs, RPM
DDDP

Subject: QT-IRT Consult to NDA 207695

This memo is an addendum to our consult to you dated 4/20/2016 regarding the adequacy of the applicant's QT assessment of Crisaborole. The QT-IRT reviewed the following materials:

- QT-IRT consult to DDDP (dated 4/20/2016); and
- QT-IRT review of the TQT Study AN2728-TQT-108 (dated 5/20/2014 under IND 77537).

QT-IRT Comments for DDDP

This revised consult is to clarify the QT-IRT comments to DDDP in our previous consult (4/20/2016) on the applicant's QT assessment of crisaborole.

1. Although the TQT study was negative at the doses/exposures evaluated and there was no evidence of a crisaborole-QTc relationship, the limitation of the study is the exposures achieved do not cover the clinical exposures to crisaborole in patients enrolled in the phase 3 clinical trials.
2. The applicant submitted safety ECGs collected at baseline and Day 8 in in the two Phase 3 trials as supportive evidence that there are no effects on the QTc interval. We agree that there are no findings in these limited safety ECGs based on categorical analysis of the QTc intervals—no subjects had QTcF >480 ms or a change in QTcF from baseline >30 ms. These data, however, cannot be used to exclude a mean increase in QTc interval around the regulatory threshold (<10 ms) per the ICH E14 guidelines.
3. Based on the totality of clinical data presented in the cardiac safety report and TQT study, there is no evidence that crisaborole has a clinically meaningful effect on the QTc

interval, and we are not recommending that the applicant performs any additional QT assessments.

4. With regards to the label, we recommend that the description of the TQT study acknowledges the limitation in dose/exposure. We defer final labeling decisions to DDDP.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In the thorough QT study in subjects who had treatment areas up to 60% body surface area, TRADENAME has not led to clinically significant effects on heart rate (HR), PR, and QRS interval durations or electrocardiogram (ECG) morphology, including prolongation of QTc.

In the Phase 3 studies in pediatrics and adults, no subject had QTcF > 480 ms or change of QTcF from baseline > 30 ms.

BACKGROUND

Crisaborole (AN2728), a phosphodiesterase 4 (PDE4) inhibitor, is being developed as a topical treatment (topical ointment, 2%) for inflammatory skin diseases. In the current NDA, the proposed indication is for the treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older.

The QT-IRT previously reviewed the TQT study (dated 5/20/2014 under IND 77537) and concluded that no significant QTc prolongation effect of Crisaborole (15 g/day and 45 g/day with designated treatment areas of 30% and 60% of body surface area respectively) was detected in this TQT study. No evident exposure-QTc relationship for crisaborole was observed in the TQT study; however the highest concentration in the TQT study was <180 ng/mL (with mean steady state C_{max} of 87.4 ng/mL at the 45 g/day dose).

The observed concentration in pediatric AD trial was higher than the concentration reached in the TQT trial (see the following table). In the MUSE pediatric AD study (AN2728-AD-102), the mean crisaborole C_{max} of 205 ng/mL was observed in the group of subjects of age 6 to 11 years old (with highest C_{max} value of 1,170 ng/mL). The PK data across the studies reveals an apparent relationship between exposure and %BSA treated with Crisaborole Topical Ointment, 2%.

Table 9: Key Pharmacokinetic Results in Pediatric and Adult Subjects following Multiple Dosing with Crisaborole Topical Ointment, 2%

Crisaborole PK Parameter	MUSE (Pediatric AD, 2-17 years) 27%–92% BSA ^a (AN2728-AD-102)	MUSE (Adult Psoriasis) 25%–80% BSA (AN2728-PSR-106)	TQT (Healthy Adults) 60% BSA (AN2728-TQT-108)	DDI (Healthy Adults) 60% BSA (AN2728-PK-101)
	Day 8 (N = 34)	Day 8 (N = 33)	Day 9 (N = 59)	Day 7 (N = 23)
T_{max} (hours)				
Median (range)	3.00 ^b (3.0–24.0)	2.00 (0.983–8.00)	3.07 (1.07–8.07)	4.00 (1–4.03)
C_{max} (ng/mL)				
Mean (SD)	127 ^a (196)	109 (73.7)	87.4 (29.6)	81.1 (17.8)
AUC_{0-12} (ng·h/mL)				
Mean (SD)	949 ^c (1240)	748 (455)	697 (205)	681 ^d (140)
$t_{1/2}$ (hours)				
Mean (SD)	NC ^e	9.77 (2.68)	11.0 (2.47)	9.27 ^d (6.62)

AD, atopic dermatitis; AUC_{0-12} , area under the plasma concentration-time curve from time zero to 12 hours; BSA, body surface area; C_{max} , maximum observed plasma concentration; DDI = drug-drug interaction; MUSE, maximal use systemic exposure; NC, not calculated; PK, pharmacokinetic; $t_{1/2}$, apparent first-order terminal elimination half-life; SD, standard deviation; T_{max} , time to maximum measured plasma concentration; TQT, thorough QT/QTc.

a BSA values represent the actual range enrolled.

b N = 33.

c N = 32.

d N = 22.

e $t_{1/2}$ was not calculated because of the limited number of samples collected in this pediatric population.

