CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207695Orig1s000

<u>LABELING</u>

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

EUCRISA™ (crisaborole) ointment, 2%, for topical use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
EUCRISA is a phosphodiesterase 4 inhibitor indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Apply a thin layer twice daily to affected areas. (2)
- For topical use only. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Ointment, 2%. (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to crisaborole or any component of the formulation. (4)

----------WARNINGS AND PRECAUTIONS----------
Hypersensitivity reactions: If signs and symptoms of hypersensitivity occur, discontinue EUCRISA immediately and initiate appropriate therapy. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reaction occurring in ≥1% in subjects is application site pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Anacor Pharmaceuticals at 1-844-4ANACOR [1-844-426-2267] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EUCRISA is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

Apply a thin layer of EUCRISA twice daily to affected areas.
EUCRISA is for topical use only and not for ophthalmic, oral, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Ointment: 20 mg of crisaborole per gram (2%) of white to off-white ointment.

4 CONTRAINDICATIONS

EUCRISA is contraindicated in patients with known hypersensitivity to crisaborole or any component of the formulation *[see Warnings and Precautions (5. 1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with EUCRISA. Hypersensitivity should be suspected in the event of severe pruritus, swelling and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, discontinue EUCRISA immediately and initiate appropriate therapy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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.

In two double-blind, vehicle-controlled clinical trials (Trial 1 and Trial 2), 1012 subjects 2 to 79 years of age with mild to moderate atopic dermatitis were treated with EUCRISA twice daily for 4 weeks. The adverse reaction reported by ≥1% of EUCRISA-treated subjects is listed in Table 1.

Table 1: Adverse Reaction Occurring in ≥1% of Subjects in Atopic Dermatitis Trials through Week 4

Adverse Reaction	EUCRISA N=1012 n (%)	Vehicle N=499 n (%)
Application site pain[a]	45 (4)	6 (1)

[a] Refers to skin sensations such as burning or stinging.

Less common (<1%) adverse reactions in subjects treated with EUCRISA included contact urticaria *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There is 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 pregnant rats and rabbits during organogenesis at doses up to 5 and 3 times, respectively, the maximum recommended human dose (MRHD) [*see Data*].

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

Rat and rabbit embryo-fetal development was assessed after oral administration of crisaborole. Crisaborole did not cause adverse effects to the fetus at oral doses up to 300 mg/kg/day in pregnant rats during the period of organogenesis (5 times the MRHD on an AUC comparison basis). No treatment-related fetal malformations were noted after oral treatment with crisaborole in pregnant rats at doses up to 600 mg/kg/day (18 times the MRHD on an AUC comparison basis) during the period of organogenesis. Maternal toxicity was produced at the high dose of 600 mg/kg/day in pregnant rats and was associated with findings of decreased fetal body weight and delayed skeletal ossification. Crisaborole did not cause adverse effects to the fetus at oral doses up to the highest dose tested of 100 mg/kg/day in pregnant rabbits during the period of organogenesis (3 times the MRHD on an AUC comparison basis).

In a prenatal/postnatal development study, pregnant 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 20 of lactation). Crisaborole did not have any adverse effects on fetal development at doses up to 600 mg/kg/day (18 times the MRHD on an AUC comparison basis). Maternal toxicity was produced at the high dose of 600 mg/kg/day in pregnant rats and was associated with findings of stillbirths, pup mortality, and reduced pup weights.

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 is systemically absorbed. The lack of clinical data during lactation precludes a clear determination of the risk of EUCRISA to a breastfed infant. Therefore, the developmental 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.

8.4 Pediatric Use

The safety and effectiveness of EUCRISA have been established in pediatric patients age 2 years and older for topical treatment of mild to moderate atopic dermatitis. Use of EUCRISA in this age group is supported by evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled 28-day trials which included 1,313 pediatric subjects 2 years and older *[see Adverse Reactions (6.1) and Clinical Studies (14)]*. The safety and effectiveness of EUCRISA in pediatric patients below the age of 2 years have not been established.

