CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21537Orig1s000

Trade Name:	Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial
Sponsor:	Akorn Operating Company LLC
Approval Date:	August 12, 2022

CENTER FOR DRUG EVALUATION AND RESEARCH

215737Orig1s000

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APPLICATION NUMBER:

215737Orig1s000

APPROVAL LETTER

ANDA 215737

ANDA APPROVAL

Akorn Operating Company LLC
1925 West Field Court, Suite 300
Lake Forest, IL 60045
Attention: John Franolic
Vice President, Regulatory Affairs

Dear John Franolic:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 23, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts.

Reference is also made to the complete response letter issued by this office on May 10, 2022, and to any amendments thereafter.

Reference is also made to FDA's Competitive Generic Therapy Designation – Grant letter dated March 4, 2021.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Cetrotide for Injection, 0.25 mg/vial, of EMD Serono Inc.

We note that Akorn Operating Company LLC (Akorn) was granted a Competitive Generic Therapy (CGT) designation for Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial. Akorn is the "first approved applicant" for Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial, as defined in section 505(j)(5)(B)(v)(III) of the FD&C Act. Therefore, with this approval, Akorn is eligible for 180 days of CGT exclusivity for Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial, under section 505(j)(5)(B)(v) of the FD&C Act. This exclusivity will begin to run from the date of the first commercial marketing of the CGT (including the commercial marketing of the listed drug) by Akorn, as specified in section 505(j)(5)(B)(v) of the FD&C Act. Furthermore, in accordance with section 505(j)(5)(B)(v)(I) of the FD&C Act, this 180-day

CGT exclusivity will not block approval of other applications until Akorn has commenced commercial marketing. Please submit a correspondence to this ANDA informing the Agency of the date you begin commercial marketing. Please also submit notice of first commercial marketing via e-mail to the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov. This e-mail should be sent the same day you commence commercial marketing. Reference is also made to the Special Forfeiture Rule for Competitive Generic Therapy in section 505(j)(5)(D)(iv) of the FD&C Act. Please be aware that, pursuant to this forfeiture rule, you will forfeit your eligibility for the 180-day CGT exclusivity period for Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial, if you fail to market this CGT within 75 days after the date on which the approval of this application is made effective.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts; therefore, we remind you that you must comply with the postmarketing safety reporting requirements for an approved combination product (21 CFR Part 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with

annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: https://www.fda.gov/media/128163/download).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at https://www.fda.gov/media/73013/download. Information and Instructions for completing the form can be found at https://www.fda.gov/media/132152/download. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling

[21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled "Changes to an Approved NDA or ANDA" at https://www.fda.gov/media/71846/download.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

John Ibrahim

Digitally signed by John Ibrahim
Date: 8/12/2022 01:01:40PM
GUID: 542af06d0124375c12e8c1d9fc86e87c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215737Orig1s000

LABELING

Sealing label

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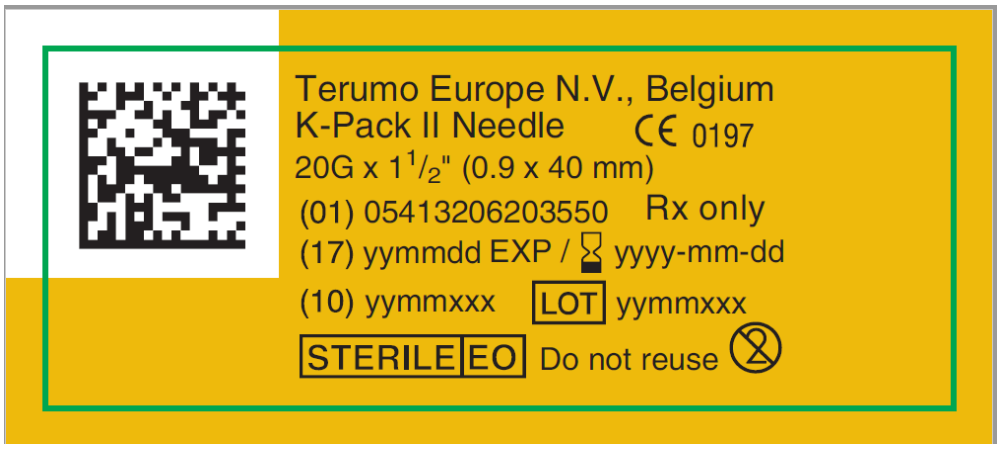

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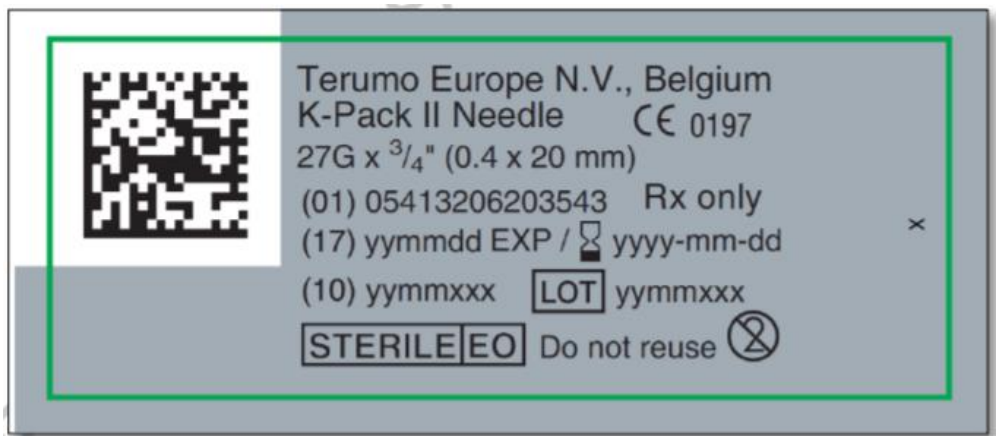
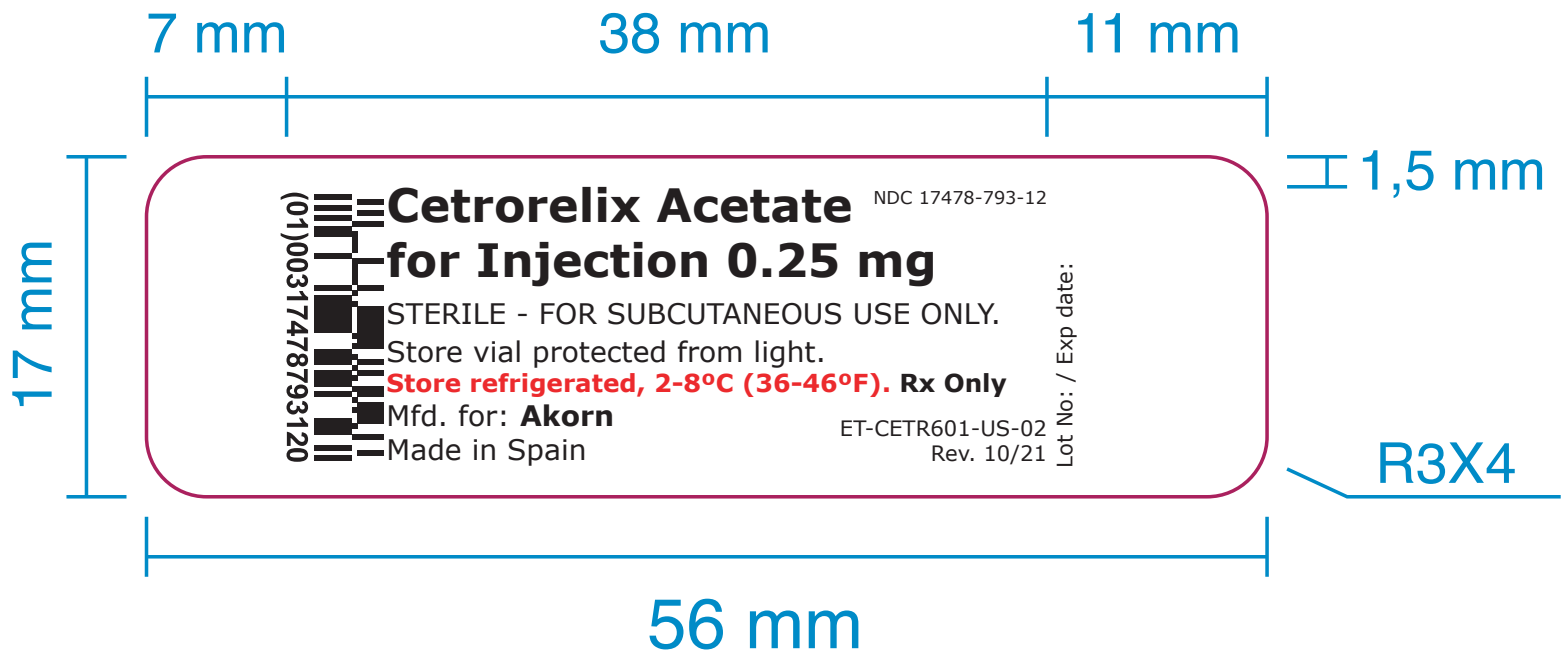


CONFIDENTIAL
INFORMATION

Shipping carton label

Item: KN-2038RB

Item: KN-2719RB



(01)00317478793120

Cetrorelix Acetate for Injection 0.25 mg

NDC 17478-793-12

STERILE – FOR SUBCUTANEOUS USE ONLY

Contains:
one vial with lyophilized powder for reconstitution, one pre-filled syringe with diluent, one 20-gauge needle and one 27-gauge needle.

Store the packaged tray in the outer carton.
Store refrigerated, 2-8°C (36-46°F).

Rx Only

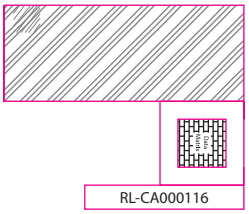
Manufactured for: **Akorn Operating Company LLC**
Lake Forest, IL 60045

Made in Spain

CTRXAL Rev. 10/21

Lot No:

Exp date:



(01)00317478793120

Open this side →

One vial contains: 0.26-0.27 mg cetrorelix acetate
(equivalent to 0.25 mg cetrorelix) and 54.80 mg mannitol.
One pre-filled syringe with diluent contains 1 mL Sterile Water
for Injection, USP

Manufactured for:
Akorn Operating Company LLC
Lake Forest, IL 60045

Made in Spain

N 3 17478-793-12 0

CTRXAC Rev. 10/21

Cetrorelix Acetate
for Injection 0.25 mg

One carton contains one packaged tray which contains:
1 vial with lyophilized powder for reconstitution
1 pre-filled syringe with diluent
1 20-gauge needle
1 27-gauge needle

(Serialized Data Carrier)

Cetrorelix Acetate for Injection 0.25 mg

NDC 17478-793-12

Sterile – for subcutaneous use only

Rx Only

Store refrigerated, 2-8°C (36-46°F).

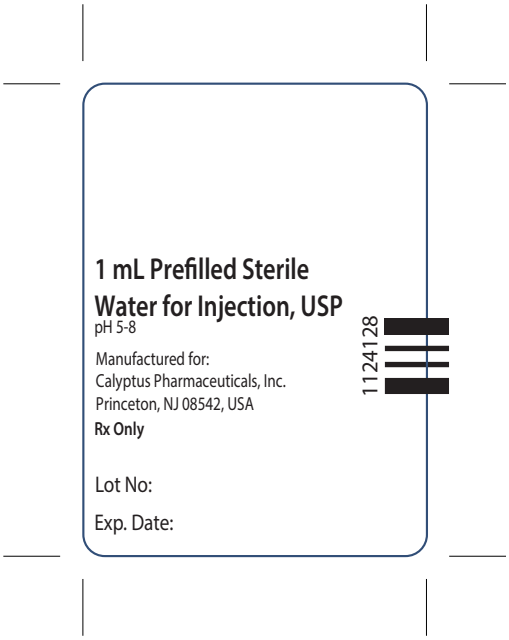
One carton contains one packaged tray which contains:
1 vial with lyophilized powder for reconstitution
1 pre-filled syringe with diluent
1 20-gauge needle
1 27-gauge needle

RL-CT0005O2

Lot No:

Lot No of the Diluent:

See package insert for dosage information. For single use only. Reconstitute only with the diluent provided. Use immediately after reconstitution.
Keep out of the reach of children. Store the packaged tray in the outer carton. Store refrigerated, 2-8°C (36-46°F).
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088



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Replaces in time:	**n/a**
Printdate:	**21-10-2019**
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File name:	**1124128.WFI.CALYPTUS.1ML.ET.US**
Made by:	**Richard van Zanten**

Customer Approval: **Document entirely checked and approved for implementation**
Name:
Job Title:
Country:
Date:
Signature:

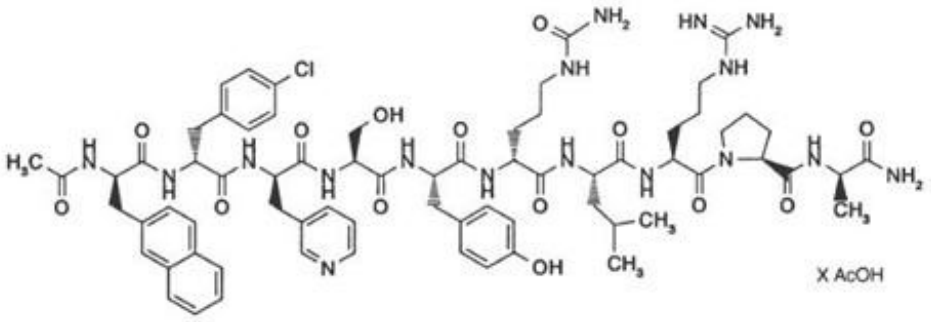
Technical Approval:
Name:
Signature:

Cetrorelix Acetate for Injection 0.25 mg
FOR SUBCUTANEOUS USE ONLY

DESCRIPTION

Cetrorelix acetate for injection is a synthetic decapeptide with gonadotropin-releasing hormone (GnRH) antagonistic activity. Cetrorelix acetate is an analog of native GnRH with substitutions of amino acids at positions 1, 2, 3, 6, and 10. The molecular formula is Acetyl-D-3-(2′-naphtyl)-alanine-D-4-chlorophenylalanine-D-3-(3′-pyridyl)-alanine-L-serine-L-tyrosine-D-citruline-L-leucine-L-arginine-L-proline-D-alanine-amide, and the molecular weight is 1431.06, calculated as the anhydrous free base. The structural formula is as follows:

Cetrorelix acetate



(Ac-D-Nal$_1$-*D*-Cpa$_2$-*D*-Pal$_3$-Ser$_4$-Tyr$_5$-*D*-Cit$_6$-Leu$_7$-Arg$_8$-Pro$_9$-*D*-Ala$_{10}$-NH$_2$)

Cetrorelix Acetate for Injection 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (pH 5-8), that comes supplied in a 1.0 mL pre-filled syringe. Each vial of cetrorelix acetate for injection 0.25 mg contains 0.26-0.27 mg cetrorelix acetate, equivalent to 0.25 mg cetrorelix, and 54.80 mg mannitol.

CLINICAL PHARMACOLOGY

GnRH induces the production and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the gonadotrophic cells of the anterior pituitary. Due to a positive estradiol (E2) feedback at midcycle, GnRH liberation is enhanced resulting in an LH-surge. This LH-surge induces the ovulation of the dominant follicle, resumption of oocyte meiosis and subsequently luteinization as indicated by rising progesterone levels.

Cetrorelix acetate for injection competes with natural GnRH for binding to membrane receptors on pituitary cells and thus controls the release of LH and FSH in a dose-dependent manner. The onset of LH suppression is approximately one hour with the 3 mg dose and two hours with the 0.25 mg dose. This suppression is maintained by continuous treatment and there is a more pronounced effect on LH than on FSH. An initial release of endogenous gonadotropins has not been detected with cetrorelix acetate for injection, which is consistent with an antagonist effect.

The effects of cetrorelix acetate for injection on LH and FSH are reversible after discontinuation of treatment. In women, cetrorelix acetate for injection delays the LH-surge, and consequently ovulation, in a dose-dependent fashion. FSH levels are not affected at the doses used during controlled ovarian stimulation. Following a single 3 mg dose of cetrorelix acetate for injection, duration of action of at least 4 days has been established. A dose of cetrorelix acetate for injection 0.25 mg every 24 hours has been shown to maintain the effect.

Pharmacokinetics

The pharmacokinetic parameters of single and multiple doses of cetrorelix acetate for injection in adult healthy female subjects are summarized in Table 1.

Table 1: Pharmacokinetic parameters of Cetrorelix Acetate for Injection following 3 mg single or 0.25 mg single and multiple (daily for 14 days) subcutaneous (sc) administration.

	Single dose 3 mg	**Single dose 0.25 mg**	**Multiple dose 0.25 mg**
No. of subjects	12	12	12
t_{max}*[h]	1.5 (0.5-2)	1.0 (0.5-1.5)	1.0 (0.5-2)
$t_{1/2}$*[h]	62.8 (38.2-108)	5.0 (2.4-48.8)	20.6 (4.1-179.3)
C_{max} [ng/ml]	28.5 (22.5-36.2)	4.97 (4.17-5.92)	6.42 (5.18-7.96)
AUC [ng·h/ml]	536 (451-636)	31.4 (23.4-42.0)	44.5 (36.7-54.2)
CL† [ml/min·kg]	1.28‡		
Vz †[l/kg]	1.16‡		

t_{max} Time to reach observed maximum plasma concentration
$t_{1/2}$ Elimination half-life
C_{max} Maximum plasma concentration; multiple dose $C_{ss, max}$
AUC Area under the curve; single dose $AUC_{0\text{-}inf}$, multiple dose AUCt
CL Total plasma clearance
Vz Volume of distribution
Geometric mean (95% CI_{ln}),

* median (min-max)

† arithmetic mean,

‡ Based on iv administration (n=6, separate study 0013)

Absorption

Cetrorelix acetate for injection is rapidly absorbed following subcutaneous injection, maximal plasma concentrations being achieved approximately one to two hours after administration. The mean absolute bioavailability of cetrorelix acetate for injection following subcutaneous administration to healthy female subjects is 85%.

Distribution

The volume of distribution of cetrorelix acetate for injection following a single intravenous dose of 3 mg is about 1 l/kg. *In vitro* protein binding to human plasma is 86%.

Cetrorelix acetate for injection concentrations in follicular fluid and plasma were similar on the day of oocyte pick-up in patients undergoing controlled ovarian stimulation. Following subcutaneous administration of cetrorelix acetate for injection 0.25 mg and 3 mg, plasma concentrations of cetrorelix were below or in the range of the lower limit of quantitation on the day of oocyte pick-up and embryo transfer.

Metabolism

After subcutaneous administration of 10 mg cetrorelix acetate for injection to females and males, cetrorelix acetate for injection and small amounts of (1-9), (1-7), (1-6), and (1-4) peptides were found in bile samples over 24 hours.

In *in vitro* studies, cetrorelix acetate for injection was stable against phase I- and phase II-metabolism. Cetrorelix acetate for injection was transformed by peptidases, and the (1-4) peptide was the predominant metabolite.

Excretion

Following subcutaneous administration of 10 mg cetrorelix to males and females, only unchanged cetrorelix was detected in urine. In 24 hours, cetrorelix and small amounts of the (1-9), (1-7), (1-6), and (1-4) peptides were found in bile samples. 2-4% of the dose was eliminated in the urine as unchanged cetrorelix, while 5-10% was eliminated as cetrorelix and the four metabolites in bile. Therefore, only 7-14% of the total dose was recovered as unchanged cetrorelix and metabolites in urine and bile up to 24 hours. The remaining portion of the dose may not have been recovered since bile and urine were not collected for a longer period of time.

Special Populations

Pharmacokinetic investigations have not been performed either in subjects with impaired renal or liver function, or in the elderly, or in children (see PRECAUTIONS).

Pharmacokinetic differences in different races have not been determined.

There is no evidence of differences in pharmacokinetic parameters for cetrorelix acetate for injection between healthy subjects and patients undergoing controlled ovarian stimulation.

Drug-Drug Interactions

No formal drug-drug interaction studies have been performed with cetrorelix acetate for injection (see PRECAUTIONS).

Clinical Studies

Seven hundred thirty-two (732) patients were treated with cetrorelix acetate for injection in five (two Phase 2 dose-finding and three Phase 3) clinical trials. The clinical trial population consisted of Caucasians (95.5%) and Black, Asian, Arabian and others (4.5%). Women were between 19 and 40 years of age (mean: 32). The studies excluded subjects with polycystic ovary syndrome (PCOS), subjects with low or no ovarian reserve, and subjects with stage III-IV endometriosis.

Two dose regimens were investigated in these clinical trials, either a single dose per treatment cycle or multiple dosing. In the Phase 2 studies, a single dose of 3 mg was established as the minimal effective dose for the inhibition of premature LH surges with a protection period of at least 4 days. When cetrorelix acetate for injection is administered in a multidose regimen, 0.25 mg was established as the minimal effective dose. The extent and duration of LH-suppression is dose dependent.

In the Phase 3 program, efficacy of the single 3 mg dose regimen of cetrorelix acetate for injection and the multiple 0.25 mg dose regimen of cetrorelix acetate for injection was established separately in two adequate and well controlled clinical studies utilizing active comparators. A third non-comparative clinical study evaluated only the multiple 0.25 mg dose regimen of cetrorelix acetate for injection. The ovarian stimulation treatment with recombinant FSH or human menopausal gonadotropin (hMG) was initiated on day 2 or 3 of a normal menstrual cycle. The dose of gonadotropins was administered according to the individual patient's disposition and response.

In the single dose regimen study, cetrorelix acetate for injection 3 mg was administered on the day of controlled ovarian stimulation when adequate estradiol levels (400 pg/mL) were obtained, usually on day 7 (range day 5-12). If hCG was not given within 4 days of the 3 mg dose of cetrorelix acetate for injection, then 0.25 mg of cetrorelix acetate for injection was administered daily beginning 96 hours after the 3 mg injection until and including the day of hCG administration.

In the two multiple dose regimen studies, cetrorelix acetate for injection 0.25 mg was started on day 5 or 6 of COS. Both gonadotropins and cetrorelix acetate for injection were continued daily (multiple dose regimen) until the injection of human chorionic gonadotropin (hCG).

Oocyte pick-up (OPU) followed by *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) as well as embryo transfer (ET) were subsequently performed. The results for cetrorelix acetate for injection are summarized below in Table 2.