Source: Summary of clinical pharmacology, Page 56.

Standard 12-lead ECGs were performed in 615 subjects (Child 411, Adolescent 139, Adult 65) in the two Phase 3 Studies AN2728-AD-301 and AN2728-AD-302 (single tracing at baseline and on Day 8). No subject with QTcF > 480 ms or change of QTcF from baseline > 30 ms was observed in the Phase 3 studies.

According to the cardiovascular safety report,

- ECG interval values including mean HR, PR interval, QRS duration, and QTcF interval were normal and showed minimal mean changes from Baseline. No important emergent morphology changes were detected. Findings were nearly identical after application of either crisaborole or vehicle.
- Given the absence of relevant findings, it is concluded that there were no adverse ECG findings reaching levels of concern in children, adolescents, and adults (ages 2 years and older) with mild to moderate AD, after application of crisaborole 2% BID for 8 days. Specifically, no evidence of repolarization prolongation was found.

Thank you for requesting our input into the development of this product under NDA 207695. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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/s/

JIANG LIU
08/01/2016

CHRISTINE E GARNETT
08/02/2016

LABEL AND LABELING REVIEW

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

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

Date of This Review:	July 5, 2016
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 207695
Product Name and Strength:	Eucrisa (crisaborole) Ointment, 2%
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Anacor Pharmaceuticals, Inc.
Submission Date:	January 7, 2016
OSE RCM #:	2016-220
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader (Acting):	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

Anacor Pharmaceuticals, Inc. submitted NDA 207695 for Eucrisa (crisaborole) 2% ointment on January 7, 2016. Thus, the Division of Dermatology and Dental Products (DDDP) requested we evaluate the container labels, carton labeling, and prescribing information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and other areas of improvement. DMEPA identified areas in the labels and labeling that can be improved to increase the readability and prominence of important information and promote the safe use and handling of the product. We provide recommendations in 4.1 for the container label and carton labeling to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to promote the safe use of the product. We recommend the following be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR ANACOR PHARMACEUTICALS, INC.

- A. General Comments (all container labels and carton labeling)
 - 1. Replace "Tradename" with the conditionally acceptable proprietary name, Eucrisa.
 - 2. Increase the font size of the route of administration statement, "For Topical Use Only". As currently presented, the statement is less prominent than the net quantity and Rx only statements.
 - 3. Revise the dosage statement to read "**Dosage:** Apply twice daily to the affected areas. See package insert for full prescribing information." and relocate to appear above the statement "Each gram contains...".
 - 4. Revise the storage information to include the temperature unit after each numerical temperature reading. For example: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F)"
- B. Carton Labeling
 - 1. Place the statement "Not for ophthalmic, oral, or intravaginal use" below the statement "For Topical Use Only" to ensure that this important information is not overlooked.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for crisaborole ointment 2% that Anacor Pharmaceuticals, Inc. submitted on January 7, 2016.

Table 2. Relevant Product Information for crisaborole 2%	
Initial Approval Date	Pending
Active Ingredient	Crisaborole
Indication	Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older
Route of Administration	Topical
Dosage Form	Ointment
Strength	2%
Dose and Frequency	Apply twice daily to affected areas
How Supplied	60 g and 100 g laminate tubes
Storage	20°C - 25°C; excursions permitted to 15°C - 30°C (59°F - 86°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following crisaborole labels and labeling submitted by Anacor Pharmaceuticals, Inc. on January 7, 2016.

- Container Label
- Carton Labeling
- Professional Sample Container Label
- Professional Sample Carton Labeling

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CARLOS M MENA-GRILLASCA
07/05/2016

MISHALE P MISTRY
07/06/2016

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT #11518**

Consultant Reviewer: Jean Kim MD, MA, Medical Officer, ODE1-DPP
Consultation Requestor: Lydia Springs, MSHS, RPM, ODEIII-DDDP
Subject of Request: NDA 207695-Eucrisa (Crisaborole) 2% Ointment
Date of Request: 5/26/2016
Date Received: 5/26/2016
Desired Completion Date: 6/27/2016

I. Executive Summary

The Sponsor (Anacor Pharmaceuticals) submitted a NDA currently under review by the Division of Dermatology and Dental Products (DDDP) for crisaborole (Eucrisa) 2% ointment for the indication of atopic dermatitis (AD) on 1/7/2016. Efficacy was evaluated in two Phase 3 randomized, placebo-controlled, double-blind trials (AN2728-AD-301 and AN2728-AD-302). There was also an open-label long-term safety trial (AN2728-AD-303) using completers from AD-301 and AD-302.

Psychiatric adverse events were identified by DDDP and the Division of Psychiatry Products (DPP) was consulted to review the study data and provide input on whether these psychiatric adverse event (AE) trends are a valid safety signal, and if so, what labeling guidance should be provided. Overall, the rates of psychiatric AEs found in the studies was low, and did not demonstrate statistically significant differences between the study drug population and placebo. However, there remain some possible class effects with phosphodiesterase-4 (PDE-4) inhibitors and psychiatric AEs that could warrant ongoing monitoring and caution.