8.5 Geriatric Use

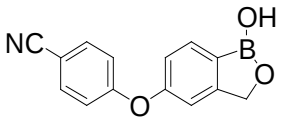
Clinical studies of EUCRISA did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

EUCRISA contains 2% crisaborole (w/w) in a petrolatum-based, white to off-white ointment and is for topical use. The active ingredient, crisaborole, is a phosphodiesterase-4 (PDE-4) inhibitor.

Crisaborole is described chemically as 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-[2,1]-benzoxaborole. The empirical formula is $C_{14}H_{10}BNO_3$ and the molecular weight is 251.1 g/mol.

The structural formula is represented below:



Crisaborole drug substance is freely soluble in common organic solvents such as isopropyl alcohol and propylene glycol, and insoluble in water.

Each gram of EUCRISA contains 20 mg of crisaborole in an ointment containing white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated hydroxytoluene, and edetate calcium disodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Crisaborole is a phosphodiesterase 4 (PDE-4) inhibitor. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. The specific mechanism(s) by which crisaborole exerts its therapeutic action for the treatment of atopic dermatitis is not well defined.

12.2 Pharmacodynamics

At therapeutic doses, EUCRISA ointment is not expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics (PK) of EUCRISA were investigated in 33 pediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and a mean ± SD body surface area involvement of 49 ± 20% (range 27% to 92%). In this study, subjects applied approximately 3 mg/cm^2 of EUCRISA ointment (dose range was approximately 6 g to 30 g per application) twice daily for 8 days.

Plasma concentrations were quantifiable in all the subjects. The mean ± SD maximum plasma concentration (C_{max}) and area under the concentration time curve from 0 to 12 hours post dose (AUC_{0-12}) for crisaborole on Day 8 were 127 ± 196 ng/mL and 949 ± 1240 ng*h/mL, respectively. Systemic concentrations of crisaborole were at steady state by Day 8. Based on the ratios of AUC_{0-12} between Day 8 and Day 1, the mean accumulation factor for crisaborole was 1.9.

Distribution

Based on an in vitro study, crisaborole is 97% bound to human plasma proteins.

Elimination

Metabolism

Crisaborole is substantially metabolized into inactive metabolites. The major metabolite 5-(4-cyanophenoxy)-2-hydroxyl benzylalcohol (metabolite 1), is formed via hydrolysis; this metabolite is further metabolized into downstream metabolites, among which 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid (metabolite 2), formed via oxidation, is also a major metabolite.

PK of metabolites 1 and 2 were assessed in the PK study described above and the systemic concentrations were at or near steady state by Day 8. Based on the ratios of AUC_{0-12} between Day 8 and Day 1, the mean accumulation factors for metabolites 1 and 2 were 1.7 and 6.3, respectively.

Excretion

Renal excretion of metabolites is the major route of elimination.

Drug Interaction Studies

In vitro studies using human liver microsomes indicated that under the conditions of clinical use, crisaborole and metabolite 1 are not expected to inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4.

In vitro human liver microsomes studies for metabolite 2 showed that it did not inhibit activities of CYP2C19, 2D6, and 3A4; was a weak inhibitor of CYP1A2 and 2B6; and a moderate inhibitor of CYP2C8 and 2C9. The most sensitive enzyme, CYP2C9, was further investigated in a clinical trial using warfarin as a CYP2C9 substrate. The results of this study showed no drug interaction potential.

In vitro studies in human hepatocytes showed that under the conditions of clinical use, crisaborole and metabolites 1 and 2 are not expected to induce CYP enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 30, 100, and 300 mg/kg/day crisaborole were administered to rats once daily. A drug-related increased incidence of benign granular cell tumors in the uterus with cervix or vagina (combined) was noted in 300 mg/kg/day crisaborole treated female rats (2 times the MRHD on an AUC comparison basis). The clinical relevance of this finding is unknown.

In a dermal carcinogenicity study in CD-1 mice, topical doses of 2%, 5% and 7% crisaborole ointment were administered once daily. No drug-related neoplastic findings were noted at topical doses up to 7% crisaborole ointment (2 times the MRHD on an AUC comparison basis).

Crisaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

No effects on fertility were observed in male or female rats that were administered oral doses up to 600 mg/kg/day crisaborole (18 times the MRHD on an AUC comparison basis) prior to and during early pregnancy.

14 CLINICAL STUDIES

Two multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials (Trials 1 and 2) treated a total of 1522 subjects 2 to 79 years of age (86.3% of subjects were 2 to 17 years of age) with a 5% to 95% treatable body surface area. At baseline, 38.5% of the subjects had an Investigator's Static Global Assessment [ISGA] score of 2 (mild), and 61.5% had an ISGA score of 3 (moderate), in the overall assessment of atopic dermatitis (erythema, induration/papulation, and oozing/crusting) on a severity scale of 0 to 4.

In both trials, subjects were randomized 2:1 to receive EUCRISA or vehicle applied twice daily for 28 days. The primary efficacy endpoint was the proportion of subjects at Day 29

who achieved success, defined as an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with a 2-grade or greater improvement from baseline, comparing EUCRISA-treated subjects to vehicle-treated subjects.

Efficacy results from the two trials are summarized in Table 2.

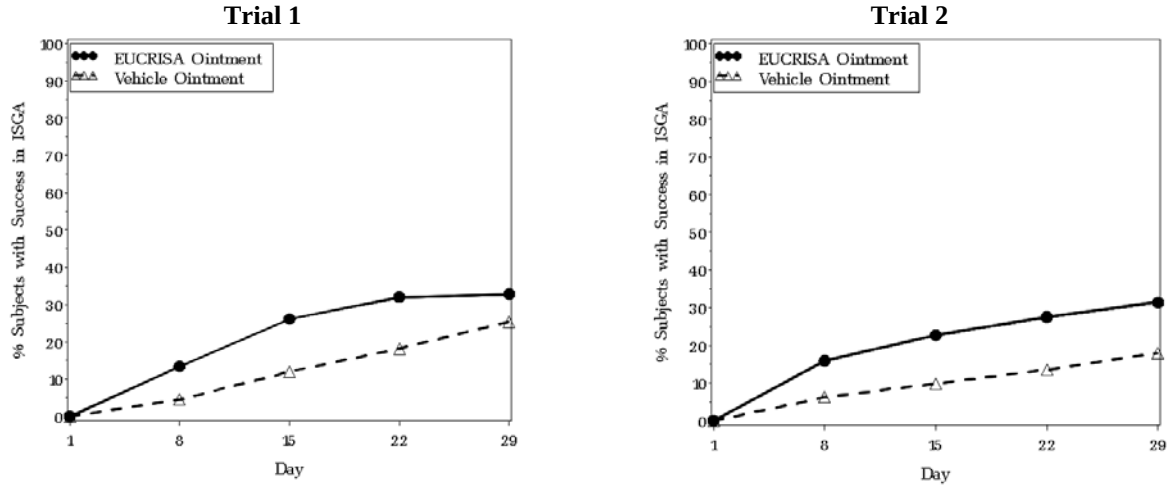
Table 2: Primary Efficacy Outcomes in Subjects with Mild to Moderate Atopic Dermatitis at Day 29

	Trial 1		Trial 2	
	EUCRISA (N=503)	Vehicle (N=256)	EUCRISA (N=513)	Vehicle (N=250)
Success in ISGA[a]	32.8%	25.4%	31.4%	18.0%

[a] Defined as an ISGA score of Clear (0) or Almost Clear (1) with a 2-grade or greater improvement from baseline.

The success rates over time are presented in Figure 1.

Figure 1: Success in ISGA[a] Over Time in Subjects with Mild to Moderate Atopic Dermatitis



[a] Success is defined as an ISGA score of Clear (0) or Almost Clear (1) with a 2-grade or greater improvement from baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EUCRISA is a white to off-white ointment containing 2% crisaborole and is supplied in 60 g and 100 g laminate tubes.