Table 2: Results of Phase 3 Clinical Studies with Cetrorelix Acetate for Injection 3 mg in a single dose (sd) regimen and 0.25 mg in a multiple dose (md) regimen

Parameter	Cetrorelix Acetate for Injection 3 mg (sd, active comparator study)	Cetrorelix Acetate for Injection 0.25 mg (md, active comparator study)	Cetrorelix Acetate for Injection 0.25 mg (md, non-comparative study)
No. of subjects	115	159	303
hCG administered [%]	98.3	96.2	96.0
Oocyte pick-up [%]	98.3	94.3	93.1
LH-surge [%] (LH ≥ 10 U/L and P* ≥ 1 ng/mL) †	0.0	1.9	1.0
Serum E_2 [pg/ml] at day hCG‡, §	1125 (470-2952)	1064 (341-2531)	1185 (311-3676)
Serum LH [U/L] at day hCG‡, §	1.0 (0.5-2.5)	1.5 (0.5-7.6)	1.1 (0.5-3.5)
No. of follicles ≥ 11 mm at day hCG¶	11.2±5.5	10.8±5.2	10.4±4.5
No. of oocytes: IVF¶ ICSI¶	9.2±5.2 10.0±4.2	7.6±4.3 10.1±5.6	8.5±5.1 9.3±5.9
Fertilization rate: IVF¶ ICSI¶	0.48±0.33 0.66±0.29	0.62±0.26 0.63±0.29	0.60±0.26 0.61±0.25
No. of embryos transferred¶	2.6±0.9	2.1±0.6	2.7±1.0
Clinical pregnancy rate [%] per attempt	22.6	20.8	19.8
per subject with ET	26.3	24.1	23.3

* Progesterone

† Following initiation of cetrorelix acetate for injection therapy

‡ Morning values

§ Median with 5th – 95th percentiles

¶ Mean ± standard deviation

In addition to IVF and ICSI, one pregnancy was obtained after intrauterine insemination. In the five Phase 2 and Phase 3 clinical trials, 184 pregnancies have been reported out of a total of 732 patients (including 21 pregnancies following the replacement of frozen-thawed embryos).

In the 3 mg regimen, 9 patients received an additional dose of 0.25 mg of cetrorelix acetate for injection and two other patients received two additional doses of 0.25 mg cetrorelix acetate for injection. The median number of days of cetrorelix acetate for injection multiple dose treatment was 5 (range 1-15) in both studies.

No drug related allergic reactions were reported from these clinical studies.

INDICATIONS AND USAGE

Cetrorelix acetate for injection is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.

CONTRAINDICATIONS

Cetrorelix acetate for injection is contraindicated under the following conditions:

1. Hypersensitivity to cetrorelix acetate, extrinsic peptide hormones or mannitol.
2. Known hypersensitivity to GnRH or any other GnRH analogs.
3. Known or suspected pregnancy, and lactation (see PRECAUTIONS).
4. Severe renal impairment

WARNINGS

Cetrorelix acetate for injection should be prescribed by physicians who are experienced in fertility treatment. Before starting treatment with cetrorelix acetate for injection, pregnancy must be excluded (see CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

General

Cases of hypersensitivity reactions, including anaphylactoid reactions with the first dose, have been reported during post-marketing surveillance (see ADVERSE REACTIONS). A severe anaphylactic reaction associated with cough, rash, and hypotension, was observed in one patient after seven months of treatment with cetrorelix acetate for injection (10 mg/day) in a study for an indication unrelated to infertility.

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with cetrorelix acetate for injection is not advised in women with severe allergic conditions.

Information for Patients

Prior to therapy with cetrorelix acetate for injection, patients should be informed of the duration of treatment and monitoring procedures that will be required. The risk of possible adverse reactions should be discussed (see ADVERSE REACTIONS). Cetrorelix acetate for injection should not be prescribed if a patient is pregnant.

If cetrorelix acetate for injection is prescribed to patients for self-administration, information for proper use is given in the Patient Leaflet (see below).

Laboratory Tests

After the exclusion of preexisting conditions, enzyme elevations (ALT, AST, GGT, alkaline phosphatase) were found in 1-2% of patients receiving cetrorelix acetate for injection during controlled ovarian stimulation. The elevations ranged up to three times the upper limit of normal. The clinical significance of these findings was not determined.

During stimulation with human menopausal gonadotropin, cetrorelix acetate for injection had no notable effects on hormone levels aside from inhibition of LH surges.

Drug Interactions

No formal drug interaction studies have been performed with cetrorelix acetate for injection.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been performed with cetrorelix acetate. Cetrorelix acetate was not genotoxic *in vitro* (Ames test, HPRT test, chromosome aberration test) or *in vivo* (chromosome aberration test, mouse micronucleus test). Cetrorelix acetate induced polyploidy in CHL-Chinese hamster lung fibroblasts, but not in V79-Chinese hamster lung fibroblasts, cultured peripheral human lymphocytes or in an *in vitro* micronucleus test in the CHL-cell line. Treatment with 0.46 mg/kg cetrorelix acetate for 4 weeks resulted in complete infertility in female rats which was reversed 8 weeks after cessation of treatment.

Pregnancy

(see CONTRAINDICATIONS)

Cetrorelix acetate for injection is contraindicated in pregnant women.

When administered to rats for the first seven days of pregnancy, cetrorelix acetate did not affect the development of the implanted conceptus at doses up to 38 μg/kg (approximately 1 time the recommended human therapeutic dose based on body surface area). However, a dose of 139 μg/kg (approximately 4 times the human dose) resulted in a resorption rate and a post implantation loss of 100%. When administered from day 6 to near term to pregnant rats and rabbits, very early resorptions and total implantation losses were seen in rats at doses from 4.6 μg/kg (0.2 times the human dose) and in rabbits at doses from 6.8 μg/kg (0.4 times the human dose). In animals that maintained their pregnancy, there was no increase in the incidence of fetal abnormalities.

The fetal resorption observed in animals is a logical consequence of the alteration in hormonal levels effected by the antigonadotrophic properties of cetrorelix acetate for injection, which could result in fetal loss in humans as well. Therefore, this drug should not be used in pregnant women.

Nursing Mothers

It is not known whether cetrorelix acetate for injection is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of cetrorelix acetate for injection on lactation and/or the breast-fed child have not been determined, cetrorelix acetate for injection should not be used by nursing mothers.

Geriatric Use

Cetrorelix acetate for injection is not intended to be used in subjects aged 65 and over.

ADVERSE REACTIONS

The safety of cetrorelix acetate for injection in 949 patients undergoing controlled ovarian stimulation in clinical studies was evaluated. Women were between 19 and 40 years of age (mean: 32). 94.0% of them were Caucasian. Cetrorelix acetate for injection was given in doses ranging from 0.1 mg to 5 mg as either a single or multiple dose.

Table 3 shows systemic adverse events, reported in clinical studies without regard to causality, from the beginning of cetrorelix acetate for injection treatment until confirmation of pregnancy by ultrasound at an incidence ≥ 1% in cetrorelix acetate for injection treated subjects undergoing COS.

Table 3: Adverse Events in ≥1%

(WHO preferred term)	**Cetrorelix Acetate for Injection N=949 % (n)**
Ovarian Hyperstimulation Syndrome*	3.5 (33)
Nausea	1.3 (12)
Headache	1.1 (10)

* Intensity moderate or severe, or WHO Grade II or III, respectively

Local site reactions (e.g. redness, erythema, bruising, itching, swelling, and pruritus) were reported. Usually, they were of a transient nature, mild intensity and short duration. During post-marketing surveillance, cases of mild to moderate Ovarian Hyperstimulation syndrome and infrequent cases of hypersensitivity reactions including anaphylactoid reactions have been reported.

Two stillbirths were reported in Phase 3 studies of cetrorelix acetate for injection.

Congenital Anomalies

Clinical follow-up studies of 316 newborns of women administered cetrorelix acetate for injection were reviewed. One infant of a set of twin neonates was found to have anencephaly at birth and died after four days. The other twin was normal. Developmental findings from ongoing baby follow-up included a child with a ventricular septal defect and another child with bilateral congenital glaucoma.

Four pregnancies that resulted in therapeutic abortion in Phase 2 and Phase 3 controlled ovarian stimulation studies had major anomalies (diaphragmatic hernia, trisomy 21, Klinefelter syndrome, polymalformation, and trisomy 18). In three of these four cases, intracytoplasmic sperm injection (ICSI) was the fertilization method employed; in the fourth case, *in vitro* fertilization (IVF) was the method employed.

The minor congenital anomalies reported include: supernumerary nipple, bilateral strabismus, imperforate hymen, congenital nevi, hemangiomata, and QT syndrome.

The causal relationship between the reported anomalies and cetrorelix acetate for injection is unknown. Multiple factors, genetic and others (including, but not limited to ICSI, IVF, gonadotropins, and progesterone) make causal attribution difficult to study.

To report SUSPECTED ADVERSE REACTIONS, contact Akorn Operating Company LLC at 1-800-932-5676 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

There have been no reports of overdosage with cetrorelix acetate for injection 0.25 mg or 3 mg in humans. Single doses up to 120 mg cetrorelix acetate for injection have been well tolerated in patients treated for other indications without signs of overdosage.

DOSAGE AND ADMINISTRATION

Ovarian stimulation therapy with gonadotropins (FSH, hMG) is started on cycle Day 2 or 3. The dose of gonadotropins should be adjusted according to individual response. Cetrorelix acetate for injection 0.25 mg may be administered subcutaneously once daily during the early- to mid-follicular phase.

Cetrorelix acetate for injection 0.25 mg is administered on either stimulation day 5 (morning or evening) or day 6 (morning) and continued daily until the day of hCG administration.

When assessment by ultrasound shows a sufficient number of follicles of adequate size, hCG is administered to induce ovulation and final maturation of the oocytes. No hCG should be administered if the ovaries show an excessive response to the treatment with gonadotropins to reduce the chance of developing ovarian hyperstimulation syndrome (OHSS).

Administration

Cetrorelix acetate for injection 0.25 mg can be administered by the patient herself after appropriate instructions by her doctor.

Directions for using Cetrorelix Acetate for Injection 0.25 mg with the enclosed needles and pre-filled syringe:

1. Wash hands thoroughly with soap and water.
2. Flip off the plastic cover of the vial and wipe the aluminum ring and the rubber stopper with an alcohol swab.
3. Twist the injection needle with the yellow mark (20 gauge) on the pre-filled syringe.
4. Push the needle through the center of the rubber stopper of the vial and slowly inject the solvent into the vial.
5. Leaving the syringe in the vial, gently swirl the vial until the solution is clear and without residues. Avoid forming bubbles.
6. Draw the total contents of the vial into the syringe. If necessary, invert the vial and pull back the needle as far as needed to withdraw the entire contents of the vial.
7. Replace the needle with the yellow mark by the injection needle with the grey mark (27 gauge).
8. Invert the syringe and push the plunger until all air bubbles have been expelled.
9. Choose an injection site in the lower abdominal area, preferably around, but staying at least one inch away from the navel. Choose a different injection site each day to minimize local irritation. Use a second alcohol swab to clean the skin at the injection site and allow alcohol to dry. Gently pinch up the skin surrounding the site of injection.

10. Inject the prescribed dose as directed by your doctor, nurse or pharmacist.
11. Use the syringe and needles only once. Dispose of the syringe and needles properly after use. If available, use a medical waste container for disposal.

HOW SUPPLIED

Cetrorelix Acetate for Injection 0.25 mg is available in a carton of one packaged tray (NDC 17478-793-12).

Each packaged tray contains: one glass vial containing 0.26 - 0.27 mg cetrorelix acetate (corresponding to 0.25 mg cetrorelix), one pre-filled glass syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8), one 20 gauge needle (yellow) and one 27 gauge needle (grey).

Storage

Store Cetrorelix Acetate for Injection 0.25 mg refrigerated, 2-8°C (36-46°F). Store the packaged tray in the outer carton in order to protect from light.

Rx only

Manufactured for:

Akorn Operating Company LLC

Lake Forest, IL 60045

Made in Spain

CTRX00N Rev. 10/21

Patient Leaflet

Cetrorelix Acetate for Injection 0.25 mg

Active ingredient: cetrorelix acetate

Summary

Cetrorelix acetate for injection blocks the effects of a natural hormone, called gonadotropin-releasing hormone (GnRH). GnRH controls the secretion of another hormone, called luteinizing hormone (LH), which induces ovulation during the menstrual cycle. During hormone treatment for ovarian stimulation, premature ovulation may lead to eggs that are not suitable for fertilization. Cetrorelix acetate for injection blocks such undesirable premature ovulation.

Uses

Cetrorelix acetate for injection is used to prevent premature ovulation during controlled ovarian stimulation.

General Cautions

Do not use Cetrorelix Acetate for Injection if you

- have kidney disease
- are allergic to cetrorelix acetate, mannitol or exogenous peptide hormones (medicines similar to cetrorelix acetate for injection) or
- are pregnant, or think that you might be pregnant, or if you are breast-feeding.

Consult your doctor before taking cetrorelix acetate for injection if you have had severe allergic reactions.

Proper Use

Ovarian stimulation therapy is started on cycle Day 2 or 3. Cetrorelix acetate for injection 0.25 mg is injected under the skin once daily, as directed by your physician. When an ultrasound examination shows that you are ready, another drug (hCG) is injected to induce ovulation.

How should you use Cetrorelix Acetate for Injection?

You may self-inject cetrorelix acetate for injection after special instruction from your doctor.

To fully benefit from cetrorelix acetate for injection, please read carefully and follow the instructions given below, unless your doctor advises you otherwise.

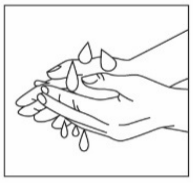
Cetrorelix acetate for injection is for injection under the skin of the lower abdominal area, preferably around, but staying at least one inch away from the belly button. Choose a different injection site each day to minimize local irritation.

Dissolve cetrorelix acetate for injection powder only with the water contained in the pre-filled syringe. Do not use a cetrorelix acetate for injection solution if it contains particles or if it is not clear.

Before you inject cetrorelix acetate for injection yourself, please read the following instructions carefully:

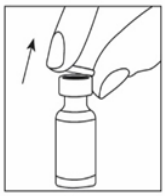
Directions for using Cetrorelix Acetate for Injection 0.25 mg with the enclosed needles and pre-filled syringe:

1. Wash your hands thoroughly with soap and water.

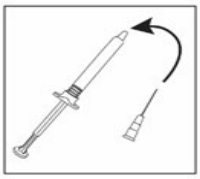


2. On a clean flat surface, lay out everything you need (one vial of powder, one pre-filled syringe, one injection needle with a yellow mark, and one injection needle with a grey mark).

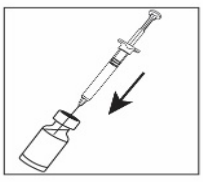
3. Flip off the plastic cover of the vial. Wipe the aluminum ring and the rubber stopper with an alcohol swab.



4. Take the injection needle with the yellow mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Twist the needle on the syringe and remove the cover of the needle.

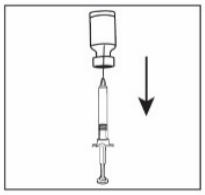


5. Push the needle through the center of the rubber stopper of the vial. Inject the water into the vial by slowly pushing down on the plunger of the syringe.

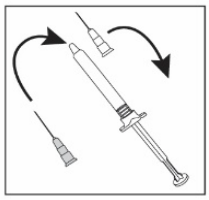


6. Leave the syringe in the vial. While carefully holding the syringe and vial, swirl gently to mix the powder and water together. When it is mixed, it will look clear and have no particles in it. Do not shake or you will create bubbles in your medicine.

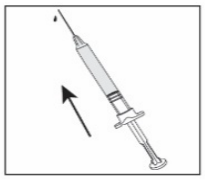
7. Draw the total contents of the vial into the syringe. If liquid is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.



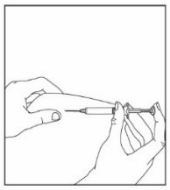
8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Twist the needle on the syringe and remove the cover of the needle.



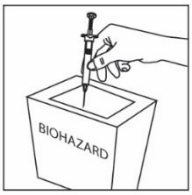
9. Invert the syringe and push the plunger until all air bubbles have been pushed out. Do not touch the needle or allow the needle to touch any surface.



10. Choose an injection site in the lower abdominal area, preferably around, but at least one inch away from the belly button. Choose a different injection site each day to minimize local irritation. Take a second alcohol swab and clean the skin at the injection site and allow alcohol to dry. Inject the prescribed dose as directed by your doctor, nurse or pharmacist.



11. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury). A medical waste container should be used for disposal.



SPECIAL ADVICE

What do you do if you have used too much Cetrorelix Acetate for Injection?

Contact your doctor in case of overdosage immediately to check whether an adjustment of the further ovarian stimulation procedure is required.

Possible Side Effects

Mild and short-lasting reactions may occur at the injection site like reddening, itching, and swelling. Nausea and headache have also been reported.

Call your doctor if you have any side effect not mentioned in this leaflet or if you are unsure about the effect of this medicine.

Storage

How is Cetrorelix Acetate for Injection to be stored?

Store Cetrorelix Acetate for Injection in a cool dry place protected from excess moisture and heat.

Store Cetrorelix Acetate for Injection 0.25 mg in the refrigerator at 2-8°C (36-46°F). Keep the packaged tray in the outer carton in order to protect it from light.

How long may Cetrorelix Acetate for Injection be stored?

Do not use the Cetrorelix Acetate for Injection powder or the pre-filled syringe after the expiration date, which is printed on the labels and on the carton, and dispose of the vial and the syringe properly.

How long can you keep Cetrorelix Acetate for Injection after preparation of the solution?

The solution should be used immediately after preparation.

Store the medicine out of the reach of children.

If you suspect that you may have taken more than the prescribed dose of this medicine, contact your doctor immediately. This medicine was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of the information about cetrorelix acetate for injection. Medicines are sometimes prescribed for uses other than those listed in the Leaflet. If you have any questions or concerns, or want more information about cetrorelix acetate for injection, contact your doctor or pharmacist.

This Leaflet has been approved by the U.S. Food and Drug Administration.

October 2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215737Orig1s000

LABELING REVIEW(s)

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	04/26/2022
ANDA Number(s)	215737
Review Number	2
Applicant Name	Akorn Operating Company LLC
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial
Proposed Proprietary Name	None
Submission Received Date	November 08, 2021
Primary Labeling Reviewer	Juwon Lee
Secondary Labeling Reviewer	Eunjung Chuh

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

1 LABELING COMMENTS (C2)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C2)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C2)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received November 08, 2021.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C2)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C2)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C2)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 x 0.25 mg per vial (Single-Dose Vial)	11/8/2021	Satisfactory
Blister	Final	1 mL Pre-filled syringe of Sterile Water for Injection	6/23/2021	Satisfactory
Carton	Final	1 x 0.25 mg vial of cetrorelix acetate 1 mL pre-filled syringe of Sterile Water for Injection 1 x 20 gauge needle (yellow) 1 x 27 gauge needle (grey)	11/8/2021	Satisfactory
Packaged Tray	Final	1 x 0.25 mg vial of cetrorelix acetate 1 mL pre-filled syringe of Sterile Water for Injection 1 x 20 gauge needle (yellow) 1 x 27 gauge needle (grey)	11/8/2021	Satisfactory
Syringe Labels	Final	20G (yellow) and 27G (Gray)	11/8/2021	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	10/2021	11/8/2021	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Draft	10/2021	11/8/2021	Satisfactory
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C2)

4.1 REGULATORY INFORMATION (C2)

Yes	No	
☐	☒	Are there any applicable issues in DLR's SharePoint Drug Facts ?
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION (C2)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA 021197 / S-018

Supplement Approval Date: 12/22/2017

Proprietary Name: Cetrotide

Established Name: cetrorelix acetate for injection

Description of Supplement:

This "Changes Being Effected" supplemental new drug application provides for removal of alcohol swabs currently provided with Cetrotide® (cetrorelix acetate) for Injection.

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/panorama-document?pk_panorama_document=55bc309f00aa491b162f1eb9816b792c_5955f06a01432555a86ddd549bf1cc9f_5955f06f014326367bb7d6a2a22617ff_5a3d26590027b46002c64caa88016122_090026f88181013f_TASK_Approved_COMPLETE

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

NDA 021197/S-018 (approved in 2017 per Drugs@FDA)

1. All labeling pieces (PI, vial and carton) were updated to remove reference to "alcohol swabs".
2. Additionally, the following assessments and revisions were noted in the Quality Labeling Review for S-018:
3. Removal of graphics from header
4. Segregation of 0.25 and 3mg doses throughout labeling
5. Revision of title position of table 1
6. Table 1 key reconfiguration
7. Updated revision date to "June 2017"

Below is taken from the Quality Labeling Review for S-018:

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Package Insert	June 29, 2017	June 29, 2017	April 4, 2008 (S-010)
Patient Leaflet	June 29, 2017	June 29, 2017	April 30, 2004 (S-003)
Carton and Container Labeling	June 29, 2017	June 29, 2017	April 30, 2004 (S-004)

Background and Summary Description:

Currently the Cetrotide® product is co-packaged with two alcohol swabs. This supplement provides for the removal of the alcohol swabs from the carton with subsequent changes to the labeling to indicate that the swabs are no longer co-packaged. Currently, the HOW SUPPLIED section of the label and the container and carton labeling indicate that two alcohol swabs are provided with the drug product in glass vial, diluent in syringe, and needles. Labeling will continue to instruct users to wipe the drug vial aluminum ring/rubber stopper prior to needle piercing and wipe the skin prior to injection. The supplement provides the updated HOW SUPPLIED section and the container and carton labeling showing the alcohol swabs text has been removed.

The changes are acceptable from a quality perspective in considering that the alcohol swabs have been provided as a convenience, not as an approved part of the drug product. Additionally, the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE) has evaluated the proposed change from a safety/medication errors perspective and recommends the supplement for approval.