II. Background

Crisaborole (also known as AN2728) is a novel benzoxaborole PDE-4 inhibitor developed as a topical 2% ointment for the treatment of mild to moderate AD in patients 2 years and older.

PDE-4 inhibitors are known to block hydrolyzation/degradation of cyclic AMP into AMP in cells by PDE-4, leading to increase of cAMP levels, particularly in immune cells. This blockade leads to anti-inflammatory effects. This mechanism is also postulated to have several possible central nervous system (CNS) and psychiatric effects, including antidepressant and anti-anxiety effects (isoforms 4D and 4A), procognitive and long-term memory improvement effects, increased alertness/wakefulness, and antipsychotic effects (4A) via dopamine₁ regulation in the frontal cortex.¹ (4C is noted to be mainly peripheral in

action.) Unfortunately, 4D also directly enhances emesis mechanisms in the area postrema leading to gastrointestinal/nausea side effects.

Furthermore, in terms of psychiatric effects, PDE4 may be involved in the mechanism of action for antidepressants²; rat studies have shown increased PDE4A4 expression in key brain areas after antidepressant treatment, even across various classes of antidepressants. PDE-4 inhibitors in animal studies are theorized to reduce dopamine depletion in the striatum and loss of neurons in other key brain regions like the substantia nigra, nucleus accumbens, and hippocampus. Rolipram, a PDE-4 inhibitor, was initially studied as a potential antidepressant but trials were halted due to high rates of nausea and vomiting.

III. Review of Clinical Data

A. Selection of Relevant Clinical Trials

Table 1. Crisaborole Phase 2/3 Trials in Subjects with Mild-to-Moderate AD

Trial	Trial Design (treatment period)	N (Safety Population)	Age (ITT)	Treatment Groups	Gender (ITT)
AN2728-AD-301 (Phase 3)	Randomized, double-blind, placebo-controlled trial (28 days)	503 subjects on drug (477 completed) and 256 on placebo (225 completed)	2 to 65, mean age 12.0 for drug, 12.4 for placebo	Crisaborole 2% versus placebo	332 male, 427 female
AN2728-AD-302 (Phase 3)	Randomized, double-blind, placebo-controlled trial (28 days)	510 subjects on drug (483 completed) and 247 on placebo (213 completed)	2 to 79, mean age 12.6 for drug, 11.8 for placebo	Crisaborole 2% versus placebo	343 male, 420 female
AN2728-AD-303 (Phase 3)	Open-label uncontrolled long-term safety trial with 2% crisaborole ointment (48 weeks) using subjects from AD-301 and AD-302	517 subjects, 271 completed study (246 discontinued) (357 were originally on drug, 160 originally on placebo)	2 to 65, mean age 11.7	n/a	211 male, 306 female
AN2898-AD-202	Randomized,	46 subjects, 42	19 to 73,	AN2898	25

¹ Houslay MD, et al., *Drug Discovery Today*. 2005, 10(22): 1503-1519.

² Takahashi et al., *Journal of Neuroscience*. 1999, 19(2):610-618.

(Phase 2A)	double-blind, placebo-controlled trial (42 days)	completed study (4 discontinued)	mean age 41.3 years	1%/placebo (21 subjects), Crisaborole 2%/placebo (25 subjects)	male, 21 female
AN2728-AD-204 (Phase 2)	Randomized, double-blind, uncontrolled dose response trial (29 days)	86 subjects (85 completed)	12 to 17, Mean age- 14.8 years	Crisaborole 2% and Crisaborole 0.5% BID versus QD	34 male, 52 female

Five Phase 2/3 clinical trials were performed with crisaborole ointment. I will focus on the two placebo-controlled Phase 3 trials. (The placebo control design in the Phase 2A trial AD-202 was not similar to the study designs used in Phase 3; it was an on-off crossover design.)

B. Psychiatric Inclusion/Exclusion Criteria

For Study AD-301 and AD-302, the same inclusion/exclusion criteria were used. There were no specific psychiatric criteria, although in theory one exclusion criterion could encompass psychiatric conditions: “Has any clinically significant medical disorder, condition, or disease...at Screening that in the PI’s or designee’s opinion may interfere with study objectives (e.g., expose subject to unacceptable risk by study participation, confound evaluation of treatment response or AEs, or interfere with subject’s ability to complete the study.)” It’s unclear if this criterion was used to exclude any patients with psychiatric issues in these studies. Study AD-303 used the same subjects from AD-301 and AD-302 but excluded subjects who had to discontinue the study drug for whatever reason in those trials. It is notable that the majority of subjects in Studies AD-301 and AD-302 were under age 18: 86% of 1012 crisaborole subjects and 87% of 499 placebo subjects.

In Study AD-202, which was done only in subjects 18 years and older, patients with major psychiatric histories *were* excluded. Study AD-204 was only done in subjects 12 to 17 years old and used the same criterion mentioned with AD-301 and AD-302 re: any condition interfering with study objectives/participation.