60 g tube: NDC 55724-211-21
100 g tube: NDC 55724-211-11

16.2 Storage and Handling

Store at 20–25°C (68–77°F); excursions permitted to 15–30°C (59–86°F).
[see USP Controlled Room Temperature].

Keep tube tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions*:*
Advise patients to discontinue EUCRISA and seek medical attention immediately if signs or symptoms of hypersensitivity occur *[see Warnings and Precautions (5. 1)]*.

Administration Instructions:
Advise patients or caregivers that EUCRISA is for external use only and is not for ophthalmic, oral, or intravaginal use.

Manufactured for:

Anacor Pharmaceuticals, Inc.
Palo Alto, CA 94303 USA

Issued: 12/2016

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PATIENT INFORMATION

EUCRISA™ (you-KRIS-a)

(crisaborole) ointment, 2%

Important information: EUCRISA is for use on skin (topical use) only. Do not use EUCRISA in your eyes, mouth, or vagina.

What is EUCRISA?

EUCRISA is a prescription medicine used on the skin (topical) to treat mild to moderate eczema (atopic dermatitis) in adults and children 2 years of age and older.

It is not known if EUCRISA is safe and effective in children under 2 years of age.

Who should not use EUCRISA?

Do not use EUCRISA if you are allergic to crisaborole or any of the ingredients in EUCRISA. See the end of this leaflet for a complete list of ingredients in EUCRISA.

Before using EUCRISA, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if EUCRISA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if EUCRISA passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use EUCRISA?

- Use EUCRISA exactly as your healthcare provider tells you to use it.
- Apply a thin layer of EUCRISA to the affected areas 2 times each day.
- Wash your hands after applying EUCRISA, unless hands are being treated. If someone else applies EUCRISA for you, they should wash their hands after applying EUCRISA.

What are the possible side effects of EUCRISA?

EUCRISA may cause side effects.

- **Allergic reactions.** EUCRISA may cause allergic reactions at or near the application site. These can be serious and may include hives, itching, swelling, and redness. If you have any of these symptoms, stop using EUCRISA and get medical help right away.

The most common side effect of EUCRISA is application site pain, such as burning or stinging.

This is not the only possible side effect of EUCRISA.

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

How should I store EUCRISA?

- Store EUCRISA at room temperature, between 68°F and 77°F (20°C and 25°C).
- Keep the tube tightly closed.

General information about the safe and effective use of EUCRISA

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

What are the ingredients in EUCRISA?

Active ingredient: crisaborole

Inactive ingredients: white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated hydroxytoluene, and edetate calcium disodium.

Manufactured for: Anacor Pharmaceuticals, Inc., Palo Alto, California 94303 USA

For more information, call 1-866-EUCRISA [1-866-382-7472] or go to www.myEUCRISA.com

This Patient Informa ion has been approved by the U.S. Food and Drug Administration. Issued: 12/2016

(b) (4)

Printed Side
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Glue

NDC 55724-211-21

60 g
℞ ONLY

EUCRISA™
(crisaborole) ointment, 2%

For Topical Use Only.
Not for ophthalmic, oral, or intravaginal use.

Dosage: Apply twice daily to the affected areas. See package insert for full prescribing information.

Each gram contains: 20 mg of crisaborole in an ointment containing white petrolatum USP, propylene glycol USP, mono- and diglycerides NF, paraffin NF, butylated hydroxytoluene NF, and edetate calcium disodium USP.

Storage: Store at 20°C–25°C (68°F–77°F); excursions permitted to 15°C–30°C (59°F–86°F).

Keep out of reach of children. Keep tube tightly closed.

00355724211219

NDC 55724-211-21

60 g
℞ ONLY

EUCRISA™
(crisaborole) ointment, 2%

For Topical Use Only.
Not for ophthalmic, oral, or intravaginal use.