- **NDA 021197/S-010 (Approved 04/04/2008)** is a "Changes Being Effected" supplemental new drug application which provides for revision of the Package Insert, under PRECAUTIONS,

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
subsection General, to include post-marketing information regarding hypersensitivity reactions related to the use of Cetrotide®. Note, S-010 labeling was combined labeling for the 2.5 mg and 3 mg vial. • **NDA 021197/S-019** (Approved 04/12/2018), **S-020 (Approved 04/13/2018** and **S-021** (Approved 02/12/2020) are CMC supplements that **DID NOT AFFECT LABELING.** Note, following approval of CMC S-020, per Annual Report-18 (10/11/2018) PI labeling was updated with the Annual Reportable change to reflect the removal of "Category X" under Pregnancy • **NDA 021197/S-022 (pending as of 10/04/2018)** is a CBE-0 Labeling supplement that proposes an update to the Cetrotide® **US Patient Leaflet Directions** for using Cetrotide® 0.25 by replacing the description in Step 6, "gently shake the vial until the solution is clear and without residue. Avoid forming bubbles during dissolution" with "While carefully holding the syringe and vial, swirl gently to mix the powder and water together. When it is mixed, it will look clear and have no particles in it. Do not shake or you will create bubbles in your medicine." The US Prescribing Information requires no change since it states 'swirl'. Note, although S-022 is currently pending, as a CBE-0, the change (updated directions for using Cetrotide® 0.25mg in Step 6) has already been implemented into the RLD Patient Leaflet labeling per Annual Report-19 (10/11/2019)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:
PI is current and acceptable.
The updated labeling is in line with:

- The most current in-use labeling for Cetrotide (S-018), as well as incorporated annual reportable revision following approval of S-020 (approved 04/13/2018) and S-022 (pending CBE-0)

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C2)

The Orange Book was searched on 04/26/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA 021197) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: NA **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C2)

The USP was searched on 04/26/2022

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

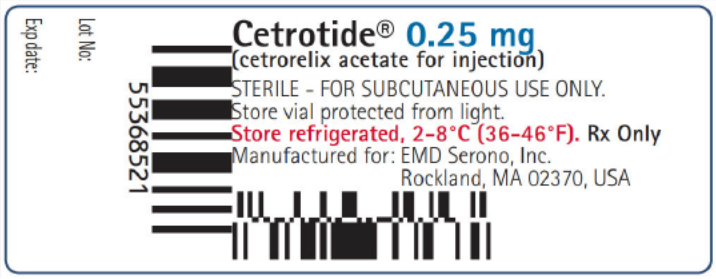
Reviewer Assessment:

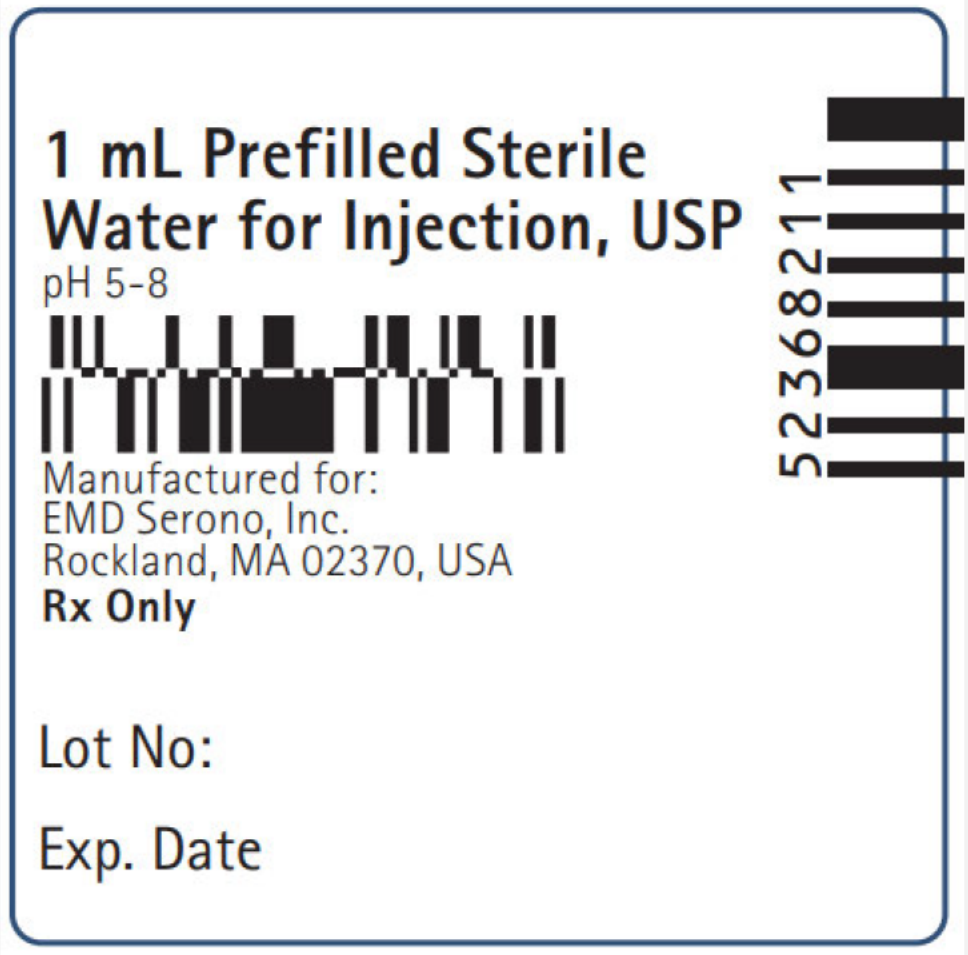
Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: NA		

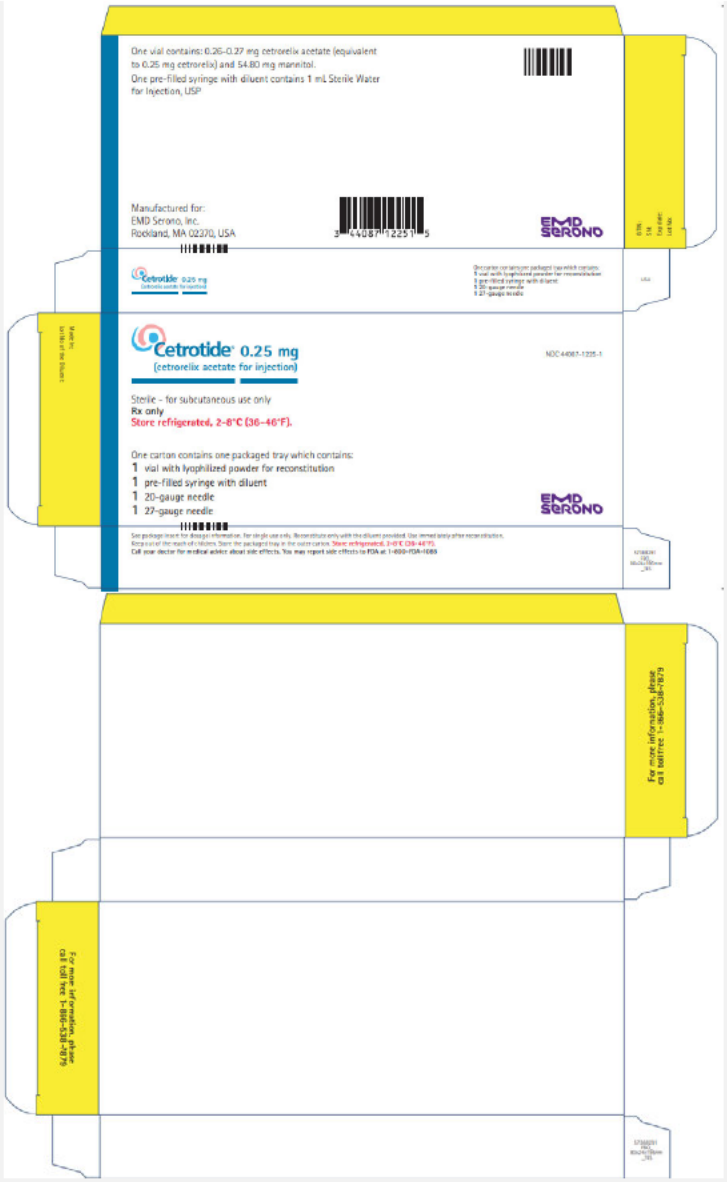
Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C2)

Model container/carton/blister labels (Source: Palantir, Annual Report-20 (10/09/2020) based on Final Labels submitted for NDA 021197/S-018 approved 12/22/2017: Annual Report-20 (10/09/2020) notes Technical Change to container/carton labeling to adopt to pack site design. NO changes to text or content from labels submitted for S-018 (approved 12/22/2017))







5 ASSESSMENT OF ANDA LABELING AND LABELS (C2)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C2)

5.1.1 DRUG PRODUCT REVIEW (C2)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

Review dated 4/11/2022: No issues.

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

10/22/21 Labeling Review#1, Minor Deficiency, Dinaxi Jetton
Labeling Review#1 does not describe any questions/issue(s) sent to or received from OPQ or DP Assessment.

Update R01a: To date, the last Labeling Review available is the 10/22/21 Labeling Review#1, Minor Deficiency, which does not have questions/issues for the DP Assessment.

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

5.1.2 DESCRIPTION (C2)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	NA
Previous ANDA Labeling	Cetrorelix acetate for injection 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (pH 5-8), that comes supplied in a 1.0 mL pre-filled syringe. Each vial of cetrorelix acetate for injection 0.25 mg contains 0.26-0.27 mg cetrorelix acetate,

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	equivalent to 0.25 mg cetrorelix, and 54.80 mg mannitol.
Current ANDA Labeling	Cetrorelix Acetate for Injection 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (pH 5-8), that comes supplied in a 1.0 mL pre-filled syringe. Each vial of cetrorelix acetate for injection 0.25 mg contains 0.26-0.27 mg cetrorelix acetate, equivalent to 0.25 mg cetrorelix, and 54.80 mg mannitol. No changes: Acceptable.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C2)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	NA
Previous ANDA Labeling	(b) (4)
Current ANDA Labeling	**HOW SUPPLIED** Cetrorelix Acetate for Injection 0.25 mg is available in a carton of one packaged tray (NDC 17478-793-12). Each packaged tray contains: one glass vial containing 0.26 - 0.27 mg cetrorelix acetate (corresponding to 0.25 mg cetrorelix), one pre-filled glass syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8), one 20 gauge needle (yellow) and one 27 gauge needle (grey). **Storage** Store Cetrorelix Acetate for Injection 0.25 mg refrigerated, 2-8°C (36-46°F). Store the packaged tray in the outer carton in order to protect from light. NDC numbers completed per previous comment: Acceptable.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C2)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b) (4)
Current ANDA Labeling	
Name and Address on	Manufactured for:

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
ANDA Prescribing Information	**Akorn Operating Company LLC** Lake Forest, IL 60045 Made in Spain Change is acceptable (consistent with form 356h).

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		OVERALL ASSESSMENT:

Deficiency	No Deficiency	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Acceptable.: All comments have been adequately addressed.

From cover letter dated 11/8/2021:

1. GENERAL COMMENTS
   a. **Comment as to whether text appears on your cap/ferrule overseal. Ensure your proposed cap/ferrule overseals are in compliance with the requirements of the USP, General Chapter <7> Labeling for Ferrules and Cap Overseals.**

      Response:
      Akorn would like to clarify that no text appears on the cap/ferrule overseal and the proposed cap/ferrule overseals are in compliance with the requirements of the USP General Chapter <7> Labeling for Ferrules and Cap Overseals.

   b. **We note per your Quality submission and the HOW SUPPLIED section of proposed labeling that your drug product is supplied in a carton of one packaged tray that includes "...one 20-gauge needle (yellow) and one 27-gauge needle (grey)." If accurate and you intend to include these needles in the packaging, submit the labeling for the needles under Module 1.14 for our review.**

      Response:
      As per agency's request, Akorn is providing the labeling for **20-gauge needle (yellow)** and **27-gauge needle (grey)** under Module 1.14.2.1 for the review.

2. CONTAINER LABEL
   a. **Drug Product Vial: Revise the presentation of the established name to appear in title case (i.e., Cetrorelix Acetate for Injection). If space permits, present "Cetrorelix Acetate" to appear in one line followed by "for Injection 0.25 mg".**

      Response:
      As per agency's request, Akorn is providing the revised **drug product vial label** with the established name in title case and in the requested presentation in Module 1.14.2.1 for the review.

   b. **Drug Product Vial: Include the National Drug Code (NDC) number and a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Ensure the bar code appears in a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf**

      Response:
      As per agency's request, Akorn is providing the revised **drug product vial label** with the "NDC 17478-793-12" and a linear bar code in vertical orientation in Module 1.14.2.1 for the review.

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is Blue. ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***

Reviewer Comments:

Acceptable: There is no text on the cap/ferrule overseal. See section 5.2 (cover letter

From C1 review:

(b) (4)

Deficiency Comments:

5.2.1.1 CONTAINER LABEL FOR SOLID INJECTABLE (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Strength** is expressed in terms of the total amount of drug per vial.
☐	☒	Container label includes **instructions for reconstitution** and resultant concentration provided, if space permits.
☐	☒	Quantity or proportion of all **inactive ingredients** listed on label as required under 21 CFR 201.100(b)(5)(iii).

Reviewer Comments:
Acceptable: Drug vial label meets "too small" exemption. All information required by regulation is adequately presented on the co-package tray label and the outer carton label.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
Acceptable: All comments have been adequately addressed.

From cover letter dated 11/8/2021:

3. CARTON LABELING

a. **Tray Label and Outer Carton label: Revise the presentation of the established name to appear in title case (i.e., Cetrorelix Acetate for Injection).**

Response:
As per agency's request, Akorn is providing the revised **tray label** and the **outer carton label** with the established name in title case in Module 1.14.2.1 for the review.

b. **Tray Label and Outer Carton label: Ensure to complete the National Drug Code (NDC) number and a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm349009.pdf**

Response:
As per agency's request, Akorn is providing the revised **tray label** and the **outer carton label** with the "NDC 17478-793-12" and a linear bar code in Module 1.14.2.1 for the review.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
Acceptable: All comments have been adequately addressed.

From cover letter dated 11/8/2021:

4. PRESCRIBING INFORMATION

a. **ADVERSE REACTIONS: Include the statement "To report SUSPECTED ADVERSE REACTIONS, contact..." as required per 21 CFR 201.57(a)(11). Include your contact information and the FDA toll free number and website.**

Response:
As per agency's request, Akorn is providing the revised **prescribing information** with the statement "**To report SUSPECTED ADVERSE REACTIONS, contact Akorn Operating Company LLC at 1-800-932-5676 or FDA at 1-800-FDA-1088 or WWW.FDA.GOV/MEDWATCH**" in ADVERSE REACTIONS section in Module 1.14.2.3 for the review.

b. **HOW SUPPLIED/ STORAGE AND HANDLING: See GENERAL comment. We note your HOW SUPPLIED section includes packaging components of "one 20-gauge needle (yellow) and one 27-gauge needle (grey)." If accurate and you intend to market these packaging components, submit the remaining labeling pieces under Module 1.14 for our review.**

Response:
As per agency's request, Akorn is providing the labeling for **20-gauge needle (yellow)** and **27-gauge needle (grey)** under Module 1.14.2.1 for the review.

c. **HOW SUPPLIED/ STORAGE AND HANDLING: Ensure to include the NDC number. If the NDC numbers are not available at the time of approval, consider stating "NDC numbers pending". We remind you that the NDC numbers must accurately be reflected in your labeling prior to marketing.**

Response:
As per agency's request, Akorn is including the "NDC 17478-793-12" in **HOW SUPPLIED** section in **prescribing information** provided in Module 1.14.2.3 for the review.

Deficiency Comments:

5.5 OTHER PATIENT LABELING (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
Patient Leaflet is the same as RLD labeling and acceptable: See section 6 for DCR assessment.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C2)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

DCR review of comparative analyses dated 12/22/2021: Acceptable with no comments.

4 CONCLUSION

From a clinical safety perspective, there are acceptable minor design differences (packaging tray and prefilled syringes) between the proposed drug delivery device and the RLD. Therefore, DCR concludes this generic combination product can be substituted for the RLD without additional training prior to use of the generic combination product; the design differences for this combination device are not expected to alter the safety profile or clinical effect of this proposed ANDA product under the conditions specified in the labeling. In summary, DCR finds the proposed drug delivery device user interface for the proposed generic acceptable from a clinical user-interface perspective.

5 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative analyses and has no comments at this time.

Deficiency Comments:

Juwon Lee

Digitally signed by Juwon Lee
Date: 4/27/2022 03:35:52PM
GUID: 508da6f700027fdcd32f67dfe9fc22f8

Esther Chuh

Digitally signed by Esther Chuh
Date: 4/27/2022 04:09:52PM
GUID: 508da70700028b78f2f9ebd95bfb4a18

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	October 13, 2021
ANDA Number(s)	215737
Review Number	1
Applicant Name	Akorn Operating Company LLC
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Cetrorelix Acetate for Injection, 0.25 mg/Vial (Single-Dose Vial)
Proposed Proprietary Name	None
Submission Received Date	June 23, 2021, August 05, 2021, August 11, 2021
Primary Labeling Reviewer	Dinaxi Jetton
Secondary Labeling Reviewer	Ellen Hwang

Review Conclusion

☐ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submissions received June 23, 2021, August 05, 2021 and August 11, 2021:

1. GENERAL COMMENTS
    a. Comment as to whether text appears on your cap/ferrule overseal. Ensure your proposed cap/ferrule overseals are in compliance with the requirements of the USP, General Chapter <7> Labeling for Ferrules and Cap Overseals.
    b. We note per your Quality submission and the HOW SUPPLIED section of proposed labeling that your drug product is supplied in a carton of one packaged tray that includes “...one 20-gauge needle (yellow) and one 27 gauge needle (grey).” If accurate and you intend to include these needles in the packaging, submit the labeling for the needles under Module 1.14 for our review.

2. CONTAINER LABEL
    a. Drug Product Vial: Revise the presentation of the established name to appear in title case (i.e., Cetrorelix Acetate for Injection). If space permits, present "Cetrorelix Acetate" to appear in one line followed by "for Injection 0.25 mg".
    b. Drug Product Vial: Include the National Drug Code (NDC) number and a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Ensure the bar code appears in a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

3. CARTON LABELING
    a. Tray Label and Outer Carton label: Revise the presentation of the established name to appear in title case (i.e., Cetrorelix Acetate for Injection).
    b. Tray Label and Outer Carton label: Ensure to complete the National Drug Code (NDC) number and a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

4. PRESCRIBING INFORMATION
    a. ADVERSE REACTIONS: Include the statement "To report SUSPECTED ADVERSE REACTIONS, contact..." as required per 21 CFR 201.57(a)(11). Include your contact information and the FDA toll free number and website.
    b. HOW SUPPLIED/ STORAGE AND HANDLING: See GENERAL comment. We note your HOW SUPPLIED section includes packaging components of “one 20 gauge needle (yellow) and one 27 gauge needle (grey).” If accurate and you intend to market these packaging components, submit the remaining labeling pieces under Module 1.14 for our review.

c. HOW SUPPLIED/ STORAGE AND HANDLING: Ensure to include the NDC number. If the NDC numbers are not available at the time of approval, consider stating "NDC numbers pending". We remind you that the NDC numbers must accurately be reflected in your labeling prior to marketing.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

1.3 POST-APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired**, and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.

- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	1 x 0.25 mg per vial (Single-Dose Vial)	08/11/2021	Revise
Blister	Draft	1 mL Pre-filled syringe of Sterile Water for Injection	06/23/2021	Satisfactory
Carton	Draft	1 x 0.25 mg vial of cetrorelix acetate 1 mL pre-filled syringe of Sterile Water for Injection 1 x 20-gauge needle (yellow) 1 x 27-gauge needle (grey)	06/23/2021	Revise
Packaged Tray	Final	1 x 0.25 mg vial of cetrorelix acetate 1 mL pre-filled syringe of Sterile Water for Injection 1 x 20-gauge needle (yellow) 1 x 27-gauge needle (grey)	08/11/2021	Revise

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Jan 2021	06/23/2021	Revise
Medication Guide	N/A	N/A		
Patient Information	Draft	Jan 2021	06/23/2021	Satisfactory
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION

4.1 REGULATORY INFORMATION

Yes	No	
☐	☒	Are there any applicable issues in DLR's SharePoint Drug Facts ?
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION

Table 3: Review Model Labeling for Prescribing Infor
(Check the box used as the Model L

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the

NDA#/Supplement# (S-000 if original): NDA021197 / S-018

Supplement Approval Date: 12/22/2017

Proprietary Name: Cetrotide

Established Name: cetrorelix acetate for injection

Description of Supplement:

This "Changes Being Effected" supplemental new drug application provides for removal of alcohol swabs current

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/panorama-document?pk_panorama_document=55bc309f00aa491b162f1eb9816b792c_5955f06a01432555a86ddd549bf1cc9f_5955f06f014326367

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

For the Record:

NDA 021197/S-018 (approved in 2017 per Drugs@FDA)

1. All labeling pieces (PI, vial and carton) were updated to remove reference to "alcohol swabs".
2. Additionally, the following assessments and revisions were noted in the Quality Labeling Review for S-018:
3. Removal of graphics from header
4. Segregation of 0.25 and 3mg doses throughout labeling
5. Revision of title position of table 1
6. Table 1 key reconfiguration
7. Updated revision date to "June 2017"

Below is taken from the Quality Labeling Review for S-018:

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Package Insert	June 29, 2017	June 29, 2017	April 4, 2008 (S-010)
Patient Leaflet	June 29, 2017	June 29, 2017	April 30, 2004 (S-003)
Carton and Container Labeling	June 29, 2017	June 29, 2017	April 30, 2004 (S-004)

Background and Summary Description:

Currently the Cetrotide® product is co-packaged with two alcohol swabs. This supplement provides for the removal of the alcohol swabs from the carton with subsequent changes to the labeling to indicate that the swabs are no longer co-packaged. Currently, the HOW SUPPLIED section of the label and the container and carton labeling indicate that two alcohol swabs are provided with the drug product in glass vial, diluent in syringe, and needles. Labeling will continue to instruct users to wipe the drug vial aluminum ring/rubber stopper prior to needle piercing and wipe the skin prior to injection. The supplement provides the updated HOW SUPPLIED section and the container and carton labeling showing the alcohol swabs text has been removed.

The changes are acceptable from a quality perspective in considering that the alcohol swabs have been provided as a convenience, not as an approved part of the drug product. Additionally, the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE) has evaluated the proposed change from a safety/medication errors perspective and recommends the supplement for approval.

- **NDA 021197/S-010 (Approved 04/04/2008)** is a "Changes Being Effected" supplemental new drug application which prov marketing information regarding hypersensitivity reactions related to the use of Cetrotide®. Note, S-010 labeling was comb

Table 3: Review Model Labeling for Prescribing Infor (Check the box used as the Model L
• **NDA 021197/S-019** (Approved 04/12/2018), **S-020 (Approved 04/13/2018** and **S-021** (Approved 02/12/2020) are CMC su Annual Report-18 (10/11/2018) PI labeling was updated with the Annual Reportable change to reflect the removal of "Categ • **NDA 021197/S-022 (pending as of 10/04/2018)** is a CBE-0 Labeling supplement that proposes an update to the Cetrotide® " (b) (4) " with " (b) (4) The US P pending, as a CBE-0, the change (updated directions for using Cetrotide® 0.25mg in Step 6) has already been implemented

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up to date** with the RLD/Model labeling.