C. Psychiatric Safety Monitoring

Assessments (including AE monitoring) were done at Screening, Baseline (up to 35 days after Screening), and then weekly during AD-301 and AD-302 until Day 36 (about one week after last treatment). No formal psychiatric symptom rating scales were used such as the Columbia Suicide Severity Rating Scale (C-SSRS) or Patient Health Questionnaire-8 Item (PHQ-8). Quality-of-life questionnaires such as the Children’s Dermatology Life Quality Index (CDLQI)/ Dermatology Life Quality Index (DLQI) and Dermatitis Family Impact Questionnaire (DFI), for

parents/guardians) were used at Baseline, End of Treatment, and at Early Discontinuation if applicable. These included a few psychological questions related to skin appearance such as level of shame/sadness, being teased/avoided at school, and level of activity participation and sleep, but all are qualified in the questionnaires as secondary to skin issues only.

For Study AD-303, the same quality-of-life questionnaires were used before and after every 28-day treatment cycle and one week after. AEs were assessed at the same intervals, with an additional phone call one week after treatment cycle initiation. No other formal psychiatric symptom rating scales were used.

D. Coding of Psychiatric Adverse Events

MedDRA version 16.1 was used by the Sponsor to code AE terms to preferred terms in the Phase 3 studies for all trials reviewed. I reviewed all the AE.xpt datasets for coding accuracy and found them satisfactory from a psychiatric AE perspective. Terms were found under AEBODSYS category for Psychiatric disorder SOC. Under AEDECOD (high-level preferred terms) they were as follows: for Study 301—intentional self-injury, suicide attempt, depression, confusional state, listless, agitation, anxiety, depression, for Study 302—insomnia, bipolar disorder, suicidal ideation, depression, for Study 303—ADHD, depression, anxiety, insomnia, suicidal ideation, suicide attempt.

E. Review of Psychiatric Adverse Event Data

i. Psychiatric AE Analysis

I reviewed both the Sponsor-provided study reports and the AE.xpt datasets for reported psychiatric AEs. I also reviewed any laceration events and determined they were all likely accidental/non-psychiatric in nature except for the events that were coded already as psychiatric.

From my own dataset review, I found the following numbers of psychiatric SOC AEs:

Table 2. Psychiatric AE Subjects/Events in Phase 2/3 Crisaborole AE Trials

Study	Subjects with Psychiatric AEs	Events
AD-301	5	7
AD-302	3	4
AD-303	10	14
AD-202	0	0
AD-204	0	0

From AD-301, I chose to include one event of agitation secondary to skin reaction as per the original coding as a psychiatric event, although one might argue it could be excluded. (This subject had a prior diagnosis of ADHD as well; the Sponsor also chose to include this event.) From AD-301, I also excluded one event of self-injury that occurred after screening but prior to initiation of treatment.

Two subjects/events were duplicated between being in AD-303 and their initial Phase 3 study. (131011 and 204012). 131011 occurred at Day 36 in AD-301, and 204012 occurred at Day 24 in AD-302. I decided to remove them from the AD-303 count.

For placebo comparison, I determined the following:

Table 3. Psychiatric AE Subjects Crisaborole versus Placebo in Phase 3 AD RCTs

Study	Crisaborole 2%	Crude Rate	Placebo	Crude Rate
AD-301	5	5/502=0.99%	0	0/252=0
AD-302	2	2/510=0.39%	1	1/247=0.40%
Pooled Total	7	7/1012=0.69%	1	1/499=0.20%

Dropout rates were fairly low and treatment period was short (28 days); therefore, the crude rates are expected to be reasonably reliable for comparing the treatment groups, and exposure-adjusted reporting rates are not presented.

All subjects in AD-301 and AD-302 with psychiatric AEs were under 18 years old (Only one subject in AD-303 was over 18.) Two (1 placebo/insomnia, 1 confusional state) were ages 2 to 11 and the rest were ages 12-17. (870 of 1012 crisaborole subjects and 434 of 499 placebo subjects were under age 18, and 454 of 517 subjects in Study AD-303 were under age 18.)

The difference between the two treatment groups (drug versus placebo) for psychiatric AEs is not considered statistically significant as per Fisher's Exact Test (p value of 0.28>0.05) although power is limited.

Table 4. Psychiatric AE Subtypes in the Pool of AD-301 and AD-302*

	Crisaborole 2% (N=1012)	Placebo (N=499)
Depression**	3 (0.30%)	0
Anxiety	1 (0.10%)	0
Bipolar worsening	1 (0.10%)	0
Agitation	1 (0.10%)	0
Insomnia	0	1 (0.20%)
Suicide Attempt/Ideation	2 (0.20%)	0
Confusion/listless	1 (0.10%)	0

*Two subjects counted twice here for separate event type classifications (AD-301-115018 was coded as both suicide attempt and depression events separately here and AD-302-233005 was coded as both bipolar disorder and suicidal ideation separately.)

**Difference is non-significant (p=0.56; 2-tailed Fishers exact test).

Table 5. Psychiatric AE Subtypes in AD-303

	Crisaborole 2% (N=517)
Depression	4 (0.77%)
Anxiety	1 (0.19%)
ADHD	4 (0.77%)
Insomnia	1 (0.19%)
Suicide Attempt/Ideation	2 (0.39%)
Total	10 (1.93%)

ii. Suicidal Ideation and Behavior (SIB) and Psychiatric Hospitalizations

No deaths were reported in any of these three studies.