ANACOR®
PHARMACEUTICALS

XXXXXX-X0916

Manufactured for:
Anacor Pharmaceuticals, Inc.
Palo Alto, CA 94303

Made in Spain

Lot:

Exp:

NDC 55724-211-21

EUCRISA™
(crisaborole) ointment, 2%

60 g
℞ ONLY

7 1/4

1 3/8

1 3/8

COLORS:

(b) (4)

Reference ID: 4027634

Reference ID: 4027634

Printed Side
L020816B_A

(b) (4)

Glue

NDC 55724-211-11

EUCRISA™
(crisaborole) ointment, 2%

For Topical Use Only.
Not for ophthalmic, oral, or intravaginal use.

100 g
℞ ONLY

Dosage: Apply twice daily to the affected areas. See package insert for full prescribing information.

Each gram contains: 20 mg of crisaborole in an ointment containing white petrolatum USP, propylene glycol USP, mono- and diglycerides NF, paraffin NF, butylated hydroxytoluene NF, and edetate calcium disodium USP.

Storage: Store at 20°C–25°C (68°F–77°F); excursions permitted to 15°C–30°C (59°F–86°F).

Keep out of reach of children. Keep tube tightly closed.

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1 11/16

1 11/16

Lot:

Exp:

NDC 55724-211-11

EUCRISA™
(crisaborole) ointment, 2%

For Topical Use Only.
Not for ophthalmic, oral, or intravaginal use.

100 g
℞ ONLY

NDC 55724-211-11

EUCRISA™ (crisaborole) ointment, 2%

100 g
℞ ONLY

Manufactured for:
Anacor Pharmaceuticals, Inc.
Palo Alto, CA 94303

Made in Spain

ANACOR® PHARMACEUTICALS

XXXXXX-R0916

7 3/8

COLORS:

(b) (4)

(b) (4)

SLEEVE LENGTH 6 1/16

PRINT HEIGHT 5 1/4"

NDC 55724-211-21

EUCRISA™

(crisaborole) ointment, 2%

C/L FRONT PANEL

For Topical Use Only.

Not for ophthalmic, oral, or intravaginal use.

60 g

Rx ONLY

MAX PRINT AREA 3.42

MAX PRINT AREA 3.29

Dosage: Apply twice daily to the affected areas. See package insert for full prescribing information.

Each gram contains: 20 mg of crisaborole in an ointment containing white petrolatum USP, propylene glycol USP, mono- and di-glycerides NF, paraffin NF, butylated hydroxytoluene NF, and edetate calcium disodium USP.

Storage: Store at 20°C–25°C (68°F–77°F); excursions permitted to 15°C–30°C (59°F–86°F).

Keep out of reach of children.

Keep tube tightly closed.

Manufactured for:
Anacor Pharmaceuticals, Inc.
Palo Alto, CA 94303

XXXXXX-R0916

C/L BACK PANEL

ANACOR® PHARMACEUTICALS

00355724211219

NOTE: Lot number and Exp date are letterpressed into crimp.

Reference ID: 4027634

(b) (4)

SLEEVE LENGTH 6-5/16

PRINT HEIGHT 5 1/2

CAP END

OPEN END

NDC 55724-211-11

EUCRISA™

(crisaborole) ointment, 2%

For Topical Use Only.

Not for ophthalmic, oral, or intravaginal use.

100 g

Rx ONLY

MAX. SOLID PRINT AREA 4.399"

MAX. TYPE PRINT AREA 4.274"

Dosage: Apply twice daily to the affected areas. See package insert for full prescribing information.

Each gram contains: 20 mg of crisaborole in an ointment containing white petrolatum USP, propylene glycol USP, mono- and di-glycerides NF, paraffin NF, butylated hydroxytoluene NF, and edetate calcium disodium USP.

Storage: Store at 20°C–25°C (68°F–77°F); excursions permitted 15°C–30°C (59°F–86°F).

Keep out of reach of children.

Keep tube tightly closed.

Manufactured for:
Anacor Pharmaceuticals, Inc.
Palo Alto, CA 94303

XXXXXX-R0916

ANACOR® PHARMACEUTICALS

0035572421110

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WARNING: THIS IS AN OVERLAY. DO NOT INCLUDE DIRECTLY ON YOUR ARTWORK.

Reference ID: 4027634

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

/s/

AMY G EGAN
12/14/2016