Reviewer Comments:
Proposed ANDA labeling is in accordance with the most recent labeling of RLD Cetrotide, NDA 021197/S-018 approved 12/22/2017.
Applicant has also revised and updated proposed labeling in line with:

- The most current in-use labeling for Cetrotide (S-018), as well as incorporated annual reportable revision following approval of S-020 (approved04/13/2018) and S-022 (pending CBE-0)

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 10/13/2021

Table 4 provides Orange Book patents for the Model Labeling (NDA021197) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired**, and the applicant needs to revise labeling.

Reviewer Comments:
There are no unexpired patents or exclusivities listed in the OB

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 10/13/2021

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
		USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

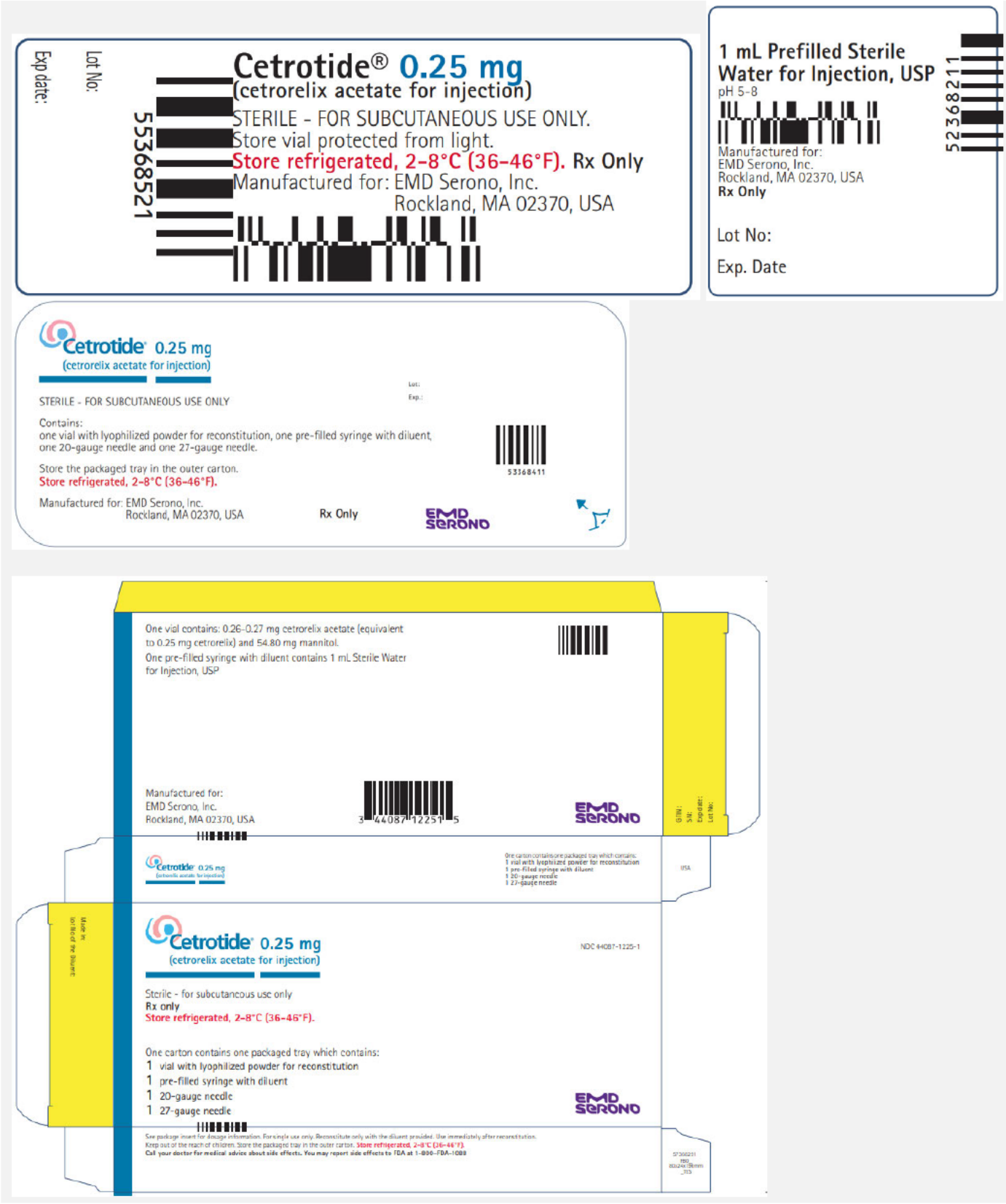
Reviewer Comments:
There is no USP Monograph for the proposed drug product.
Bioequivalence Review is pending

Deficiency Comments:

4.5 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: Palantir, Annual Report-20 (10/09/2020) based on Final Labels submitted for NDA 021197/S-018 approved 12/22/2017:)

Annual Report-20 (10/09/2020) notes Technical Change to container/carton labeling to adopt to pack site design. NO changes to text or content from labels submitted for S-018 (approved 12/22/2017)



5 ASSESSMENT OF ANDA LABELING AND LABELS

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

5.1.1 DRUG PRODUCT REVIEW

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Information submitted in Module 3.2.P.1 (Description and Composition) is consistent with the information provided in the DESCRIPTION and HOW SUPPLIED sections of PI labeling:

All the inactive ingredients used in the proposed generic drug product are qualitatively (Q1) and quantitatively (Q2) the same as that of the Reference Listed Drug (RLD).

Table 3 Qualitative (Q1) and Quantitative (Q2) Composition of the proposed drug Product – Cetrorelix Acetate for injection, 0.25 mg/Vial (Lyophilized powder) in a Single Dose Vial

Name of the Ingredient	Quality standards	Pharmaceutical function	(b) (4) Cetrorelix for Injection 0.25 mg/vial (lyophilized powder) (mg/vial)
Cetrorelix Acetate [1]	DMF	Active Pharmaceutical Ingredient	equivalent to 0.25 mg/vial of cetrorelix
Mannitol	USP	(b) (4)	54.8
(b) (4)			(b) (4)
Water for injection	USP		
(b) (4)			

The proposed drug product, Cetrorelix Acetate for Injection, 0.25 mg is supplied as a co-packaged kit (carton of one packaged tray). The kit consists of one glass vial containing Cetrorelix Acetate for Injection (lyophilized powder for reconstitution) 0.25 mg, one pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8), one 20-gauge needle (yellow) and one 27-gauge needle (grey). The proposed drug product packaging details are provided in the following tables:

(b) (4)

5.1.2 DESCRIPTION

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Cetrotide® (cetrorelix acetate for injection) 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (pH 5-8), that comes supplied in a 1.0 mL pre-filled syringe. Each vial of Cetrotide® 0.25 mg contains 0.26-0.27 mg cetrorelix acetate, equivalent to 0.25 mg cetrorelix, and 54.80 mg mannitol.
Previous ANDA Labeling	NA
Current ANDA Labeling	**C#1 Labeling (submitted 06/23/2021):** Cetrorelix acetate for injection 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (pH 5-8), that comes supplied in a 1.0 mL pre-filled syringe. Each vial of cetrorelix acetate for injection 0.25 mg contains 0.26-0.27 mg cetrorelix acetate, equivalent to 0.25 mg cetrorelix, and 54.80 mg mannitol.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**HOW SUPPLIED** Cetrotide® (cetrorelix acetate for injection) 0.25 mg is available in a carton of one packaged tray (NDC 44087-1225-1). Each packaged tray contains: one glass vial containing 0.26 - 0.27 mg cetrorelix acetate (corresponding to 0.25 mg cetrorelix), one pre-filled glass syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8), one 20 gauge needle (yellow) and one 27 gauge needle (grey). **Storage** Store Cetrotide® 0.25 mg refrigerated, 2-8ºC (36-46ºF). Store the packaged tray in the outer carton in order to protect from light.
Previous ANDA Labeling	
Current ANDA Labeling	(b) (4)

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	
Name and Address on ANDA Container/Carton	
Name and Address on ANDA Prescribing Information	
Current ANDA Labeling	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	**Module 3.2.P.3.1 (Manufacturer) of Original submission, 06/23/2021:** (b) (4)
Name and Address on ANDA Container/Carton	(b) (4)
Name and Address on ANDA Prescribing Information	

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☒	☐	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☒	☐	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.

Deficiency	No Deficiency	
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Module 3.2.P.7.1 (Summary of Container Closure System) notes the following:

Reference listed drug (RLD) Cetrotide® 0.25 mg is a co-packaged drug-device combination product, marketed as a kit containing the following constituents in a plastic tray and within an outer cardboard carton:

- A vial of sterile lyophilized 0.26 - 0.27 mg cetrorelix acetate (corresponding to 0.25 mg cetrorelix) for injection
- A pre-filled glass syringe with 1 mL of Sterile Water for Injection, USP as diluent
- A sterile 20-gauge 1½ inch needle (yellow) for reconstitution
- A sterile 27-gauge ¾ inch needle (grey) for subcutaneous injection

The proposed drug product is also a co-packaged drug-device combination product marketed as a kit with components in a plastic tray in an outer carton:

- One vial of Cetrorelix acetate for injection 0.25 mg
- One pre-filled glass syringe with 1 mL Sterile Water for Injection as a diluent
- One 20-gauge 1½ inch needle (yellow) for reconstitution
- One 27-gauge ¾ inch needle (grey) for subcutaneous injection
- **Proposed Drug Product Vial label** meets the too small exemption. As required, label includes, the established name, designated space for lot or control number and name of the manufacturer. Additionally, all other information required per regulation, appears on the co-package tray label and carton label.

3.2.P.7.5 Secondary Packing components list for Cetrorelix Acetate for Injection, 0.25 mg (kit)

Below listed are the secondary packing components of Cetrorelix Acetate for Injection, 0.25 mg kit.

- Information card with product information
- Package Insert
- Carton
- Pre-formed plastic clamshell blister tray

3.2.P.7.3 Commercial Packaging Configurations and Sizes

(b) (4)

(b) (4)

Assessment:

- **Diluent Syringe label** is adequately presented same as the RLD diluent syringe
- **Drug Product Vial label** Minor revisions will be requested

We note the proposed DP is a Combination, co-packaged DP and further assessment of the physical components will be conducted by Division of Clinical Review (DCR) in a Combination Product Comparative Analyses Review. DLR defers to DCR for final assessment.

Deficiency Comments:

Deficiency # 1 Created in C1 Container Label Response / Assessment:	Drug Product Vial: Revise the presentation of the established name to appear in title case (i.e., Cetrorelix Acetate for Injection). If space permits, present "Cetrorelix Acetate" to appear in one line followed by "for Injection 0.25 mg".
Deficiency # 2 Created in C1 Container Label	Drug Product Vial: Include the National Drug Code (NDC) number and a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Ensure the bar code appears in a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance

Response / Assessment:	for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

5.2.1 INJECTABLE PRODUCTS

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☒	☐	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is Blue. ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***

Reviewer Comments:

(b) (4)

[redacted]

Deficiency Comments:

Deficiency # 1 Created in C1 General Comments Response / Assessment:	Comment as to whether text appears on your cap/ferrule overseal. Ensure your proposed cap/ferrule overseals are in compliance with the requirements of the USP, General Chapter <7> Labeling for Ferrules and Cap Overseals.
Deficiency # 2 Created in C1 General Comments	We note per your Quality submission and the HOW SUPPLIED section of proposed labeling that your drug product is supplied in a carton of one packaged tray that includes "...one 20 gauge needle (yellow) and one 27 gauge needle (grey)." If accurate and you intend to include these needles in

	the packaging, submit the labeling for the needles under Module 1.14 for our review.
Response / Assessment:	

5.2.1.1 CONTAINER LABEL FOR SOLID INJECTABLE

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Strength** is expressed in terms of the total amount of drug per vial.
☐	☒	Container label includes **instructions for reconstitution** and resultant concentration provided, if space permits.
☐	☒	Quantity or proportion of all **inactive ingredients** listed on label as required under 21 CFR 314.94(a)(8).

Reviewer Comments:
Drug vial label meets "too small" exemption. All information required by regulation is adequately presented on the co-package tray label and the outer carton label.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
With exception of the established name:

- **Tray label** is adequately presented same as RLD tray label
- **Outer Carton label** is adequately presented same as RLD outer carton label

Minor revision noted below for both labeling pieces.

Deficiency Comments:

Deficiency # 1 Created in C1 Carton Labeling Response / Assessment:	Tray Label and Outer Carton label: Revise the presentation of the established name to appear in title case (i.e., Cetrorelix Acetate for Injection).
Deficiency # 2 Created in C1 Carton Labeling Response / Assessment:	Tray Label and Outer Carton label: Ensure to complete the National Drug Code (NDC) number and a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

5.4 PRESCRIBING INFORMATION

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☒	☐	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☒	☐	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☒	☐	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(j)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Proposed PI labeling (submitted on 06/23/2021) is in accordance with the most current PI labeling of the RLD Cetrotide, NDA 021197/S-018 approved 12/22/2017 as found on Drugs@FDA; as well as the updated RLD labeling (following approval of CMC S-020 (04/13/2018) to remove "Category X" from the Pregnancy section of labeling, as found in DARRTS (see Section 4.2, Model Labeling).

Both RLD and proposed labeling is in non-PLR format:

- The non-PLR format does not include a HIGHLIGHTS section, therefore, there is no manufacturer or FDA contact information for reporting adverse reactions. See comment below.

- There is a revision date at the end of the PI as required for non-PLR Format labeling. We will not comment and allow as proposed.

Deficiency Comments:

Deficiency # 1 Created in C1 Prescribing Information Response / Assessment:	ADVERSE REACTIONS: Include the statement "To report SUSPECTED ADVERSE REACTIONS, contact..." as required per 21 CFR 201.57(a)(11). Include your contact information and the FDA toll free number and website.
Deficiency # 2 Created in C1 Prescribing Information Response / Assessment:	HOW SUPPLIED/ STORAGE AND HANDLING: See GENERAL comment. We note your HOW SUPPLIED section includes packaging components of "one 20-gauge needle (yellow) and one 27 gauge needle (grey)." If accurate and you intend to market these packaging components, submit the remaining labeling pieces under Module 1.14 for our review.
Deficiency # 3 Created in C1 Prescribing Information Response / Assessment:	HOW SUPPLIED/ STORAGE AND HANDLING: Ensure to include the NDC number. If the NDC numbers are not available at the time of approval, consider stating "NDC numbers pending". We remind you that the NDC numbers must accurately be reflected in your labeling prior to marketing.

5.5 OTHER PATIENT LABELING

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Proposed Patient Information labeling (submitted on 06/23/2021) is in accordance with the most current approved Patient Information labeling of the RLD Cetrotide, NDA 021197/S-018, approved 12/22/2017 as found on Drugs@FDA; as well as the labeling revision noted in pending S-022 (CBE-0) revising instructional Step 6, that has already been implemented into RLD Patient Information labeling, as noted in Daily Med and per Summary of Labeling Changes in Annual Report-19 (10/11/2019). See Section 4.2, Model Labeling.

Additionally, it is noted that the DP is a combination, co-packaged product and Division of Clinical Review (DCR) will further assess the Patient Labeling submission in a Combination Product Comparative Analysis Review. DLR defers further assessment to DCR.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e., solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:
No comment

Deficiency Comments:

Dinaxi Jetton

Digitally signed by Dinaxi Jetton
Date: 10/22/2021 03:05:20PM
GUID: 53b417e400011b164ae1b5ff9ebbb351

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 10/22/2021 06:36:05PM
GUID: 5256bdc00002af3bc3fa942a9512a891

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215737Orig1s000

BIOEQUIVALANCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	215737
Drug Product Name	Cetrorelix Acetate Injection
Strength	EQ 0.25 MG BASE/ML*
Applicant Name	Akorn Operating Company LLC (originally by Calyptus Pharmaceuticals, Inc.)[1]
Applicant Address	1925 West Field Court Suite 300 Lake Forest, IL 60045
Contact Name and US Mailing Address	John Franolic, Ph.D. 1925 West Field Court Suite 300 Lake Forest, IL 60045 Email: John.Franolic@akorn.com
Contact Telephone Number	631-881-9270
Contact Fax Number	847-574-5881
Original Submission Date(s)	06/23/2021 08/30/2021 (ownership of this ANDA was transferred from Calyptus Pharmaceuticals Inc. to Akorn Operating Company LLC)
Submission Date(s) of Amendment(s) Under Review	N/A
Primary Assessor	Madhusudana Rao Chaluvadi, Ph.D., RPh, BCPS
Secondary Assessor	Meirong Hao, Ph.D.
Tertiary Assessor	Wendy Cai, Ph.D.
Waiver/Deem Bioequivalent	☒ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☐ **N/A**
Formulation	☒ **Adequate** ☐ **Inadequate**
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**
Deficiency Classification	☐ **Major** ☐ **Minor/IR** ☒ **N/A (Review is Adequate)**
Overall Review Result	☒ **Adequate** ☐ **Inadequate**
Product Specific Guidance (PSG) Referenced in Review	***Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)***

[1] \\CDSESUB1\evsprod\anda215737\0005\m1\us\12-cover-letters\cover-letter.pdf (Akorn Operating Company LLC was the US agent for Calyptus Pharmaceuticals, Inc. for the referenced ANDA prior to the ownership transfer)

	☐ **Recommended/Latest Revision Date: _____** **RLD Number: _NDA 021197_____** ☒ **N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1, 2	**Waiver/Deem Bioequivalent**	EQ 0.25 MG BASE/ML	☒ **Adequate** ☐ **Inadequate**

*: Per Orange Book, NDA 021197, the reference listed drug product is listed as EQ 0.25 MG BASE/ML. However, the current applicant, in the communications and submissions, listed as EQ 0.25 MG BASE/**Vial**. As the vial is reconstituted to 1 ml, per the assessor, this is acceptable and interchangeable. In addition, the labelling assessment,[2] and Drug Product Quality Assessment[3] did not raise any comments or concerns about this.

[2] https://panorama.fda.gov/task/view?ID=60d4892d00d6264a27e531dff0ceacc9
[3] https://panorama.fda.gov/task/view?ID=60d4892e00d6297cc669c1144542cace

1 EXECUTIVE SUMMARY

Calyptus Pharmaceuticals, Inc[1]. requested a waiver of in vivo bioequivalence (BE) testing for its test product, Cetrorelix Acetate Injection, EQ 0.25MG BASE/ML, under 21 CFR § 320.22 (b)(1). The corresponding reference listed drug (RLD) and reference standard (RS) is CETROTIDE® (Cetrorelix) injection, EQ 0.25 MG BASE/ML by EMD Serono, Inc. (NDA #021197, Approved on 08/11/2000).

The route of administration, dosage form, and strength of the test product are the same as those of the RLD product. Both test and RLD products are presented as sterile lyophilized powder intended for subcutaneous injection after reconstitution with co-packaged diluent, Sterile Water. The test product contains the same active ingredients and inactive ingredients in the same concentration as the RLD product. Therefore, the applicant's test product (including co-packaged diluent) is qualitatively (Q1) and quantitatively (Q2) the same as the RLD product. The specification for the pH of the reconstituted test product is (b) (4), whereas the pH specification for the RLD is (b) (4). The measured pH of the reconstituted test product is 4.7 for all 3 exhibit batches, which is within the pH specification of the RLD. The evaluation of pH specifications is deferred to Office Pharmaceutical Quality (OPQ).

Both test and RLD products are packaged in a carton, contain one glass vial with lyophilized drug product, one pre-filled glass syringe with 1 mL of Sterile Water for Injection, one 20-gauge needle (yellow), one 27-gauge needle (grey).

The current drug product is listed as "Combination Product: 1-Convenience Kit of Co-Package" and the Combination Product Comparative Analyses Review to be performed by the Division of Clinical Review (DCR) in the Office of Safety and Clinical Evaluation (OSCE) is currently pending[4].

Based on the information provided, the Division of Bioequivalence III (DBIII) grants the waiver request of in vivo BE study requirements for the test product, Cetrorelix injection, EQ 0.25 MG BASE/ML per the criteria set forth in Section 21 CFR § 320.22 (b)(1).

The application is **adequate**.

[4] GDRP: ANDA 215737. Combination Product Comparative Analyses Review: status: IN PROGRESS (as of 12/05/2021). https://panorama.fda.gov/project/view?ID=60d4892d00d621815de3301b72b1bef5

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[5]

Test Drug Product and Strength(s)	Cetrorelix injection, EQ 0.25 MG BASE/Vial (1 mL)
Reference Standard (RS) and Strength(s)	CETROTIDE ® (Cetrorelix) injection, EQ 0.25 MG BASE/ML
RS Holder; NDA/ANDA Number; Approval Date	EMD Serono, Inc., NDA # 021197 Approved 08/11/2000
Reference Listed Drug (RLD) and Strength(s)	CETROTIDE ® (Cetrorelix) injection, EQ 0.25 MG BASE/ML (Please see a note below)
RLD Holder; NDA/ANDA Number; Approval Date	EMD Serono, Inc., NDA # 021197 Approved 08/11/2000

Assessor's note: NDA 021197 has two strengths of EQ 0.25 MG BASE/ML and EQ 3 MG BASE/ML. The EQ 3 MG BASE/ML strength is discontinued per Orange Book (Last access date: 11/24/2021) (not listed either RLD or RS). The applicant only proposed to include of EQ 0.25 MG BASE/ML strength in the current application.