For suicidal ideation and behavior (SIB) events (all were on the study drug), I found the following:

Table 6. SIB Subjects in Crisaborole AD Phase 2/3 Trials

Study	Subjects with SIB AEs	Subject Number	Event Date
AD-301	1 (suicide attempt)	AD-301-115018	Day 27
AD-302	1 (suicidal ideation)	AD-302-233005	Day 20
AD-303	2 (suicidal ideation and suicide attempt)	AD-302-204041, AD-302-220016	Day 52 (SI), Day 198 (SA) (including time in initial drug trial)
AD-202	0		0
AD-204	0		0

Three of the four SIB events led to hospital evaluation, and two of the four led to psychiatric inpatient hospitalizations. Two had a prior psychiatric history (bipolar disorder/depression in one subject, and depression/anxiety in the other subject) and psychiatric medications noted on their initial screening. All SIB subjects were between 12 to 17 years old. (The majority of subjects in these studies are also in this age group.)

For placebo comparison, I calculated the following:

Table 7. SIB Subjects Crisaborole versus Placebo in Pooled Phase 3 AD RCTs

Study	Crisaborole 2%	Crude Rate	Placebo	Crude Rate
AD-301	1	1/502=0.20%	0	0/252=0
AD-302	1	1/510=0.20%	0	0/247=0
Pooled Total	2	2/1012=0.20%	0	0/499=0

Again, these differences are not statistically significant.

iii. Case Summaries

Brief case summaries and WHO based causality assessments of the four SIB events and one other SAE event were as follows:

Table 8. SAE and SIB Case Summaries

Subject ID	Study	Event Type	Summary	Causality Assessment
115018	301	SIB	13 year old WF subject had a reported suicide attempt (overdose on 8 tabs of 0.5mg lorazepam, four 325mg aspirin tabs, and two 200mg ibuprofen tabs) and was hospitalized for 6 days and put on Prozac with a diagnosis of depression. No prior psychiatric history noted. The subject allegedly had recent stressor of transitioning to high school. The subject had reportedly stopped taking the study drug 5 days prior to the overdose and withdrew from the study. No other medical medications noted.	<u>Unlikely</u> , due to temporality
233005	302	SIB	14 year old Pacific Islander F subject had a history of bipolar disorder and depression and arachnoid cyst since 2013, and had	<u>Possible</u> , due to temporality (symptoms worsened shortly

			<p>been on psychiatric medication already including Lamictal. Worsening of bipolar symptoms was noted as early as Day 4 (where she reportedly started Ativan), and then the subject was hospitalized with suicidal ideation at Day 20. The subject was hospitalized for 7 days and switched to Seroquel and Benadryl. The subject completed the study. No other medical medications noted.</p>	<p>after starting study drug whose half-life is 4 days, and continued to worsen) and mechanism of effect (study drug may have antidepressant effects which hypothetically could worsen mania.)</p>
204041	303	SIB	<p>13yo WF subject with no known prior psychiatric history allegedly wrote a suicide note that was found but felt not to be serious for unclear reasons and was not even reported as a serious AE, and was not referred for hospital evaluation. Was referred for counseling. No psychiatric medications noted. Was only also taking intermittent triamcinolone topical ointment.</p>	<p><u>Unassessable</u> due to lack of provided information on severity/timing of event, no case report available, although study investigators did not appear concerned enough upon evaluation to even report as SAE or send to hospital.</p>
220016	303	SIB	<p>12 year old Af-Am F subject overdosed on Benadryl in a suicide attempt and was assessed in emergency room (ER) and discharged. No prior psychiatric history noted. Subject was started on Trazodone after ER visit. Subject had reported history of being bullied due to her skin condition, and knew of a peer who had committed suicide in the last year. Study drug had reportedly not been applied for 24 days prior to event until one day before event. Subject</p>	<p><u>Possible</u> due to temporality of event after restarting drug (although levels are likely low after just 1 day); also was taking other potential mood-affecting drugs.</p>

			withdrew from the study. Had also been on fluocinolone ointment and prednisone (timing unclear).	
115012	303	Depression	13 year old WF subject was hospitalized for depression for one month in context of “situational stressors per parent.” No prior psychiatric history was noted per the initial case report, although Sponsor notes in their report that patient did have prior history of depression 3 months before the study; patient was put on Prozac, Melatonin, Trazodone, and Geodon. Intermittent study drug compliance was reported. Depression AEs were noted for this subject at Day 159, 229, and 258. Subject had also been on ethinyl estradiol for irregular menses.	<u>Unlikely</u> , given temporality (had been on study drug for months without acute changes) and other pre-existing illness.

iv. Anxiety and Insomnia

Given that anxiety and insomnia cases were extremely rare in the Phase 3 trials, I did not feel there was likely any causality issue involved between the study drug and those AEs. There were only two anxiety cases total, one (131011) in AD-301 and one (239001) in AD-303, both having been on study drug. There were only two insomnia cases total, one in AD-302 (204012) who was on placebo, and one (204029) in AD-303. Temporality in all the cases made causality unlikely as well, since the subject had been on the medication for at least two weeks or longer in all cases.

v. Concomitant Medications

Both AD-301 and AD-302 groups were taking similar percentages of concomitant psychotropic medications. This seems to indicate similar rates of psychiatric morbidity in both treatment groups.

Table 9. AD-301 and AD-302 Subjects Taking Concomitant Psychotropic Medications

Psychotropic Medications	Number of Subjects-Study Drug	Number of Subjects-Placebo
“Psychoanaleptics,” i.e. stimulants and antidepressants	64 (6.3%)	30 (6.0%)

“Psycholeptics,” i.e. benzodiazepines, sleep medications, antipsychotics	17 (1.7%)	11 (2.2%)
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Both AD-301 and AD-302 groups also were taking similar amounts of concomitant steroid medications (which have the potential to adversely affect mood, sleep, and anxiety). So it does not seem likely that steroid medications biased the comparison of psychiatric event rates.

Table 10. AD-301 and AD-302 Subjects Taking Concomitant Steroid Medications

Type of Steroid	Subjects on Drug	Subjects on Placebo
Systemic	13 (1.3%)	6 (1.2%)
Topical	26 (2.6%)	22 (4.4%)
Inhaled	52 (5.1%)	27 (5.4%)

F. Summary of Sponsor’s Standard Analyses

As per the Sponsor’s Clinical Summary of Safety report³, the Sponsor pooled and analyzed the safety data from two Phase 3 trials AD-301 and AD-302, and also looked at the overall safety data from 23 total clinical studies in the crisaborole program (which encompasses psoriasis in addition to AD), using MedDRA 16.1 for their analysis by coding for general Psychiatric SOC terms (but not a formal SMQ analysis). The overall safety population included 1340 patients with AD exposed to crisaborole), 482 healthy volunteers exposed to crisaborole), and 335 psoriasis patients exposed to crisaborole. So, a total of 2157 subjects were exposed to crisaborole. 1150 of the 1340 AD subjects (86%) exposed to crisaborole were under age 18.

In general, no psychiatric AEs were noted in these other studies (AD-202, AD-204), except for the Phase 3 AD studies I have examined.

For the pooled data from AD-301 and AD-302, the Sponsor noted (as did I) one psychiatric SAE of suicide attempt in Study AD-301 and one psychiatric SAE of suicidal ideation in Study AD-302. The sponsor states that there were no dropouts in these trials because of psychiatric AEs. However, this contradicts the case narrative for a subject in AD-301 who withdrew from the study after a suicide attempt. Overall they noted the following incidence of psychiatric AE events in the two studies:

Table 11. Sponsor Tabulation of Psychiatric AEs in AD-301 and AD-302

	Drug: Ages 2- 11	Drug: Ages 12-17	Drug: Ages 18 plus	Total Drug	Placebo: Ages 2- 11	Placebo: Ages 12- 17	Placebo: Ages 18 plus	Total Placebo
Psychiatric AEs	1 (0.2%)	5 (2.0%)	0	6 (0.6%)	1 (0.3%)	0	0	1 (0.2%)

³ Anacor Pharmaceuticals, Clinical Summary of Safety, NDA 207695. Pages 16 and 23.

For unclear reasons, the Sponsor seems to have omitted one depression AE which I included in my analysis and is present in their dataset. It may be that they combined one depression event in the same subject with a suicide attempt event (although they did not do this for another subject with both bipolar disorder event and suicidal ideation event).

For Study AD-303, two psychiatric SAEs were noted by the Sponsor, one depression and one suicide attempt (this patient was subsequently withdrawn from the study). (As I noted earlier, another event of possible suicidal ideation was not deemed serious upon assessment for unclear reasons; no full case narrative available.)

G. Scale Data

The quality-of-life scales used are not designed for the assessment of primary psychiatric symptomatology. No other psychiatric scales were used in these studies.

IV. Other Consults/History

In the United States, out of several newer selective PDE-4 inhibitors reviewed, only roflumilast has been FDA-approved for any indication (COPD).

Roflumilast did have a higher rate of psychiatric AEs versus placebo during its initial NDA approval studies, most commonly insomnia, anxiety, and depression.⁴ Three completed suicides and two suicide attempts were also noted in the COPD safety database (n=12,054) versus one suicidal ideation in placebo, although two of the completed suicides had stopped the study drug around 20-21 days before the event. A REMS was submitted in April 2010, and initially the application received a complete response. Afterwards, the Sponsor (Forest) reanalyzed their safety data using the Columbia Classification Algorithm of Suicide Assessment (C-CASA), with a pool of 21,623 patients (11,848 receiving roflumilast) from 36 total controlled parallel group studies across several indications (COPD, arthritis, diabetes mellitus, allergic rhinitis). They found two suicide attempts and one completed suicide in the study drug group, and one suicidal ideation in placebo. (They excluded the two suicides that had the 21 day lag.) The difference in suicide risk rates was felt to be statistically not significant, and a psychiatry consult by Dr. Phillip Kronstein in November 2010 agreed no major safety concern was likely present, although there was a two- to three-fold increase in rates of anxiety, depression, and insomnia in patients on roflumilast versus placebo. A warning about possible psychiatric event risk was included in the labeling accordingly.