3.2 PK/PD Information[6]

Most recent RLD label	021197s010lbl.pdf Last updated 04/04/2008
Indication	Cetrotide® (cetrorelix acetate for injection) is indicated for the inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian stimulation.
Boxed warning	None
Bioavailability	Cetrotide® is rapidly absorbed following subcutaneous injection, with maximal plasma concentrations being achieved approximately one to two hours after administration. The mean absolute bioavailability of Cetrotide® following subcutaneous administration to healthy female subjects is 85%.
Food Effect	N/A

[5] Orange Book: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021197#20405

[6] Drugs@FDA search cetrorelix (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm), Last updated on 04/04/2008 (Suppl-10; last access date: 11/24/2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021197s010lbl.pdf

Tmax	Table 1: Pharmacokinetic parameters of Cetrotide® following 3 mg single or 0.25 mg single and multiple (daily for 14 days) subcutaneous (sc) administration. **Single dose 3 mg** / **Single dose 0.25 mg** / **Multiple dose 0.25 mg** No. of subjects: 12 / 12 / 12 t_{max}* [h]: 1.5 (0.5-2) / 1.0 (0.5-1.5) / 1.0 (0.5-2)
Metabolism	Cetrotide® (cetrorelix acetate for injection) is a synthetic decapeptide. After subcutaneous administration of 10 mg Cetrotide® to females and males, Cetrotide® and small amounts of (1-9), (1-7), (1-6), and (1-4) peptides were found in bile samples over 24 hours. In in vitro studies, Cetrotide® was stable against phase I- and phase II-metabolism. Cetrotide® was transformed by peptidases, and the (1-4) peptide was the predominant metabolite.
Excretion	Following subcutaneous administration of 10 mg cetrorelix to males and females, only unchanged cetrorelix was detected in urine. In 24 hours, cetrorelix and small amounts of the (1-9), (1-7), (1-6), and (1-4) peptides were found in bile samples. 2-4% of the dose was eliminated in the urine as unchanged cetrorelix, while 5-10% was eliminated as cetrorelix and the four metabolites in bile. Therefore, only 7-14% of the total dose was recovered as unchanged cetrorelix and metabolites in urine and bile up to 24 hours. The remaining portion of the dose may not have been recovered since bile and urine were not collected for a longer period of time.
Half-life	Table 1: Pharmacokinetic parameters of Cetrotide® following 3 mg single or 0.25 mg single and multiple (daily for 14 days) subcutaneous (sc) administration. **Single dose 3 mg** / **Single dose 0.25 mg** / **Multiple dose 0.25 mg** No. of subjects: 12 / 12 / 12 t_{max}* [h]: 1.5 (0.5-2) / 1.0 (0.5-1.5) / 1.0 (0.5-2) $t_{1/2}$* [h]: 62.8 (38.2-108) / 5.0 (2.4-48.8) / 20.6 (4.1-179.3)
Maximum Daily Dose	3 mg/day
Special populations	Pharmacokinetic investigations have not been performed either in subjects with impaired renal or liver function, or in the elderly, or in children

3.3 OGD Recommendations for Drug Product

Bioequivalence based on:	**As per Section 21 Code of Federal Regulations (CFR) § 320.22 (b) (1):** For certain drug products, the *in vivo* bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained *in vivo* measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's *in vivo* bioavailability or bioequivalence may be considered self-evident based on other data in the application if the drug product: i. It is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and ii. Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.	
Source of CFR	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm (or eCFR: https://www.ecfr.gov/cgi-bin/text-idx?SID=44b528d2167bcaacfac20917ef5d7857&mc=true&tpl=/ecfrbrowse/Title21/21cfrv5_02.tpl#0)	
	Approved ANDAs:	No.

Summary of OGD or DB History	Pending ANDAs:	Per DARRTS, ANDA 214540 (CR status) The current application is the only pending application (4 ANDAs in presubmission/ preassignment status)
	Controls:	Yes.[7,8] 2 Control Correspondences (CCs) are from the current applicant. CC: 17237308[9] is requesting Q1/Q2 evaluation of the test product (please see details below the table). CC: 23396924[10] is for Confirmation for stability batch size requirement.
	Protocols:	None from current applicant
	Pending Citizen Petitions and other legal and regulatory issues:[11] If yes, please comment.	☐ Yes ☒ No

CC #17237308 (Received on 08/25/2017)

Question: Cetrorelix Acetate for Injection, 0.25mg per vial; Agency's advice of Q1/Q2 composition(s) - RLD NDA 021197.

Proposed Formulation 1:

A. Cetrorelix Acetate for Injection (lyophilized powder) in A Single-dose Vial

Ingredients	Function	mg/vial
Cetrorelix Acetate	Active	Equivalent to 0.25 mg cetrorelix base
Mannitol	(b) (4)	54.80

[7] GDRP: https://panorama.fda.gov/search?objCode=ALL&allowRedirect=false&query=cetrorelix&showResultsPage=false#?facets=%5B%7B%22fieldName%22:%22categoryID%22,%22filters%22:%5B%22categoryID_s:537669e800073f720fcf8b8f349f8fd9%22%5D%7D%5D; Search: Search: cetrorelix; Last accessed 11/24/2021

[8] NEXUS: https://cdernexus.fda.gov/suite/sites/controlled-correspondence/page/search; Search: cetrorelix; Last accessed 11/24/2021

[9] https://panorama.fda.gov/task/view?ID=59a548050017dabcef2ae19707d7f6cd

[10] https://panorama.fda.gov/task/view?ID=5b0fe99d000ed22fe1c9316aa167a96f

[11] OGD policy alert list as of 11/24/2021. https://fda.sharepoint.com/sites/CDER-OGD/OGDP%20DPAL%20Alert%20List/Forms/Active%20Docs.aspx

B. Diluent in A Pre-filled Syringe

	Function	mL/syringe
Sterile Water for Injection	(b) (4)	1

Proposed Formulation 2:

A. Cetrorelix Acetate for Injection (lyophilized powder) in A Single-dose Vial

Ingredients	Function	mg/vial
Cetrorelix Acetate	Active	Equivalent to 0.25 mg cetrorelix base
Mannitol	(b) (4)	54.80
(b) (4)		(b) (4)
Water for Injection		

B. Diluent in A Pre-filled Syringe

	Function	mL/syringe
Sterile Water for Injection	Diluent	1

Agency response: After reviewing your controlled correspondence, the preliminary view of the Office of Generic Drugs (OGD) is that, with respect to **both proposed formulations**, OGD would likely grant a waiver of in vivo bioequivalence because bioequivalence would be self-evident as per 21 CFR 320.22(b)(1). OGD has made a preliminary determination that it would not likely refuse to receive your ANDA submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act and its implementing regulations based on **both proposed formulations** pursuant to the requirements pertaining to inactive ingredients described in 21 CFR 314.101(d)(3) and 21 CFR 314.94(a)(9).

Reference is made to the definition of quantitative sameness to the reference listed drug (RLD) as stated in the Guidance for Industry: ANDA Submissions - *Refuse-to-Receive* Standards (December 2016, Revision 2).

4 APPENDIX

4.1 Formulation Data

4.1.1 Test Product Formulation[12]

Composition of the proposed drug Product – Cetrorelix Acetate for injection, 0.25 mg/Vial (Lyophilized powder) in a Single Dose Vial

Name of the Ingredient	Quality standards	Pharmaceutical function	Cetrorelix for Injection 0.25 mg/mL Bulk Solution for Lyophilization	Cetrorelix for Injection 0.25 mg/vial (lyophilized powder)
			(mg/mL)	(mg/vial)
Cetrorelix Acetate [1]	(b) (4)	Active Pharmaceutical Ingredient	equivalent to 0.25 mg/mL of cetrorelix	equivalent to 0.25 mg/vial of cetrorelix
Mannitol	(b) (4)	(b) (4)	54.8	54.8
Water for injection	(b) (4)			(b) (4)
				(b) (4)

Composition of the Diluent in a Pre-filled Syringe

Name of the Ingredient	Quality standards	Pharmaceutical function	mL/ Syringe
Sterile Water for injection	USP	Diluent	1

[12] DocuBridge: ANDA 215737, Sequence 0002 (06/23/2021), Module 3.2.P.1. Description-and-composition of the drug Product (\\CDSESUB1\evsprod\anda215737\0002\m3\32-body-data\32p-drug-prod\cetro-acet-vial\32p1-desc-comp\description-and-composition.pdf)

4.1.2 RLD Formulation

RLD (NDA021197) CETROTIDE ® (Cetrorelix) injection, EQ 0.25MG BASE/ML [13], (b) (4)

Batch Formula

Table 1: Examples of Batch Formulas for Cetrorelix Drug Product, 0.25 mg Lyophilisate

Name of Ingredient	Function	Reference to Standards
Cetrorelix acetate	Drug substance	Internal
Mannitol	(b) (4)	Ph. Eur./USP
(b) (4)		Ph. Eur./USP
Water for injection		Ph. Eur./USP

(b) (4)

(b) (4)

4.1.3 Comparison of the Test and Reference Products

Component	Test (per unit)	RLD (per unit)	% Difference From RLD*
Cetrorelix Acetate	0.25 mg per unit	0.25 mg	0.00%
mannitol	54.8 mg	54.8 mg	0.00%
(b) (4)			
Water for injection	q.s	q.s.	--
(b) (4)			

*Difference (% difference) of active and inactive ingredients between test and RLD products = (TEST – RLD) x100/RLD

[13]DocuBridge: NDA 021197. Batch Formula in module 3.2.P.3.2. \\CDSESUB1\evsprod\nda021197\0073\m3\32-body-data\32p-drug-prod\cetrotide-solutionforinjection\32p3-manuf\batch-formula.pdf
Also can be found: GDRP: NDA 021197-SUPPL-21-RESUV-220, Drug Product Review: NDA21197S21.pdf. Dated on 01/17/2019
https://panorama.fda.gov/task/view?ID=5bb4447901c617456b00796483024b9d

Comparison between RLD; Cetrotide® 0.25 mg (Cetrorelix Acetate for injection) and the proposed generic Cetrorelix Acetate for injection, 0.25 mg

Characteristic	RLD – Cetrotide® 0.25 mg (Cetrorelix Acetate for injection)	Proposed Generic Drug Product: Cetrorelix Acetate for injection, 0.25 mg
Active Ingredient	Cetrorelix Acetate	Cetrorelix Acetate
Dosage form	Lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection USP (pH 5-8).	Lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection USP (pH 5-8)
Route of Administration	Subcutaneous	Subcutaneous
Strength	0.25 mg/vial	0.25 mg/vial
Product packaging	Each carton with one packaged tray of Cetrotide® 0.25mg contains: • Drug Product: One vial containing 0.26 – 0.27 mg Cetrorelix Acetate (corresponding to 0.25 mg Cetrorelix) • Diluent: One pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8) • One 20-gauge needle (yellow) • One 27-gauge needle (grey)	Each carton with one packaged tray of Cetrorelix Acetate for injection, 0.25 mg contains: • Drug Product: One vial containing - 0.26 – 0.27 mg Cetrorelix Acetate (corresponding to 0.25 mg Cetrorelix) • Diluent: One pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8) • One 20-gauge needle (yellow) • One 27-gauge needle (grey)

Note: The above table is provided by the applicant as part of description and composition of the drug product, the RLD packaging contents (from RLD label) are verified by the assessor.

The currently approved RLD label (Section 3.2 of the current review) indicates the RLD package contains two alcohol swabs. However, the current applicant's kit does not contain alcohol swabs. Also, per a memo for NDA 21197/S-018, a revision to the carton labeling and container label was implemented to reflect the removal of alcohol swabs from the packaging.[14] In addition, Labeling assessment of the current application states that "Proposed ANDA labeling is in accordance with the most recent labeling of RLD Cetrotide, NDA 021197/S018 approved 12/22/2017".[15]

Is there an overage of the active pharmaceutical ingredient (API)?	No overage in the test product.
If the answer is yes, has the appropriate chemistry division been notified?	No

(b) (4)

[15] https://panorama.fda.gov/task/view?ID=60d4892d00d6264a27e531dff0ceacc9

If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	No

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☐ Yes ☐ No ☒ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☒ Yes ☐ No
If no, are they all within IIG (per day) limits?	☐ Yes ☐ No ☒ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☐ Yes ☐ No ☒ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

4.1.4 Comments on Formulation

- The route of administration, dosage form, and strength of the test product are the same as those of the RLD product. Both the test and RLD products are formulated as a sterile lyophilized powder packaged in a vail intended for subcutaneous injection as a solution after reconstitution with Sterile Water (included in the packaged tray separately). The detailed comparison between RLD Cetrotide® (cetrorelix acetate) 0.25 mg for injection and the proposed generic Cetrorelix Acetate for injection, 0.25 mg, as submitted by the applicant is presented below.

Characteristic	RLD – Cetrotide® 0.25 mg (Cetrorelix Acetate for injection)	Proposed Generic Drug Product: Cetrorelix Acetate for injection, 0.25 mg
Active Ingredient	Cetrorelix Acetate	Cetrorelix Acetate
Dosage form	Lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection USP (pH 5-8).	Lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection USP (pH 5-8)
Route of Administration	Subcutaneous	Subcutaneous
Strength	0.25 mg/vial	0.25 mg/vial
Product packaging	Each carton with one packaged tray of Cetrotide® 0.25mg contains: • Drug Product: One vial containing 0.26 – 0.27 mg Cetrorelix Acetate (corresponding to 0.25 mg Cetrorelix) • Diluent: One pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8) • One 20-gauge needle (yellow) • One 27-gauge needle (grey)	Each carton with one packaged tray of Cetrorelix Acetate for injection, 0.25 mg contains: • Drug Product: One vial containing - 0.26 – 0.27 mg Cetrorelix Acetate (corresponding to 0.25 mg Cetrorelix) • Diluent: One pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8) • One 20-gauge needle (yellow) • One 27-gauge needle (grey)

- As shown in the comparison table (Test Vs RLD) above, both products contain one glass vial, one pre-filled glass syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8, for both test and RLD products), one 20 gauge needle (yellow), one 27 gauge needle (grey). Therefore, for the co-packaged diluent within the test package is Q1 (Sterile Water for Injection)/Q2 (1mL) to that of the RLD. Per Description and Composition of the test product,[16] the pH of water is with specifications of 5-8 (b) (4) (b) (4) which is acceptable as the applicant (b) (4) (b) (4)

- The current drug product is a "Combination Product: 1-Convenience Kit of Co-Package" and the applicant provided Combination Product Comparative Analyses

[16] DocuBridge: ANDA 215737: Module 3.2.P.1, \\CDSESUB1\evsprod\anda215737\0002\m3\32-body-data\32p-drug-prod\cetro-acet-vial\32p1-desc-comp\description-and-composition.pdf (b) (4)

report [18], which is to be performed by the Division of Clinical Review (DCR) in the Office of Safety and Clinical Evaluation (OSCE) (currently pending)[19].

- No overages are proposed in test product formulation.[16]

- As per CC No. 17237308 included in Section 3.3, the Agency made a preliminary determination that it would likely grant a waiver of in vivo bioequivalence to both the formulations proposed by the applicant. The difference between Formulation 1 and 2 is, (b) (4) in Formulation 2. The applicant submitted Formulation 2 in the current submission.

- (b) (4)

- Based on the information above, the applicant's test formulation is qualitatively (Q1) and quantitatively (Q2) the same as the RLD product from the BE perspective.

- pH values of the test and RLD product:

Specification of pH range from NDA21197[21]:

[18] \\CDSESUB1\evsprod\anda215737\0002\m3\32-body-data\32p-drug-prod\cetro-acet-vial\32p7-cont-closure-sys\tar-cp1712.pdf
[19] GDRP: ANDA 215737. Combination Product Comparative Analyses Review: status: IN PROGRESS (as of 11/24/2021). https://panorama.fda.gov/project/view?ID=60d4892d00d621815de3301b72b1bef5
[20] https://panorama.fda.gov/task/view?ID=5fbbc84601007f0350ed7a055b422dfd
[21] DocuBridge: NDA 021197 (most current) Release Specifications-0.25 mg in module 3.2.P.5.1, submitted on 05/04/2011. \\CDSESUB1\evsprod\nda021197\0021\m3\32-body-data\32p-drug-prod\cetrotide-solutionforinjection\32p5-contr-drug-prod\32p51-spec\specifications-release.pdf


(b) (4)


(b) (4)

Therefore, the test formulation is acceptable and the waiver request for the test formulation is **granted** per 21 CFR 320.22 (b)(1).

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	215737
APPLICANT:	Calyptus Pharmaceuticals, Inc.
DRUG PRODUCT:	Cetrorelix Acetate Injection, EQ 0.25 MG BASE/ML

The Division of Bioequivalence III (DBIII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 *COMPLETED ASSIGNMENT FOR 215737 ID: 46865*

Reviewer: Chaluvadi, Madhusudan **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Cetrorelix Acetate Injection, EQ 0.25 MG BASE/ML

Items:

ID	*Letter Date*	*Productivity Category*	*Subcategory*	*Score*	*Subtotal*
46865	06/23/2021	BIO	ANDA Original [1]	1	1
46865	06/23/2021	Parallel	Waiver Injectable (Per application) [1]	1	1
46865	06/23/2021	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total:	2.25

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215737Orig1s000

CHEMISTRY REVIEW(s)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☐ Complete Response-Major
☐ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 *Choose this option when both of the following apply:* • *Quality is Adequate except for inspection deferred due to travel restriction AND* • *OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)*

U.S. FOOD & DRUG ADMINISTRATION

ANDA 215737
Assessment #2

Drug Product Name	**Active DP:** Cetrorelix Acetate for Injection; Sterile Lyophilized Cetrorelix Powder for Injection Vial (0.25 mg/vial) **Diluent DP:** 1mL Sterile Water for injection in pre-filled syringe
Dosage Form	**Active DP:** Lyophilized powder for Injectable Solution **Diluent DP:** Injectable Solution
Strength	**Active DP:** 0.25 mg/vial
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Akorn Operating Company LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
New ANDA 0002 (2)	06/23/2021	Quality
Filing/Response to IR 0003 (3)	08/05/2021	Filing, Quality
Filing/Response to IR 0004 (4)	08/11/2021	Labeling
Clinical/Response to IR 0008 (8)	09/17/2021	Clinical (Comparative Thresholds Analysis)
Quality/response to IR 0009 (9)	10/14/2021	Microbiology
Labeling/Response to DRL 0010 (10)	11/08/2021	Labeling
Quality/Response to IR 0011 (11)	02/01/2022	Drug Product, Process
Quality/Response to IR 0012 (12)	02/22/2022	Microbiology
Quality/Response to IR 0013 (13)	03/25/2022	Process
Quality/CR response 0014 (14)	05/19/2022	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance*	Qamrul Ahsan	Frank Yao
Drug Product	Qamrul Ahsan	Frank Yao
Manufacturing	Laurie Nelson	Sateesh Kumar Sathigari
Microbiology	Erika Pfeiler	Bethanie Lee

Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Christina Pleas	
Application Technical Lead	Farnoosh Fazlollahi	
Laboratory (OTR)		
Environmental		

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF#	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
(b) (4)	II	(b) (4)	Cetrorelix Acetate	Inadequate -Minor	4/7/22	R02, J. Perera 4/18/22 DMF response to 4/8/22 CR pending review
	III		(b) (4)	Adequate	11/16/17	Ref. 11/16/2017 CMC Review of NDA 21-197/16, 3rd ResubmissionOLDP/DPMA1, J.Salemme Overall Evaluation: Approval With post approval commitment for CDRH deficiencies, 6/12/20 DMF (b) (4) Microbiology Review M02R01-ADEQUATE, Ash Bekele
	III					
	III					
	III					
	III					
	III					

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	021197	021197, CETROTIDE® (Cetrorelix Acetate for Injection) 0.25 mg; Eq. 0.25 mg base/mL; EMD SERONO INC

1. **CONSULTS:** None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY (APPROVALS ONLY)

For more details about the items in this template, please see the Executive Summary (Approvals Only) chapter of the ANDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

All IQA disciplines are adequate. Application is recommended for the approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Cetrorelix acetate for injection is a synthetic decapeptide with gonadotropin-releasing hormone (GnRH) antagonistic activity. Cetrorelix acetate for injection 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (pH 5-8), that comes supplied in a 1.0 mL pre-filled syringe. Each vial of cetrorelix acetate for injection 0.25 mg contains 0.26-0.27 mg cetrorelix acetate, equivalent to 0.25 mg cetrorelix, and 54.80 mg mannitol. Cetrorelix acetate for injection 0.25 mg is available in a carton of one packaged tray. Each packaged tray contains: one glass vial containing 0.26 - 0.27 mg cetrorelix acetate (corresponding to 0.25 mg cetrorelix), one pre-filled glass syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8), one 20 gauge needle (yellow) and one 27 gauge needle (grey). The DP should be stored refrigerated, 2-8°C (36-46°F) and the packaged tray should be stored in the outer carton in order to be protected from

light. The end user may self-inject Cetrorelix for Injection after special instruction from her doctor and following the directions for use.

Is the Firm's proposed recommended dissolution method/specification found acceptable by Biopharmaceutics?	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications comply with the current USP?	☐ Yes ☐ DS ☐ DP ☐ No ☒ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D recommendations (regarding elemental impurities)?	☒ Yes ☐ No ☐ N/A

Proposed Indication(s) including Intended Patient Population	Cetrorelix acetate for injection is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.
Duration of Treatment	Per Package Insert
Maximum Daily Dose	3.0 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance and Drug Product:

Cetrorelix acetate is an analog of native GnRH with substitutions of amino acids at positions 1, 2, 3, 6, and 10. The molecular formula is Acetyl-D-3-(2´-naphtyl)-alanine-D-4-chlorophenylalanine-D-3-(3´-pyridyl)-alanine-Lserine-L-tyrosine-D-citruline-L-leucine-L-arginine-Lproline-D-alanine-amide, and the molecular weight is 1431.06, (b) (4). There is no official USP Monograph of the DS. The proposed specification for the DS is in-line with the referenced DMF.

The proposed generic drug product Cetrorelix Acetate for injection 0.25 mg is a co-packaged drug-device combination product in a plastic tray and within a carton. Cetrorelix Acetate for injection, 0.25 mg/vial is a non-compendial drug product. The proposed drug product, Cetrorelix Acetate for injection, 0.25 mg kit with (b) (4) Diluent, is qualitatively (Q1) and quantitatively (Q2) the same RLD. Applicant submitted adequate pharmaceutical development in support of the proposed product quality. Proposed DP include all CQAs for the formulation, in-line with the RLD and approved ANDAs. Proposed container closure system (CCS) for the lyophilized Cetrorelix Acetate for Injection is glass vial with stopper and the CCS for the diluent, sterile water for injection, is pre-filled glass syringe, similar to the RLD. The proposed CCS meets the USP

<660>, <381>, and <87/88>. In addition, applicant submitted syringe functional performance evaluation and specification for break-loose and glide force. Current stability data up to 18 months for long-term condition is adequate to support the proposed 24 months shelf-life.

(b) (4)

[redacted]

(b) (4)

[redacted]

CHAPTER II: DRUG PRODUCT

ANDA Number	215737
Assessment Cycle Number	2
Drug Product (DP) Name / Strength	**Active DP:** Cetrorelix Acetate for Injection; Sterile Lyophilized Cetrorelix Powder for Injection Vial (0.25 mg/vial) **Diluent DP:** 1mL Sterile Water for injection in pre-filled syringe
Route of Administration	Subcutaneous Use Only
Drug Product Manufacturer	Akorn Operating Company LLC 8/30/21 0005(5): transferred from CalyptusCalyptus Pharmaceuticals IncDP Maufacturer: GP Pharm S.A.
RLD/RS Information (Brand Name of Product, Applicant)	CETROTIDE® (Cetrorelix Acetate for Injection) 0.25 mg; Eq. 0.25 mg base/mL; EMD SERONO INC
RLD/RS Number	NDA 021197
Proposed Indication	For the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.