Other PDE-4 inhibitors have been examined before for psychiatric AE issues, such as apremilast which showed some substantial but not statistically significant elevation of insomnia and depression events relative to placebo (2.4% versus 1.0% and 1.4% versus 0.4% respectively). SIB

⁴ Kronstein, Roflumilast DPP Consult 11236, November 2010.

events were rare and similar to placebo (one in each treatment arm.) Description of this issue in labeling was recommended, as well as prospective use of screening scales like the C-SSRS.⁵

(b) (4)

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⁵ Kronstein, Apremilast DPP Consult 11411, January 2014.
(b)(4)

⁷ Rolan et al, *Expert Opin Pharmacother*, 20097. 10(17):2897-2904.
(b) (4)

8
9 (b) (4)

V. Conclusions and Recommendations

Overall the rates of psychiatric AEs were low in the crisaborole treatment group in the Phase 3 AD studies reviewed above. It is unclear, however, if the low rates are in part due to lack of formal psychiatric symptom monitoring in these trials. There was a slightly higher incidence of psychiatric AEs in the treatment group versus placebo (0.69% versus 0.20%) in the two placebo-controlled Phase 3 trials, but these differences were not statistically significant.

Causality assessments from the case narratives for the SIB events only seemed possible for two of the four cases reviewed based on temporality and hypothetical mania induction in one case. For depression, anxiety, and insomnia events in these studies, causality seemed unlikely.

Sponsor analysis was limited (as discussed above) by some case omissions, and lack of use of formal psychiatric scales or monitoring methods.

Nearly all the events occurred in a vulnerable adolescent population known for increased baseline mood and suicidal behavior risk, especially with the disease-related additional stressors of skin appearance and peer/school pressure. There were no clear trends noted with prior psychiatric history, or study drug dosing/timing (except two SIB events that seemed to occur within one to three days of study drug initiation or reinitiation), or concomitant medications being taken, or gender/race (except that all the psychiatric AEs involving mood/anxiety/SIB except for one occurred in females).

Other PDE-4 inhibitors have been known to have some psychiatric and CNS effects, and a class association cannot be completely ruled out at this time. Adolescents are also known to be more physiologically vulnerable to suicidal and mood effects from medications (antidepressants, Accutane) and psychosocial factors.

It is difficult to know for certain if there is no psychiatric risk, or minimal risk, based on the currently available safety data on crisaborole. The overall rates of psychiatric AEs appear

extremely low in these Phase 3 studies, although there was also no formal psychiatric monitoring.

I recommend use of screening tools such as the C-SSRS and/or the Physician Depression Questionnaire (PDQ) prospectively for future clinical trials with crisaborole. I would note that all screening tools for suicidality are limited in terms of any ability to predict or prevent SIB events.

I also recommend a general advisory/addition in labeling such as the following in the Adverse Reactions section of labeling:

In Phase 3 clinical trials, there were four cases of suicidal ideation and behavior noted in the treatment group versus none in placebo, out of a study population of about 1013 subjects on the study drug and 503 on placebo.

Also, given some similar events occurring in pre- and post-marketing data for currently marketed PDE-4 inhibitors like roflumilast and apremilast (Section 5.2 and Section 5.1 of their labeling respectively), it may be worth considering whether a class-wide warning or precaution in labeling should be considered, such as the following: *Psychiatric Events including Suicidality-- Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts, or other mood changes, and if such changes occur to contact their healthcare provider. Carefully weigh the risks and benefits of treatment with crisaborole in patients with a history of depression and/or suicidal thoughts or behavior.*

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/s/

JEAN S KIM
06/23/2016

JASMINE C GATTI
06/23/2016

MITCHELL V Mathis
06/23/2016



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 20, 2016

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Lydia Springs, RPM
DDDP

Subject: QT-IRT Consult to NDA 207695

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 2/23/2016 regarding the adequacy of crisaborole's QT assessment. The QT-IRT received and reviewed the following materials:

- Your consult;
- Summary of clinical pharmacology;
- Summary of clinical safety;
- Cardiovascular safety report; and
- QT-IRT's previous review for TQT Study AN2728-TQT -108 (dated 5/20/2014 under IND 77537).

QT-IRT Comments for DDDP

It appears that there is no substantial increase in cardiac adverse events after application of crisaborole compared to that from vehicle in Phase 3 trials; however ECG monitoring in Phase 3 trials is mainly for patient safety and detecting outliers. ECG monitoring in Phase 3 trials is not adequate for QT assessment (or ruling out clinically relevant QT effect).

The thorough QT study demonstrates that no significant QTc prolongation effect of crisaborole at a dose of 2% crisaborole ointment up to 45 g/day (designated treatment areas which

represented ~ 60% of body surface area (BSA)); however the highest concentration in the TQT study was <180 ng/mL (with mean steady state C_{max} of 87.4 ng/mL at the 45 g/day dose). In the MUSE pediatric AD study (AN2728-AD-102), the mean crisaborole C_{max} of 205 ng/mL was observed in the group of subjects of age 6 to 11 years old (with highest C_{max} value of 1,170 ng/mL). Although according to the sponsor, no safety signals were noted upon review of treatment emergent AEs in those subjects, the effect of crisaborole on the QTc interval in those patients cannot be reliably predicted based on currently available preclinical and clinical information. Because exposure to crisaborole increases with %BSA treated, additional thorough QT assessment might be needed in subjects with treatment areas substantially larger than 60% of BSA if the division is interested in further characterizing the potential of crisaborole to prolong QTc interval at high clinical exposures.