Assessment Recommendation: **Adequate**

If Inadequate-Major, select Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Assessment Summary:

Cetrorelix Acetate for injection 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with co-packaged diluent, Sterile Water for Injection, USP (pH 5-8) in 1 mL pre-filled syringe. Each drug vial contains 0.26-0.27 mg Cetrorelix Acetate, equivalent to 0.25 mg Cetrorelix, and 54.80 mg mannitol. (b) (4)

(b) (4)

(b) (4)

Justification of specifications:

The limits for specified and unspecified impurities are based upon a maximum daily dose of 3.0 mg/day (Per RLD/NDA review).

	ICH Impurity Threshold (MDD = 3.0 mg)		
	Report	**Identification**	**Qualification**
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	0.5%	1.0%

ICH Q3A(R2) threshold don't apply to Peptides.

Risk Assessment

(b) (4)

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Cetrorelix Acetate for Injection, 0.25 mg:

The proposed drug product, Cetrorelix Acetate for Injection, 0.25 mg is supplied as a co-packaged kit (carton of one packaged tray). The kit consists of one glass vial containing Cetrorelix Acetate for Injection (lyophilized powder for reconstitution) 0.25 mg, one pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8), one 20-gauge needle (yellow) and one 27-gauge needle (grey).

Cetrorelix Acetate for Injection, 0.25 mg kit drug product packaging

Component of Drug Product Packaging	Description of the Component
Drug product vial (Cetrorelix Acetate for Injection, 0.25 mg)	One vial containing Cetrorelix Acetate for Injection, 0.25 mg (white to off-white lyophilized cake for reconstitution) in Type I, 2 mL borosilicate colourless glass vial, stoppered with 13 mm grey lyophilization stopper and sealed with flip off 13 mm blue anonym cap aluminium seals.
Pre-filled syringe with diluent	One pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8) as diluent for drug product reconstitution.
20-gauge needle (yellow)	One sterile 20-gauge 1½ inch needle (yellow) for reconstitution of drug product.
27gauge needle (grey)	One sterile 27-gauge ¾ inch needle (grey) for subcutaneous Injection of reconstituted drug product.

Comparison between RLD; Cetrotide® 0.25 mg (Cetrorelix Acetate for injection) and the proposed generic Cetrorelix Acetate for injection, 0.25 mg

Characteristic	RLD – Cetrotide® 0.25 mg (Cetrorelix Acetate for injection)	Proposed Generic Drug Product: Cetrorelix Acetate for injection, 0.25 mg
Active Ingredient	Cetrorelix Acetate	Cetrorelix Acetate
Dosage form	Lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection USP (pH 5-8).	Lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection USP (pH 5-8)
Route of Administration	Subcutaneous	Subcutaneous
Strength	0.25 mg/vial	0.25 mg/vial

Product packaging	Each carton with one packaged tray of Cetrotide® 0.25mg contains: • Drug Product: One vial containing 0.26 – 0.27 mg Cetrorelix Acetate (corresponding to 0.25 mg Cetrorelix) • Diluent: One pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8) • One 20-gauge needle (yellow) • One 27-gauge needle (grey)	Each carton with one packaged tray of Cetrorelix Acetate for injection, 0.25 mg contains: • Drug Product: One vial containing - 0.26 – 0.27 mg Cetrorelix Acetate (corresponding to 0.25 mg Cetrorelix) • Diluent: One pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8) • One 20-gauge needle (yellow) • One 27-gauge needle (grey)

Quantitative and Qualitative Composition of the DP (SD 11, 02/01/2022)

Ingredient	Quality Standard	Function	(b) (4) Cetrorelix for Injection, 0.25 mg/vial (Lyophilized Powder)	
			mg/vial	% w/w
Cetrorelix Acetate[1]	(b) (4)	Active Pharmaceutical Ingredient	Equivalent to 0.25 mg/vial of Cetrorelix	(b) (4)
Mannitol			4.8	
Water for Injection				

(b) (4)

Composition of the Proposed Drug Product – Cetrorelix Acetate for injection, 0.25 mg/Vial (Lyophilized powder) in a Single Dose Vial:

Name of the Ingredient	Quality standards	Pharmaceutical function	(b) (4)	Cetrorelix for Injection 0.25 mg/vial (lyophilized powder)
				(mg/vial)
Cetrorelix Acetate [1]	DMF	Active Pharmaceutical Ingredient		equivalent to 0.25 mg/vial of cetrorelix
Mannitol	USP	(b) (4)		54.8
(b) (4)				(b) (4)
Water for injection	USP			
(b) (4)				
				(b) (4)

Inactive Ingredients Levels used in the Proposed Drug Product – Cetrorelix Acetate for Injection, 0.25mg/Vial:

Name of the Inactive Ingredient	Proposed quantity of the Inactive Ingredient in (mg/vial)	Maximum potency per unit dose as per FDA's IID database for Subcutaneous route /UNII number
Mannitol USP	54.8	220.5 mg / 3OWL53L36A
		(b) (4)

Overages:

No overages are used in the proposed generic drug product formulation.

Elemental Iron:

The proposed generic drug product does not contain elemental iron. Accordingly, the proposed generic product complies to the elemental iron requirements per 21 CFR 73.1200 (c).

Description and Composition of the Diluent

Description of the Diluent:

The proposed drug product, Cetrorelix Acetate for Injection, 0.25 mg is supplied as a co-packaged kit (carton of one packaged tray). The kit consists of one glass vial containing Cetrorelix Acetate (lyophilized powder for reconstitution) equivalent to 0.25 mg Cetrorelix base, one pre-filled syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8), one 20- gauge needle (yellow) and one 27-gauge needle (grey).

Composition of the Diluent in a Pre-filled Syringe:

Name of the Ingredient	Quality standards	Pharmaceutical function	mL/ Syringe
Sterile Water for injection	USP	Diluent	1

Assessment: ***~~{Inadequate}~~Adequate R01a***

- Cetrorelix Acetate for injection, 0.25 mg/vial is a non-compendial drug product.

(b) (4)

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the ANDA IQA Guide

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

10/22/21 Labeling Review#1, Minor Deficiency, Dinaxi Jetton
Labeling Review#1 does not describe any questions/issue(s) sent to or received from OPQ or DP Assessment.

Update R01a: To date, the last Labeling Review available is the 10/22/21 Labeling Review#1, Minor Deficiency, which does not have questions/issues for the DP Assessment.

Update R02: To date, the last Labeling Review available is the 04/26/2022 Labeling Review#2, Acceptable, reviewed by Juwon Lee, which does not have questions/issues for the DP Assessment.

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date: Qamrul Ahsan, 12/2/2021, 12/10/2021, 12/15/2021, 03/30/2022, 04/07/2022, 05/18/2022
Secondary Drug Product Assessor Name and Date: Reynold Tan, 12/7/21, 12/17/21, 4/1/22, 4/11/22
R#02: Yongneng (Frank) Yao, 21July2022.

Frank Yongneng Yao

Digitally signed by Frank Yongneng Yao
Date: 7/21/2022 12:25:26AM
GUID: 59c3e86000a607655166828d4fefbf5e

Qamrul Ahsan

Digitally signed by Qamrul Ahsan
Date: 7/21/2022 09:28:29AM
GUID: 578e4c1a003dd6d33824bb0276b07b18

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☒ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☐ Complete Response-Major
☐ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 *Choose this option when both of the following apply:* • *Quality is Adequate except for inspection deferred due to travel restriction AND* • *OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)*

ANDA #215737
Assessment #1

Drug Product Name	**Active DP:** Cetrorelix Acetate for Injection; Sterile Lyophilized Cetrorelix Powder for Injection Vial (0.25 mg/vial) **Diluent DP:** 1mL Sterile Water for injection in pre-filled syringe
Dosage Form	**Active DP:** Lyophilized powder for Injectable Solution **Diluent DP:** Injectable Solution
Strength	**Active DP:** 0.25 mg/vial
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Akorn Operating Company LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
New ANDA 0002 (2)	06/23/2021	Quality
Filing/Response to IR 0003 (3)	08/05/2021	Filing, Quality
Filing/Response to IR 0004 (4)	08/11/2021	Labeling
Clinical/Response to IR 0008 (8)	09/17/2021	Clinical (Comparative Thresholds Analysis)
Quality/response to IR 0009 (9)	10/14/2021	Microbiology
Labeling/Response to DRL 0010 (10)	11/08/2021	Labeling
Quality/Response to IR 0011 (11)	02/01/2022	Drug Product, Process
Quality/Response to IR 0012 (12)	02/22/2022	Microbiology
Quality/Response to IR 0013 (13)	03/25/2022	Process

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance*	Qamrul Ahsan	Reynold Tan
Drug Product	Qamrul Ahsan	Reynold Tan
Manufacturing	Laurie Nelson	Sateesh Kumar Sathigari
Microbiology	Erika Pfeiler	Bethanie Lee
Biopharmaceutics	N/A	N/A

Regulatory Business Process Manager	Christina Pleas	
Application Technical Lead	Reynold Tan	
Laboratory (OTR)		
Environmental		

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF#	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
(b) (4)	II	(b) (4)	Cetrorelix Acetate	Inadequate -Minor	4/7/22	R02, J. Perera 4/18/22 DMF response to 4/8/22 CR pending review
	III		P S (b) (4)	Adequate	11/16/17	Ref. 11/16/2017 CMC Review of NDA 21-197/16, 3rd ResubmissionOLDP/DPMA1, J.Salemme Overall Evaluation: Approval With post approval commitment for CDRH deficiencies, 6/12/20 DMF (b) (4) Microbiology Review M02R01-ADEQUATE, Ash Bekele
	III		P C			
	III		P C			
	III		P C			
	III		G G			
	III		V 1			

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	021197	021197, CETROTIDE® (Cetrorelix Acetate for Injection) 0.25 mg; Eq. 0.25 mg base/mL; EMD SERONO INC

1. **CONSULTS:** N/A

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A	PFS does not have any of the 3 features that merit a CDRH device consult: • incorporate a sharps injury prevention feature, OR • incorporate a glass luer, OR • is a glass syringe to deliver medication by a nozzle other than a staked needle		
Clinical (PharmTox)	N/A			
Clinical (Comparative Thresholds Analyses)	Adequate	No comments	12/22/ 2021	Shabnam Faroughi
Other	N/A			

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

For more details about the items in this template, please see the Abbreviated Executive Summary (CR Only) chapter of the ANDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Minor

*The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter –**Minor**.*

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance (DS): Inadequate-Minor

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

DMF (b) (4), for drug substance Cetrorelix Acetate manufactured by (b) (4) is inadequate. The drug substance is (non)compendial. Deficiencies were identified for inadequate status of DMF, an error in the DS specification table for the Specific Optical Rotation criteria, and inadequate calculation of methods' mass balance.

Drug Product (DP): Inadequate-Minor

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

The drug product is a copackaged lyophilized powder for injectable solution (Active DP) and 1mL of WFI fill in a syringe (Diluent DP). DP is noncompendial. Deficiencies request lower the limit of Total Impurities, updated stability data, and revised Post-Approval Stability Commitment.

Labeling: Adequate

No labeling issue was found.

B. Manufacturing: Adequate

1. Primary Justification:

2. Secondary Justification (if necessary)

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

Manufacturing Integrated Assessment

Process: Adequate

(b) (4)

Facilities: Adequate

All manufacturing facilities are recommended for approval based on facility history with similar products, unit operations and testing capabilities.

C. Biopharmaceutics: Choose an item. **N/A**

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

N/A; the drug product is a lyophilized powder for injectable solution.

D. Microbiology: Adequate

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

Active DP is sterile through sterile filtration and aseptic processing. No deficiencies were identified this Assessment cycle.

E. List of Deficiencies for Complete Response

1. **Overall Quality Deficiencies - Optional (Deficiencies that affect multiple sub-disciplines)**
   N/A

2. **Drug Substance Deficiencies**

(b) (4)

(b) (4)

4. **Labeling Deficiencies (Please contact OGD if you identify any Labeling deficiencies with your comments)**
   None

5. **Manufacturing Deficiencies**
   None

6. **Biopharmaceutics Deficiencies**
   N/A

7. **Microbiology Deficiencies**
   None

8. **Other Deficiencies (Specify discipline, such as Environmental)**
   N/A

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

N/A

Application Technical Lead Name and Date: Reynold Tan, 5/2/22

Reynold Tan

Digitally signed by Reynold Tan
Date: 5/02/2022 12:04:02PM
GUID: 508da6f600027f10d05adcd85197c2aa

ANDA # 215737
Assessment #1a

Drug Product Name	Cetrorelix Acetate for Injection; Sterile Lyophilized Cetrorelix Powder for Injection
Dosage Form	Solid (Lyo) Injectable DP + Prefilled Syringe w/Diluent (1mL WFI) Kit containing: • A vial of sterile lyophilized 0.26 - 0.27 mg cetrorelix acetate (corresponding to 0.25 mg cetrorelix) for injection • A pre-filled glass syringe with 1 mL of diluent (Sterile Water for Injection, USP) • A sterile 20-gauge 1½ inch needle (yellow) for reconstitution • A sterile 27-gauge ¾ inch needle (grey) for subcutaneous injection
Strength	0.25 mg/vial
Route of Administration	Subcutaneous Use Only
Rx/OTC Dispensed	Rx
Applicant	Akorn Operating Company LLC 8/30/21 0005(5): transferred from Calyptus - Pharmaceuticals Inc.
US agent, if applicable	(b) (4) [redacted]

Submission(s) Assessed	Document Date	Discipline(s) Affected
0002 (2)	06/23/2021	Quality
0003 (3)	08/05/2021	Filing, Quality
0004 (4)	08/11/2021	Labeling
0008 (8)	09/17/2021	Clinical (Comparative Thresholds Analysis)
0009 (9)	10/14/2021	Microbiology
0010 (10)	11/08/2021	Labeling
0011 (11)	02/01/2022	Drug Product, Process
0012 (12)	02/22/2022	Microbiology
0013 (13)	03/25/2022	Process

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF#	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
(b) (4)	II	(b) (4)	Cetrorelix Acetate	Inadequate -Minor	4/7/22	R02, J. Perera 4/18/22 0006(6) response to CR pending review
	III		(b) (4)	Adequate	11/16/17	Ref. 11/16/2017 CMC Review of NDA 21-197/16, 3rd ResubmissionOLDP/DPMA1, J.Salemme Overall Evaluation: Approval With post approval commitment for CDRH deficiencies, 6/12/20 DMF (b) (4) Microbiology Review M02R01-ADEQUATE, Ash Bekele
	III					
	III					
	III					
	III					
	III					

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	021197	021197, CETROTIDE® (Cetrorelix Acetate for Injection) 0.25 mg; Eq. 0.25 mg base/mL; EMD SERONO INC

2. CONSULTS: N/A

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A	PFS does not have any of the 3 features that merit a CDRH device consult: • incorporate a sharps injury prevention feature, OR • incorporate a glass luer, OR • is a glass syringe to deliver medication by a nozzle other than a staked needle		
Clinical (PharmTox)	N/A			
Clinical (Comparative Thresholds Analyses)	Adequate	No comments	12/22/ 2021	Shabnam Faroughi
Other	N/A			

Part I. Assessment of 11/15/2021 Sequence 0006 SD 7 Response to Discipline Review Letter:

This amendment is in response to the Discipline Review Letter from the Agency dated December 20, 2021.

A. Drug Substance

Deficiency# 1: DMF# (b) (4) for Cetrorelix Acetate has been reviewed and found inadequate. The DMF holder, (b) (4) has been notified of the deficiencies. Please work with your DMF holder to resolve any issues with the DMF in a timely manner. Please be aware that the quality review of the ANDA cannot be fully completed until all DMF deficiencies are adequately resolved. Please consult with your DMF holder and provide the updated relevant drug substance sections (e.g., specification, method validation/verification) for further Agency evaluation.

Firm's Response:

Akorn acknowledges that DMF (b) (4) is currently inadequate and that the quality review of the ANDA cannot be completed until all DMF deficiencies are adequately resolved. (b) (4)

(b) (4)

Reviewer's assessment: ***Inadequate***

DMF (b) (4) is inadequate on 12/13/2021, R05 reviewed by Jayani Perera. Standard deficiency language will be sent to the A215737 applicant, R01a.

(b) (4)

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(b) (4)

CHAPTER I: DRUG SUBSTANCE

Drug Substance Name	Cetrorelix Acetate
ANDA Number	215737
Applicant Name	Akorn Operating Company LLC 8/30/21 0005(5): transferred from CalyptusCalyptus Pharmaceuticals Inc.
Assessment Cycle Number	1a
DMF Number (if applicable)	(b) (4)
DMF Status	Inadequate-Minor
DMF Holder	(b) (4)

Assessment Recommendation: **Inadequate-Minor**

If Inadequate-Major, select Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Assessment Summary:

(b) (4)

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the ANDA IQA Guide

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

10/22/21 Labeling Review#1, Minor Deficiency, Dinaxi Jetton
Labeling Review#1 does not describe any questions/issue(s) sent to or received from OPQ or DP Assessment.

Update R01a: To date, the last Labeling Review available is the 10/22/21 Labeling Review#1, Minor Deficiency, which does not have questions/issues for the DP Assessment.

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date: Qamrul Ahsan, 12/2/2021, 12/10/2021, 12/15/2021, 03/30/2022, 04/07/2022
Secondary Drug Product Assessor Name and Date: Reynold Tan, 12/7/21, 12/17/21, 4/1/22, 4/11/22

Reynold Tan

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Date: 5/02/2022 11:59:50AM
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Qamrul Ahsan

Digitally signed by Qamrul Ahsan
Date: 5/03/2022 12:33:37AM
GUID: 578e4c1a003dd6d33824bb0276b07b18

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☒ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☐ Complete Response-Major
☐ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 *Choose this option when both of the following apply:* • *Quality is Adequate except for inspection deferred due to travel restriction AND* • *OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)*

ANDA #215737
Assessment #1

Drug Product Name	**Active DP:** Cetrorelix Acetate for Injection; Sterile Lyophilized Cetrorelix Powder for Injection Vial (0.25 mg/vial) **Diluent DP:** 1mL Sterile Water for injection in pre-filled syringe
Dosage Form	**Active DP:** Lyophilized powder for Injectable Solution **Diluent DP:** Injectable Solution
Strength	**Active DP:** 0.25 mg/vial
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Akorn Operating Company LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
New ANDA 0002 (2)	06/23/2021	Quality
Filing/Response to IR 0003 (3)	08/05/2021	Filing, Quality
Filing/Response to IR 0004 (4)	08/11/2021	Labeling
Clinical/Response to IR 0008 (8)	09/17/2021	Clinical (Comparative Thresholds Analysis)
Quality/response to IR 0009 (9)	10/14/2021	Microbiology
Labeling/Response to DRL 0010 (10)	11/08/2021	Labeling
Quality/Response to IR 0011 (11)	02/01/2022	Drug Product, Process
Quality/Response to IR 0012 (12)	02/22/2022	Microbiology
Quality/Response to IR 0013 (13)	03/25/2022	Process

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance*	Qamrul Ahsan	Reynold Tan
Drug Product	Qamrul Ahsan	Reynold Tan
Manufacturing	Laurie Nelson	Sateesh Kumar Sathigari
Microbiology	Erika Pfeiler	Bethanie Lee
Biopharmaceutics	N/A	N/A

Regulatory Business Process Manager	Christina Pleas	
Application Technical Lead	Reynold Tan	
Laboratory (OTR)		
Environmental		

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF#	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
(b) (4)	II	(b) (4)	Cetrorelix Acetate	Inadequate -Minor	4/7/22	R02, J. Perera
	III		(b) (4)	Adequate	11/16/17	Ref. 11/16/2017 CMC Review of NDA 21-197/16, 3rd ResubmissionOLDP/DPMA1, J.Salemme Overall Evaluation: Approval With post approval commitment for CDRH deficiencies, 6/12/20 DMF (b) (4) Microbiology Review M02R01-ADEQUATE, Ash Bekele
	III					
	III					
	III					
	III					
	III					

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	021197	021197, CETROTIDE® (Cetrorelix Acetate for Injection) 0.25 mg; Eq. 0.25 mg base/mL; EMD SERONO INC

1. **CONSULTS:** N/A

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A	PFS does not have any of the 3 features that merit a CDRH device consult: • incorporate a sharps injury prevention feature, OR • incorporate a glass luer, OR • is a glass syringe to deliver medication by a nozzle other than a staked needle		
Clinical (PharmTox)	N/A			
Clinical (Comparative Thresholds Analyses)	Adequate	No comments	12/22/ 2021	Shabnam Faroughi
Other	N/A			

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

For more details about the items in this template, please see the Abbreviated Executive Summary (CR Only) chapter of the ANDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Minor

*The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter –**Minor**.*

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance (DS): Inadequate-Minor

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

DMF (b) (4), for drug substance Cetrorelix Acetate manufactured by (b) (4), is inadequate. The drug substance is (non)compendial. (b) (4)

(b) (4)

Drug Product (DP): Inadequate-Minor

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

The drug product is a copackaged lyophilized powder for injectable solution (Active DP) and 1mL of WFI fill in a syringe (Diluent DP). DP is noncompendial. Deficiencies request lower the limit of Total Impurities, updated stability data, and revised Post-Approval Stability Commitment.

Labeling: Adequate

No labeling issue was found.

B. Manufacturing: Adequate

1. Primary Justification:
2. Secondary Justification (if necessary)
3. Tertiary Justification (if necessary):
4. Insert additional justification below (if necessary)

Manufacturing Integrated Assessment

Process: Adequate

(b) (4)

Facilities: Adequate

(b) (4)

C. Biopharmaceutics: Choose an item. **N/A**

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

N/A; the drug product is a lyophilized powder for injectable solution.

D. Microbiology: Adequate

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

Active DP is sterile through sterile filtration and aseptic processing. No deficiencies were identified this Assessment cycle.

E. List of Deficiencies for Complete Response

(b) (4)

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Laurie Nelson

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Sateesh Kumar Sathigari

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Date: 4/14/2022 01:42:53PM
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ANDA # 215737
Assessment #1a

Drug Product Name	Cetrorelix Acetate for Injection; Sterile Lyophilized Cetrorelix Powder for Injection
Dosage Form	Solid (Lyo) Injectable DP + Prefilled Syringe w/Diluent (1mL WFI) Kit containing: • A vial of sterile lyophilized 0.26 - 0.27 mg cetrorelix acetate (corresponding to 0.25 mg cetrorelix) for injection • A pre-filled glass syringe with 1 mL of diluent (Sterile Water for Injection, USP) • A sterile 20-gauge 1½ inch needle (yellow) for reconstitution • A sterile 27-gauge ¾ inch needle (grey) for subcutaneous injection
Strength	0.25 mg/vial
Route of Administration	Subcutaneous Use Only
Rx/OTC Dispensed	Rx
Applicant	Akorn Operating Company LLC 8/30/21 0005(5): transferred from Calyptus - Pharmaceuticals Inc.
US agent, if applicable	(b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
0002 (2)	06/23/2021	Quality
0003 (3)	08/05/2021	Filing, Quality
0004 (4)	08/11/2021	Labeling
0008 (8)	09/17/2021	Clinical (Comparative Thresholds Analysis)
0009 (9)	10/14/2021	Microbiology
0010 (10)	11/08/2021	Labeling
0011 (11)	02/01/2022	Drug Product, Process
0012 (12)	02/22/2022	Microbiology
0013 (13)	03/25/2022	Process

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF#	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
(b) (4)	II	(b) (4)	Cetrorelix Acetate	Inadequate -Minor	4/7/22	R02, J. Perera
	III		(b) (4)	Adequate	11/16/17	Ref. 11/16/2017 CMC Review of NDA 21-197/16, 3rd ResubmissionOLDP/DPMA1, J.Salemme Overall Evaluation: Approval With post approval commitment for CDRH deficiencies, 6/12/20 DMF (b) (4) Microbiology Review M02R01-ADEQUATE, Ash Bekele
	III					
	III					
	III					
	III					
	III					

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	021197	021197, CETROTIDE® (Cetrorelix Acetate for Injection) 0.25 mg; Eq. 0.25 mg base/mL; EMD SERONO INC

2. CONSULTS: N/A

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A	PFS does not have any of the 3 features that merit a CDRH device consult: • incorporate a sharps injury prevention feature, OR • incorporate a glass luer, OR • is a glass syringe to deliver medication by a nozzle other than a staked needle		
Clinical (PharmTox)	N/A			
Clinical (Comparative Thresholds Analyses)	Adequate	No comments	12/22/ 2021	Shabnam Faroughi
Other	N/A			

Part I. Assessment of 11/15/2021 Sequence 0006 SD 7 Response to Discipline Review Letter:

This amendment is in response to the Discipline Review Letter from the Agency dated December 20, 2021.

A. Drug Substance

Deficiency# 1: DMF (b) (4) for Cetrorelix Acetate has been reviewed and found inadequate. The DMF holder, (b) (4) has been notified of the deficiencies. (b) (4)

(b) (4)

Firm's Response:

Akorn acknowledges that DMF (b) (4) is currently inadequate and that the quality review of the ANDA cannot be completed until all DMF deficiencies are adequately resolved. (b) (4)

(b) (4)

Reviewer's assessment: ***Inadequate***

DMF (b) (4) is inadequate on 12/13/2021, R05 reviewed by Jayani Perera. Standard deficiency language will be sent to the A215737 applicant, R01a.

(b) (4)

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the ANDA IQA Guide

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

10/22/21 Labeling Review#1, Minor Deficiency, Dinaxi Jetton
Labeling Review#1 does not describe any questions/issue(s) sent to or received from OPQ or DP Assessment.

Update R01a: To date, the last Labeling Review available is the 10/22/21 Labeling Review#1, Minor Deficiency, which does not have questions/issues for the DP Assessment.

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date: Qamrul Ahsan, 12/2/2021, 12/10/2021, 12/15/2021, 03/30/2022, 04/07/2022
Secondary Drug Product Assessor Name and Date: Reynold Tan, 12/7/21, 12/17/21, 4/1/22, 4/11/22

Reynold Tan

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Date: 4/11/2022 01:07:38PM
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Qamrul Ahsan

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Date: 4/11/2022 01:08:54PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215737Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	
ANDA Number	215737
Assessment Cycle Number	01
Drug Product Name / Strength	Cetrorelix Acetate for Injection/ Eq. 0.25mg base/vial
Route of Administration	Subcutaneous
Applicant Name	Calyptus Pharmaceuticals, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification:

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary:

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Initial submission (eCTD seq. 0002)	06/23/2021
IR Response (eCTD seq. 0009)	10/14/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a kit comprised of a lyophilized drug product in a vial, a prefilled syringe with diluent, and two needles.

Note that Avital Shimanovich was the primary assessor on this ANDA until she left the Agency in August 2021. Submissions after this time were assessed by Erika Pfeiler.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

(b) (4)

[redacted]

Select Number of Approved Comparability Protocols: 0

Microbiology Assessment

The drug product is composed of co-packaged components including a Cetrorelix Acetate for Injection as a sterile lyophilized DP for reconstitution in a vial, a pre-filled syringe with 1 mL of sterile WFI as diluent, one yellow 20-Gauge needle, and one grey 27-Gauge needle.

The yellow 20-Gauge and grey 27-Gauge K-Pack II needles are sourced from [redacted] (b) (4)

Assessment: ***Adequate***

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Erika Pfeiler

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Bethanie Lee

Digitally signed by Bethanie Lee
Date: 10/19/2021 08:49:15AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

90455Orig1s000

OTHER REVIEW(S)

Clinical Review of Comparative Analyses
Division of Clinical Review (DCR)
Office of Safety and Clinical Evaluation (OSCE), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA	215737
Drug Product/Strength(s)	Cetrorelix Acetate Injection, 0.25 mg/mL
ANDA Applicant	Akorn Operating Company LLC (Original submission by Calyptus Pharmaceuticals Inc.)
RLD Product Name **RLD#/Approval Date** **RLD/RS Sponsor**	Cetrotide; Cetrorelix Acetate Injection, 0.25 mg/mL NDA 021197, August 11, 2000 EMD Serono Inc.
Primary Reviewer	Shabnam Foroughi, M.D. Physician, DCR/OSCE/OGD
Secondary Reviewer	Michelle Lin, M.D. Senior Physician, DCR/OSCE/OGD
Tertiary Reviewer	Andrew Fine, Pharm.D. Senior Advisor, DCR/OSCE/OGD
Submission Date(s)	June 23, 2021: Original Submission September 17, 2021: Response to Clinical Information Request (IR) dated September 7, 2021
Date of Review	December 22, 2021
GDUFA Goal Date	April 22, 2022
Comparative Threshold Analyses Conclusion	☐ No Design Differences - Acceptable ☒ Minor Design Differences - Acceptable ☐ Other Design Differences ☐ Acceptable ☐ Not acceptable
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)
Recommendation (see Section 6)	**Comments to the Applicant via:** ☐ Information Request (IR) ☒ None
	INTERNAL Comments to: ☐ Division of Labeling Review ☐ Office of Pharmaceutical Quality

1 INTRODUCTION AND BACKGROUND

This comparative analyses (CA) review evaluates the delivery device constituent part of the combination product intended to administer the drug product and any associated product labeling and packaging. This review focuses on the analysis of the user interface[1] for the drug-device combination product (drug and a delivery device intended to administer a drug) comparing the proposed generic and the RLD.

1.1 Summary of Drug Product Information Pertinent to Review

The reference listed drug (RLD), Cetrotide (cetrorelix acetate) injection, 0.25 mg/mL (NDA 021197), is a drug-device combination product, approved on August 11, 2000. Upon initial approval, Cetrotide was available both in 0.25 mg and 3 mg dosages. However, the Sponsor (EMD Serono Inc.) made the decision to discontinue the sales of the Cetrotide 3 mg on May 2013 (b) Cetrotide, a synthetic decapeptide with antagonistic activity against gonadotropin-releasing hormone (GnRH), is indicated for the inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation. Cetrotide 0.25 mg may be administered subcutaneously once daily during the early-to mid-follicular phase (simulation day 5 or day 6) until the day of human gonadotropin (hCG) administration. There is currently no generic version of cetrorelix acetate injection.[3]

The RLD, Cetrotide, is supplied as a packaged tray including a glass vial of cetrorelix acetate as a sterile lyophilized powder, a prefilled glass syringe of diluent (1 mL sterile water), one 20-gauge needle and one 27-gauge needle. The RLD package may contain one of the two approved prefilled syringes: (b) (4) Cetrotide is intended for administration by the patient after proper instructions by the doctor. Patients are instructed to mix the sterile water and the drug product in the vial and to withdraw the entire content of the vial back into the same syringe. Then, using the new injection needle, they are instructed to inject the entire content subcutaneously. The most recent RLD labeling approved on December 22, 2017, includes the Prescribing Information insert and Patient Leaflet.[6]

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[1] User interface refers to all components of the combination product with which a user interacts.
[2] NDA 021197 Cetrotide. Applicant submission (Sequence 0041, Received 2013-07-24) Module 1.2 Cover Letters, Cover Letter-July 24, 2013
\\CDSESUB1\evsprod\nda021197\0041\m1\us\12-cover-letter\cover-letter-20130724.pdf
[3] Search for 'cetrorelix acetate' of online Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations on 11/17/2021; https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm
[4] NDA-021197-SUPP-16-RESUB-188_Upload CORRECTED Final Decision_Approved, ver 4. Uploaded by R Cantave on12/29/2017. CDER Informatics Platform.
https://panorama.fda.gov/document/view?ID=5a469b1c001f6561436c572cd689e7cf
[5] NDA-021197-SUPPL-20_Upload Final Decision_Approved. Ver 3. Uploaded by R Cantave on 4/11/2018. CDER Informatics Platform. https://panorama.fda.gov/document/view?ID=5ace0c77003198906ff0533025fa9e35
[6] Drugs@FDA; Reviewer search for 'NDA 021197' on 11/17/2021; Supplements, SUPPL-18 (12/22/2017), Labeling---Label not available, Approval letter available
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/021197Orig1s018ltr.pdf
Most recently approved RLD labeling is available at CDER Informatics Platform at:
https://panorama.fda.gov/internal/document/preview?versionID=610a9063002256cb6b45112da4913f72&ID=610a9063002256ca1a69fdf78a4717fe

Calyptus Pharmaceuticals Inc. submitted an abbreviated new drug application (ANDA) 215737 on June 23, 2021, for the drug-device combination product, cetrorelix aetate injection. The proposed product is supplied as a packed tray containing a single-dose vial of cetrorelix acetate 0.25 mg as a sterile lyophilized powder, a single-dose prefilled glass syringe of diluent (1 mL sterile water), one 20-gauge needle and one 27-gauge needle. There has been a transfer of ownership since the time of the original submission to Akorn Operating Company LLC (the Applicant).[7]

DCR sent an information request (IR) letter to the Applicant on September 7, 2021 requesting their comparative analyses, high resolution pictures, and samples.[8] The Applicant responded on September 17, 2021, and provided samples.[9] DCR evaluated the samples and reviewed the comparative analyses report provided by the Applicant.

1.2 Other Relevant Information

In addition to this application, there is one more ANDA (214540) submitted to OGD referencing NDA 021197 in Complete Response status in CDER Informatics Platform.[10] DCR performed the comparative analyses assessment for ANDA 214540.[11] Similar to the RLD, the applicant for ANDA 214540 also proposed supplying the drug product in a flip-top vial and co-packaged with sterile water in a prefilled syringe and two needles. DCR determined the proposed combination product was acceptable. In addition, there have been twenty-eight controlled correspondences (CC) and one pre-ANDA meeting referencing NDA 021197.[12] One of the CC (Ref # 17237308) was submitted by this Applicant and was related to drug product formulation. None of the previous CC and pre-ANDA meeting are relevant to this review.

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[7] ANDA 215737 Cetrorelix. Applicant submission (Sequence 0005, Received 2021-08-30). Module 1.2 Cover Letters, Cover Letter
\\CDSESUB1\evsprod\anda215737\0005\m1\us\12-cover-letters\cover-letter.pdf
[8] ANDA 215737 Information Request K. Townsend, 09/07/2021
https://panorama.fda.gov/internal/document/preview?versionID=6137b33d0034b92f423e4fcd7965aa7b&ID=6137b2830056d4df53594f3e4f4d2dd9
[9] ANDA 215737 Cetrorelix Acetate. Applicant submission (Sequence 0008, Received 2021-09-17). Module 1.2 Cover Letters, Cover Letter 0008 Response to IR Clinical 09-07-2021
\\CDSESUB1\evsprod\anda215737\0008\m1\us\cover-letter-0008.pdf
[10] Search for ANDA referencing NDA 021197 by DCR on 11/30/2021 in CDER informatics Platform
[11] ANDA 214540; A214540N000DCR-Review01-Cetrorelix Acetate Injection.pdf, uploaded by A Fine on 07/11/2021, CDER informatics Platform
https://panorama.fda.gov/internal/document/preview?versionID=60ec4c3b007aa8e5e4dd3ff3694b5a39&ID=60eb75e500679170a5644fb83aa3a166
[12] Search for CC referencing NDA 021197 by DCR on 11/30/2021 in CDER informatics Platform

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW AND DISCUSSION

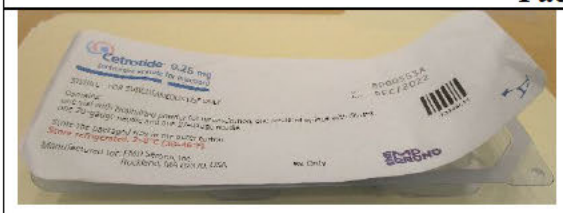
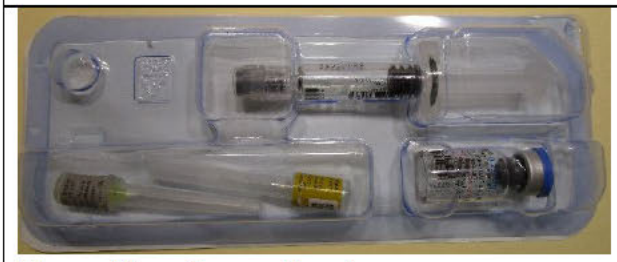
DCR conducted a comparative analysis of the user interface of the proposed generic combination product and its RLD, Cetrotide (NDA 021197). DCR also reviewed the CA report provided by the Applicant.[13]

2.1 Physical comparison of the Proposed Delivery Device to the RLD

DCR examined the delivery device constituent part of the proposed product and the RLD using photos and samples provided by the Applicant. DCR noted that the RLD sample provided by the Applicant had a different prefilled syringe than the RLD sample used for the pictures by the Applicant in their CA report (See Table 1 & Section 2.1). As previously mentioned, (Section 1.1), the RLD may be packaged with one of two approved prefilled syringes.

A photo comparison of the samples (Proposed and RLD) is provided in Table 1 below. The Applicant noted that the syringe, needles, and vial are the same as the RLD (based on their comparison to Syringe Option 2). The Applicant identified the differences in the shape (b) (4) and size of the packaging tray but noted that overall, the physical differences identified are minor.

Table 1: Comparison of Samples - Photos of Proposed Cetrorelix and RLD

RLD (NDA 021197)	Proposed (ANDA 215737)
Packaging Tray	(b) (4)
	
 Tray with syringe option 1	

[13] ANDA 215737 Cetrorelix Acetate. Applicant submission (Sequence 0002, Received 2021-06-23). Module 3.2.P.7 Container Closure System, Threshold Analysis Report-TAR-CP1712 \\CDSESUB1\evsprod\anda215737\0002\m3\32-body-data\32p-drug-prod\cetro-acet-vial\32p7-cont-closure-sys\tar-cp1712.pdf

RLD (NDA 021197)	Proposed (ANDA 215737)
 Tray with syringe option 2	(b) (4)
Syringe	
 Syringe option 1  Syringe option 2	(b) (4)
Needles	
 	(b) (4)
Vial	
	(b) (4)

Source: RLD NDA 021197 Photos Taken by DCR Reviewer at FDA (White Oak) on 12/04/2021.
ANDA 215737 Cetrorelix. Applicant submission (Sequence 0008, Received 2021-09-17). Module 3.2.P.7 Container Closure System Cover Letters, Cover Letter, Test Drug Product Batch CP 1712 Photos
\\CDSESUB1\evsprod\anda215737\0008\m3\32-body-data\32p-drug-prod\cetrorelix-acetate-for-injection-0-25-mg\vial-injection\32p7-cont-closure-sys\test-cp1712-photos.pdf
The two pictures marked with the red star (★) represent pictures of the RLD (tray and syringe) provided by the Applicant

Reviewer Comments:

- *Packaging Tray: Both products contain the drug vial, the prefilled water for injection syringe, and the two needles co-packaged in a clear tray. The proposed product has a hinged lid that snaps in place with an arrow mark with text "Open this side" guiding the*

user in opening the lid. The RLD has a heat-sealed tray cover that needs to be peeled open with an arrow mark on one corner of the label guiding the user in peeling the cover. The overall dimensions of both packages were similar.

- *Syringe: Each kit contains one prefilled glass syringe of diluent (1 mL sterile water). The differences observed in the syringes are the color of the cap (gray in the RLD and (b) (4) t in the proposed), finger grip (clear white in RLD and (b) (4) in the proposed), plunger (clear white in the RLD and (b) (4) in the proposed), and plunger stopper (gray in the RLD and (b) (4) in the proposed). Of note, the second option for the RLD prefilled syringe is the same as the proposed generic in appearance.*
- *Needles: Both products contain both 20 (yellow) and 27 (gray) gauge needles. The needles for the proposed product and the RLD are identical.*
- *Vial: Each product contains a clear vial with blue flip-off cap, aluminum seal, and gray rubber stopper with side vent that are similar.*

DCR concurs with the Applicant's identified differences of the packaging tray and also noted the differences between the prefilled syringes that could not have been identified by the Applicant since their RLD sample had the same prefilled syringe as the proposed generic (tray with Syringe Option 2).

2.2 Comparative Task Analysis

The Applicant conducted a Comparative Task Analysis of the administration procedures between the proposed generic product and the RLD.[14] A tabular comparison of the general tasks is outlined in Table 2 below. The Applicant concluded the tasks are the "same".

Table 2: Comparison of Tasks of Proposed Cetrorelix to RLD

RLD (NDA 021197)	Proposed (ANDA 215737)
1. Wash hands thoroughly with soap and water. 2. Flip off the plastic cover of the vial and wipe the aluminum ring and the rubber stopper with an alcohol swab. 3. Twist the injection needle with the yellow mark (20 gauge) on the pre-filled syringe. 4. Push the needle through the center of the rubber stopper of the vial and slowly inject the solvent into the vial. 5. Leaving the syringe in the vial, gently swirl the vial until the solution is clear and without residues. Avoid forming bubbles. 6. Draw the total contents of the vial into the syringe. If necessary, invert the vial and pull back the needle as far as needed to withdraw the entire contents of the vial.	1. Wash hands thoroughly with soap and water. 2. Flip off the plastic cover of the vial and wipe the aluminum ring and the rubber stopper with an alcohol swab. 3. Twist the injection needle with the yellow mark (20-gauge) on the prefilled syringe. 4. Push the needle through the center of the rubber stopper of the vial and slowly inject the solvent into the vial. 5. Leaving the syringe in the vial, gently swirl the vial until the solution is clear and without residues. Avoid forming bubbles. 6. Draw the total contents of the vial into the syringe. If necessary, invert the vial and pull back the needle as far as needed to withdraw the entire contents of the vial.

[14] ANDA 215737 Cetrorelix Acetate. Applicant submission (Sequence 0002, Received 2021-06-23). Module 3.2.P.7 Container Closure System, Threshold Analysis Report-TAR-CP1712 \\CDSESUB1\evsprod\anda215737\0002\m3\32-body-data\32p-drug-prod\cetro-acet-vial\32p7-cont-closure-sys\tar-cp1712.pdf

RLD (NDA 021197)	Proposed (ANDA 215737)
7. Replace the needle with the yellow mark by the injection needle with the grey mark (27 gauge). 8. Invert the syringe and push the plunger until all air bubbles have been expelled. 9. Choose an injection site in the lower abdominal area, preferably around, but staying at least one inch away from the navel. If you are on a multiple dose (0.25 mg) regimen, choose a different injection site each day to minimize local irritation. Use the second alcohol swab to clean the skin at the injection site and allow alcohol to dry. Gently pinch up the skin surrounding the site of injection. 10. Inject the prescribed dose as directed by your doctor, nurse, or pharmacist. 11. Use the syringe and needles only once. Dispose of the syringe and needles properly after use. If available, use a medical waste container for disposal.	7. Replace the needle with the yellow mark by the injection needle with the grey mark (27-gauge). 8. Invert the syringe and push the plunger until all air bubbles have been expelled. 9. Choose an injection site in the lower abdominal area, preferably around, but staying at least one inch away from the navel. If you are on a multiple dose (0.25 mg) regimen, choose a different injection site each day to minimize local irritation. Use a second alcohol swab to clean the skin at the injection site and allow alcohol to dry. Gently pinch up the skin surrounding the site of injection. 10. Inject the prescribed dose as directed by your doctor, nurse or pharmacist. 11. Use the syringe and needles only once. Dispose of the syringe and needles properly after use. If available, use a medical waste container for disposal.

Source: Most recently approved RLD labeling from CDER Informatics Platform at:
https://panorama.fda.gov/internal/document/preview?versionID=610a9063002256cb6b45112da4913f72&ID=610a9063002256ca1a69fdf78a4717fe
ANDA 215737 Cetrorelix Acetate. Applicant submission (Sequence 0002, Received 2021-06-23). Module 3.2.P.7 Container Closure System, Threshold Analysis Report-TAR-CP1712
\\CDSESUB1\evsprod\anda215737\0002\m3\32-body-data\32p-drug-prod\cetro-acet-vial\32p7-cont-closure-sys\tar-cp1712.pdf

Reviewer Comments:

- *DCR concurs with the Applicant that there is no difference between the critical tasks as outlined in Table 2 for the proposed product and the RLD.*
- *The differences in the syringe cap color, syringe finger grip, and plunger stopper observed in the physical comparison (Section 2.1) between the syringe option 1 for the RLD and the proposed syringe are acceptable minor differences as they do not impact any user tasks.*
- *DCR observed two task differences between the RLD and the proposed product, opening the package tray, and the removal of the syringe cap between the RLD syringe option 1 and the proposed syringe.*
- *The difference in opening the package tray is an acceptable minor difference because it does not impact a critical task. The product is also not for emergency use, so the end user has time to determine how to open the package tray.*
- *The difference noted between the syringe option 1 for the RLD and the proposed syringe, the removal of the cap via a twisting motion (RLD) versus the removal of the cap via a pulling motion (proposed product), does not affect a critical task, and this task is self-evident (common tasks for removing caps or lids). Furthermore, this difference is also observed between the two RLD syringe options; syringe option 2 for the RLD uses a pulling motion for cap removal. Since this product is not intended for emergency use, the end user has time to determine how to remove the cap without additional training. Therefore, this is an acceptable minor difference.*

2.3 Labeling comparison of Proposed to the RLD

The latest RLD labeling was approved on December 22, 2017 (Supplement 18), and includes the Prescribing Information insert and Patient Leaflet. The RLD labeling is available at CDER Informatics Platform at:
https://panorama.fda.gov/internal/document/preview?versionID=610a9063002256cb6b45112da4913f72&ID=610a9063002256ca1a69fdf78a4717fe

For the labeling threshold analysis of this drug-device combination product, DCR conducted a side-by-side, line-by-line comparison of the relevant sections of the labeling for the RLD and the proposed generic product that relates to the use of the device, specifically the Dosage and Administration, Dosage forms and Strengths, and How Supplied/Storage and Handling of the Prescribing Information (PI). The "Directions for Use" contained in the Dosage and Administration section were discussed above in section 2.2 Comparative Task Analysis. Additionally, this analysis includes comparison of the Patient Leaflet with administration instructions. Except for the delivery device-related part of labeling, the review of the remainder of the labeling is deferred to the Division of Labeling Review (DLR). Expected changes such as substituting the brand name, the list of inactive ingredients, and manufacturing information will not be mentioned, as these are consistent with allowable labeling changes due to differences in manufacture described under 21 CFR 314.94(a)(8)(iv).