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

(b)(4)

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of TRADENAME on the QTc interval was evaluated in a Phase 1 randomized placebo and positive controlled parallel thorough QTc study in 180 healthy subjects. In subjects with the designated treatment areas up to 60% of body surface area, TRADENAME did not prolong QTc to any clinically relevant extent. The effect of crisaborole on the QTc interval in patients with treatment areas substantially larger than 60% of body surface area was not characterized.

BACKGROUND

Crisaborole (AN2728), a phosphodiesterase 4 (PDE4) inhibitor, is being developed as a topical treatment (topical ointment, 2%) for inflammatory skin diseases. The current NDA is indicated for the treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older.

The QT-IRT previously reviewed the TQT study (dated 5/20/2014 under IND 77537) and concluded that no significant QTc prolongation effect of Crisaborole (15 g/day and 45 g/day with designated treatment areas of 30% and 60% of body surface area respectively) was detected in this TQT study. No evident exposure-QTc relationship for crisaborole was observed in the TQT study; however the highest concentration in the TQT study was <180 ng/mL (with mean steady state C_{max} of 87.4 ng/mL at the 45 g/day dose).

The observed concentration in pediatric AD trial was higher than the concentration reached in the TQT trial (see the following table). In the MUSE pediatric AD study (AN2728-AD-102), the mean crisaborole C_{max} of 205 ng/mL was observed in the group of subjects of age 6 to 11 years

old (with highest C_{max} value of 1,170 ng/mL). The PK data across the studies reveals an apparent relationship between exposure and %BSA treated with Crisaborole Topical Ointment, 2%.

Table 9: Key Pharmacokinetic Results in Pediatric and Adult Subjects following Multiple Dosing with Crisaborole Topical Ointment, 2%

Crisaborole PK Parameter	MUSE (Pediatric AD, 2-17 years) 27%–92% BSA ^a (AN2728-AD-102)	MUSE (Adult Psoriasis) 25%–80% BSA (AN2728-PSR-106)	TQT (Healthy Adults) 60% BSA (AN2728-TQT-108)	DDI (Healthy Adults) 60% BSA (AN2728-PK-101)
	Day 8 (N = 34)	Day 8 (N = 33)	Day 9 (N = 59)	Day 7 (N = 23)
T_{max} (hours)				
Median (range)	3.00 ^b (3.0–24.0)	2.00 (0.983–8.00)	3.07 (1.07–8.07)	4.00 (1–4.03)
C_{max} (ng/mL)				
Mean (SD)	127 ^a (196)	109 (73.7)	87.4 (29.6)	81.1 (17.8)
AUC_{0-12} (ng·h/mL)				
Mean (SD)	949 ^c (1240)	748 (455)	697 (205)	681 ^d (140)
$t_{1/2}$ (hours)				
Mean (SD)	NC ^e	9.77 (2.68)	11.0 (2.47)	9.27 ^d (6.62)

AD, atopic dermatitis; AUC_{0-12} , area under the plasma concentration-time curve from time zero to 12 hours; BSA, body surface area; C_{max} , maximum observed plasma concentration; DDI = drug-drug interaction; MUSE, maximal use systemic exposure; NC, not calculated; PK, pharmacokinetic; $t_{1/2}$, apparent first-order terminal elimination half-life; SD, standard deviation; T_{max} , time to maximum measured plasma concentration; TQT, thorough QT/QTc.

a BSA values represent the actual range enrolled.

b N = 33.

c N = 32.

d N = 22.

e $t_{1/2}$ was not calculated because of the limited number of samples collected in this pediatric population.

Source: Summary of clinical pharmacology, Page 56.

Standard 12-lead ECGs were performed in 615 subjects (Child 411, Adolescent 139, Adult 65) in the two Phase 3 Studies AN2728-AD-301 and AN2728-AD-302 (single tracing at baseline and on Day 8). No subject with QTcF > 480 ms or change of QTcF from baseline > 30 ms was observed in the Phase 3 studies. According to the cardiovascular safety report,

- ECG interval values including mean HR, PR interval, QRS duration, and QTcF interval were normal and showed minimal mean changes from Baseline. No important emergent morphology changes were detected. Findings were nearly identical after application of either crisaborole or vehicle.
- Given the absence of relevant findings, it is concluded that there were no adverse ECG findings reaching levels of concern in children, adolescents, and adults (ages 2 years and older) with mild

to moderate AD, after application of crisaborole 2% BID for 8 days. Specifically, no evidence of repolarization prolongation was found.

Thank you for requesting our input into the development of this product under NDA 207695. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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/s/

JIANG LIU
04/20/2016

CHRISTINE E GARNETT
04/20/2016