Table 3: **Applicant's Proposed Labeling Status**

Milestone for DLR Discipline	Yes/No (if yes include date)
Labeling DRL/IR sent?	Yes, 10/25/2021[15]
Applicant replied to DRL/IR with modified proposed labeling?	Yes, 11/08/2021
Submission Date of proposed labeling used for this review:	11/08/2021

Division of Labeling Review completed their review on October 25, 2021 and none of the deficiencies identified was user-interface related.

[15] ANDA 215737; Discipline Review Letter Labeling, uploaded by J Larmie-Gyamfi on 10/25/2021, CDER informatics Platform
https://panorama.fda.gov/internal/document/preview?versionID=6176ebfb00e45305efd08a440b3a6219&ID=6176ebb700d9f3c5eda7656b3ca4226b

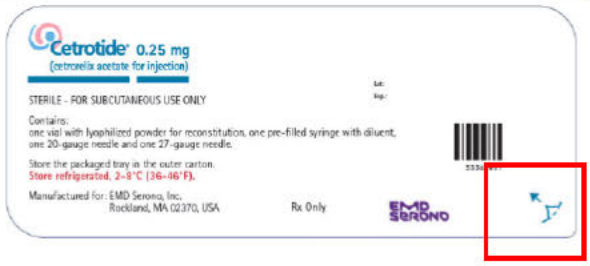
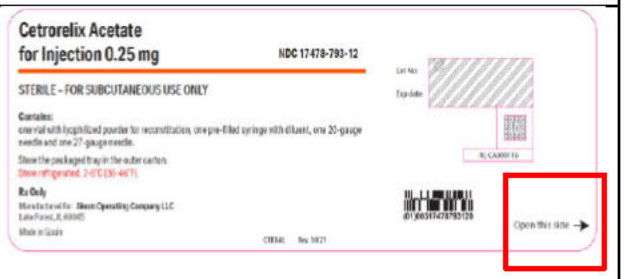
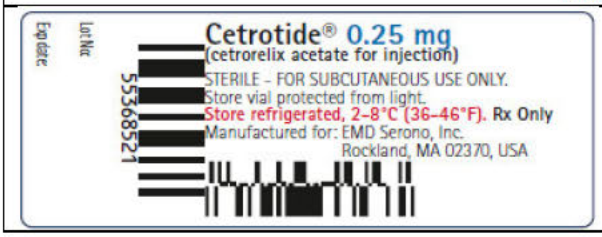
Table 4: Labeling Comparison of Proposed Cetrorelix to RLD

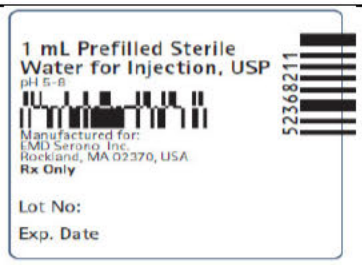
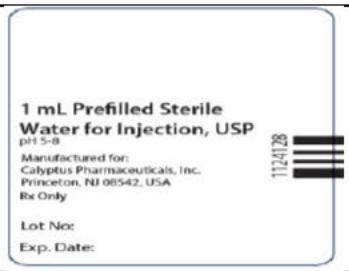
Delivery Device-Related Labeling:	**Yes/No/NA**
(1) Any difference in the **Dosage and Administration (Section 2 of PI)**?	No
(2) Any difference in the **Dosage Forms and Strengths (Section 3 of PI)**?	No
(3) Any difference in the **How Supplied/Storage and Handling (Section 16 of PI)**?	No
(4) Any differences in the administration instructions **on the Carton Label (if available)**?	N/A
(5) Any other differences in the **packaging (e.g., carton, container) labeling (if applicable)**?	**Yes**

N/A=not applicable

The Applicant performed a comparative labeling analysis and concluded there were only color and layout differences between the proposed labeling and the RLD labeling as related to carton, tray, vial, and syringe labels. The Applicant also noted that the redrawn artwork drawings in the Patient Leaflet are substantially similar between the proposed generic and the RLD. Finally, the Applicant acknowledged the deficiencies by DLR and submitted revised labeling for the applicable sections of labeling on November 8, 2021. The following tables presents a side-by-side comparison of the relevant sections of the labeling differences between the Applicant's proposed product and the RLD. The relevant differences are in "red squares".

Table 5: Comparison of Labels of Proposed Cetrorelix and the RLD

RLD (NDA 021197)	**Proposed (ANDA 215737)**
Tray Label	
	
Vial Label	
	

RLD (NDA 021197)	Proposed (ANDA 215737)
Syringe Label	
	

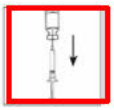
Source: ANDA 215737 Cetrorelix Acetate. Applicant submission (Seq 0002, Received 2021-06-23) Module 1.14.1.1 Draft Carton and Container Labels
\\CDSESUB1\evsprod\anda215737\0002\m1\us\114-labeling\draft-labeling\draft-carton-container-label\draft-syringe-label.pdf
ANDA 215737 Cetrorelix Acetate. Applicant submission (Seq 0010, Received 2021-11-08) Module 1.14. 2.1 Final Carton or Container Labels
\\CDSESUB1\evsprod\anda215737\0010\m1\us\final-tray-label.pdf
\\CDSESUB1\evsprod\anda215737\0010\m1\us\final-vial-label.pdf
ANDA 215737 Cetrorelix Acetate. Applicant submission (Seq 0002, Received 2021-06-23) Module 1.14. 3.3 Labeling Text for Reference Listed Drug
\\CDSESUB1\evsprod\anda215737\0002\m1\us\114-labeling\listed-drug-label\label-text-ref-listed-drug\rld-carton-label.pdf
\\CDSESUB1\evsprod\anda215737\0002\m1\us\114-labeling\listed-drug-label\label-text-ref-listed-drug\rld-card-label.pdf
\\CDSESUB1\evsprod\anda215737\0002\m1\us\114-labeling\listed-drug-label\label-text-ref-listed-drug\rld-container-label.pdf

Reviewer Comments:

- *Tray Label: The RLD product has an illustration that indicates "peeling" back of the tray label from the bottle left corner. The proposed product lists the name of the product larger in black ink and has a text "open this side" with an arrow on the bottom left corner of the tray label. The difference in direction for opening the tray is acceptable and reflects the difference in the task (see Section 2.2).*
- *Vial Label: The proposed product lists the name of the product larger in black ink.*
- *Syringe Label: The proposed syringe label is similar to the RLD label with the only difference of missing the horizontal bar code and neither has a graduation mark.*

Table 4: Comparison of Patient Leaflet of Proposed Cetrorelix and RLD

RLD (NDA 021197)	Proposed (ANDA 214540)
1. Wash your hands thoroughly with soap and water. 	1. Wash your hands thoroughly with soap and water. 
2. On a clean flat surface, lay out everything you need (one vial of powder, one prefilled syringe, one injection needle with a yellow mark, and one injection 	2. On a clean flat surface, lay out everything you need (one vial of powder, one prefilled syringe, one injection needle with a yellow mark, and one injection 

RLD (NDA 021197)	Proposed (ANDA 214540)
needle with a grey mark).	needle with a grey mark).
3. Flip off the plastic cover of the vial. Wipe the aluminum ring and the rubber stopper with an alcohol swab. 	3. Flip off the plastic cover of the vial. Wipe the aluminum ring and the rubber stopper with an alcohol swab. 
4. Take the injection needle with the yellow mark and remove the wrapping. Take the prefilled syringe and remove the cover. Twist the needle on the syringe and remove the cover of the needle. 	4. Take the injection needle with the yellow mark and remove the wrapping. Take the prefilled syringe and remove the cover. Twist the needle on the syringe and remove the cover of the needle. 
5. Push the needle through the center of the rubber stopper of the vial. Inject the water into the vial by slowly pushing down on the plunger of the syringe. 	5. Push the needle through the center of the rubber stopper of the vial. Inject the water into the vial by slowly pushing down on the plunger of the syringe. 
6. Leave the syringe in the vial. While carefully holding the syringe and vial, swirl gently to mix the powder and water together. When it is mixed, it will look clear and have no particles in it. Do not shake or you will create bubbles in your medicine. 	6. Leave the syringe in the vial. While carefully holding the syringe and vial, swirl gently to mix the powder and water together. When it is mixed, it will look clear and have no particles in it. Do not shake or you will create bubbles in your medicine. 
7. Draw the total contents of the vial into the syringe. If liquid is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of 	7. Draw the total contents of the vial into the syringe. If liquid is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of 

RLD (NDA 021197)	Proposed (ANDA 214540)
the needle and the liquid. It is important to withdraw the entire contents of the vial.	the needle and the liquid. It is important to withdraw the entire contents of the vial.
8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Twist the needle on the syringe and remove the cover of the needle. 	8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Twist the needle on the syringe and remove the cover of the needle. 
9. Invert the syringe and push the plunger until all air bubbles have been pushed out. Do not touch the needle or allow the needle to touch any surface. 	9. Invert the syringe and push the plunger until all air bubbles have been pushed out. Do not touch the needle or allow the needle to touch any surface. 
10. Choose an injection site in the lower abdominal area, preferably around, but at least one inch away from the belly button. Choose a different injection site each day to minimize local irritation. Take a second alcohol swab and clean the skin at the injection site and allow alcohol to dry. Inject the prescribed dose as directed by your doctor, nurse or pharmacist. 	10. Choose an injection site in the lower abdominal area, preferably around, but at least one inch away from the belly button. Choose a different injection site each day to minimize local irritation. Take a second alcohol swab and clean the skin at the injection site and allow alcohol to dry. Inject the prescribed dose as directed by your doctor, nurse or pharmacist. 
11. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury). A medical waste container should be used for disposal. 	11. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury). A medical waste container should be used for disposal. 

Source: See Section 2.3 Latest RLD Labeling

ANDA 215737 Cetrorelix Acetate. Applicant submission (Sequence 0002, Received 2021-06-23). Module 3.2.P.7 Container Closure System, Threshold Analysis Report-TAR-CP1712
\\CDSESUB1\evsprod\anda215737\0002\m3\32-body-data\32p-drug-prod\cetro-acet-vial\32p7-cont-closure-sys\tar-cp1712.pdf

Reviewer Comments:

- *There are no differences in the text of the directions for use in the Patient Leaflet in the proposed package insert and the RLD package insert.*
- *For the difference in removal of the syringe cap (see Section 2.2), the directions in the Patient Leaflet (step 4) states, "Take the prefilled syringe and remove the cover." The instructions are not specific to the syringe cap type. This is acceptable as the removal of the different syringe caps are common tasks (pulling or twisting) for removing caps or lids. In addition, since the product is not intended for emergency use, the end user has time determine how to remove the cap.*
- *The Applicant has used their own drawings that represent the product correctly and are similar to the ones used for the RLD in order to illustrate the Directions for Use. DLR did not comment about the illustrations.*

From a clinical perspective, DCR concurs with the Applicant that these design differences are minor and acceptable. The proposed generic product is expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. It should be noted however that at the time of this review the final decision from DLR and their final approval of the labeling used for this review is pending.

3 DESIGN DIFFERENCES SUMMARY

There are device design differences, as well as differences in labeling, observed between the proposed delivery device and the RLD. The table below summarizes these differences and applicable reviewer assessment.

Table 5: Summary of Differences between the Proposed Cetrorelix and the RLD

Differences	Applicant's Classification (minor/ other)	Reviewer's Classification (minor/ other)
1. Packaging Tray - cover type, related task and labeling	Minor	Minor
2. Syringe and plunger - dimension and material	No difference as compared to syringe option 2	Minor
3. Syringe cap – shape and related task	No difference as compared to syringe option 2	Minor
4. Patient Leaflet - illustrations	Minor	Minor

N/A=not applicable

4 CONCLUSION

From a clinical safety perspective, there are acceptable minor design differences (packaging tray and prefilled syringes) between the proposed drug delivery device and the RLD. Therefore, DCR concludes this generic combination product can be substituted for the RLD without additional training prior to use of the generic combination product; the design differences for this combination device are not expected to alter the safety profile or clinical effect of this proposed ANDA product under the conditions specified in the labeling. In summary, DCR finds the proposed drug delivery device user interface for the proposed generic acceptable from a clinical user-interface perspective.

5 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative analyses and has no comments at this time.

☐ Major
☐ Minor
☒ N/A (Review is Adequate)

Shabnam Foroughi

Digitally signed by Shabnam Foroughi
Date: 12/22/2021 08:23:06AM
GUID: 6127df7300cdb9a2f8c0302808683ae7

Michelle Lin

Digitally signed by Michelle Lin
Date: 12/22/2021 08:40:05AM
GUID: 54d38202000634e5d954bf97ad5d95f2

Andrew Fine

Digitally signed by Andrew Fine
Date: 12/22/2021 09:51:07AM
GUID: 50174afb000001af8e1e5e9e9cb6265d

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215737Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL AP or TA (NEW STRENGTH)**

RPM and TL: Emmanuel Kerry & Andrew Taylor

ANDA #: 215737 Applicant: Akorn Operating Company LLC
Established Product Name: Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose

Basis of Submission (BOS)/RLD (Application#/Proprietary Name/Applicant): N021197, Cetrotide, EMD Serono Inc.
If BOS discontinued: [insert hyperlink to FRN] ☐ Safety/effectiveness FRN pending

Select, as applicable:

☒ RX ☐ OTC
☐ History of tentative or split approval action
☐ Shared Bio Studies (list ANDA number(s)) ☐ Shared Labeling (list ANDA number(s) _____)
☐ Memo uploaded for PAL item or OGDP confirmation
Priority: ☒ First Generic Approval (i.e., no other generics approved) ☐ Drug Shortage ☐ PEPFAR ☒ CGT
☐ Other priority _____
Misc: ☐ REMS ☒ Combination product ☐ Suitability Petition ☐ 180-day language ☐ MOU ☐ PEPFAR

☒ ***RPM Has Verified the Following:*** **Date: 7/27/2022**

1. ANDA number, NDA/RLD, Drug product and strength(s) are correct on all discipline/subdiscipline reviews
2. All submissions have been reviewed: Relevant disciplines are adequate and finalized/archived in the appropriate system of record
3. Most recent BE guidance is included in the review or a memo has been uploaded
4. No RLD updates or changes to exclusivity/patents impact endorsed labeling
5. All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d). (Not applicable to supplements)
6. OSIS Clinical Endpoint and Bioequivalence Site Inspections acceptable or not applicable
7. No blocking legal or regulatory issue (refer to Policy Alert Tracker)
8. OGD Communications has been notified if Priority Approval (First generic, Drug Shortage, PEPFAR, CGT, other OGD Communications priorities)
9. OMIR is Approve with no new facility alerts and a DP and API manufacturer listed in Submission Facility Status View
10. No open issues or tasks in Platform
11. No pending consults
12. Filing review completed for NSA or reformulation
13. PNR review is current
14. Correct language, format and content in action letter (e.g., relevant contact from 356h form)
15. Endorsements are within 29 days

Discipline Completion Dates:

Bioequivalence **12/14/2021** Labeling **4/27/2022** Clinical **N/A**	Integrated Quality Assessment: **7/25/2022** If there is no IQA, provide the applicable date(s): • Chemistry **N/A** • Microbiology N/A • Biopharmaceutics/Dissolution N/A DMF No(s). (b) (4) Date(s) Acceptable 7/14/22

Additional Notes (if applicable)

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 7/28/2022
Name: IM

Patent/Exclusivity Certification:

☐ **No Relevant Patents** ☒ **PI** ☐ **PII** ☐ **PIII** ☐ **PIV** ☐ **section viii**

Reminders:

- Check the policy alert list for any pending exclusivity determinations
- Verify in the Orange Book there are no unexpired ODE's that cover the active moiety
- Confirm the ANDA is not blocked by other ANDA's eligibility for 180-day CGT exclusivity
- Confirm S/E determination completed for RLDs in the discontinued section of the OB

RLD = **Cetrotide** NDA# **21197** ☐ **RX or** ☐ **OTC**
Date Checked in Orange Book#: **7/28/2022**

Type of Letter:

☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL AP or TA (NEW STRENGTH)

Forfeiture Information

- Confirm whether the first applicant remains eligible for 180-day exclusivity (i.e., that a forfeiture event under section 505(j)(5)(D) has not occurred) and document the determination

Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐
If yes, the date forfeiture memo was completed
Date _____ ANDA # _____

Competitive Generic Therapy 75 Day Special Forfeiture Rule:
First Applicant: ANDA # _____
Date of Approval: _____
75 Day Date: _____

180 Day Exclusivity Information

Is applicant eligible for H-W 180 day exclusivity Yes ☐ No ☐
☐ Sole
☐ Shared
Is applicant eligible for CGT 180 day exclusivity Yes ☒ No ☐
☒ Sole
☐ Shared
Is applicant blocked by a triggered CGT 180 day exclusivity
Yes ☐ No ☐
If no, the date and time checked for notification of commercial marketing: Date _____ Time: _____

Comments:
BOS = Cetrotide (NDA 21197) Application submission 6/23/2021 for the 0.25 mg/mL strength with a PI certification. Acknowledgment letter signed 8/12/2021.

There are no unexpired patents or exclusivities listed in the OB to the NDA. The applicant requested the ANDA receive CGT designation and the request was granted with the 3/4/2021 letter.

Akorn Operation Company LLC's ANDA is eligible for Full Approval with CGT 180-day exclusivity as the first CGT designated ANDA for the NDA drug product.

180 Day/CGT Exclusivity Status/Landscape: CGT 180-day granted to this ANDA
If known, impact on pending exclusivity determinations: N/A
If Tentative Approval, if known, anticipated full approval date: N/A

2. *Final Decision*

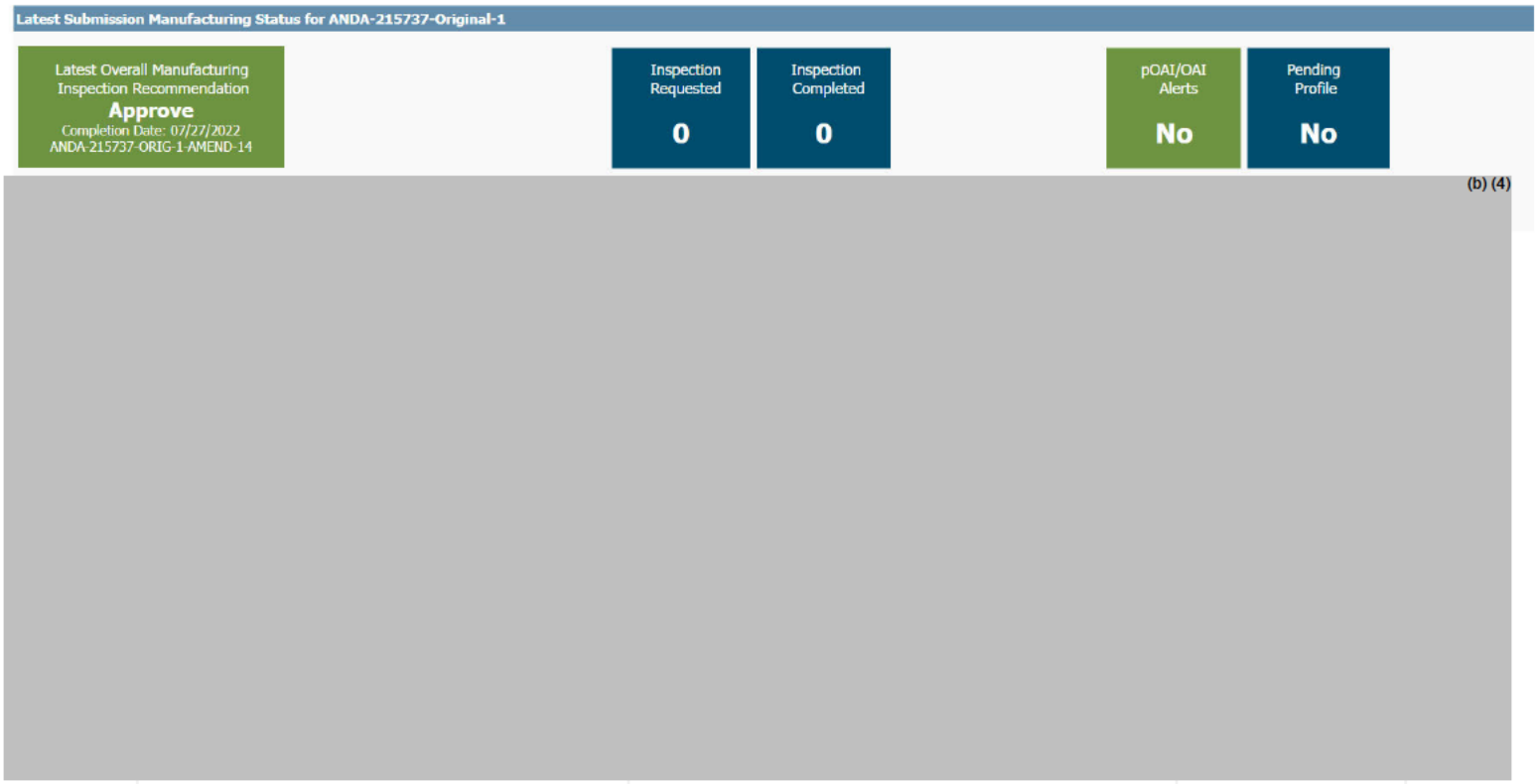
Date: **8/12/2022**
Name: **JI**

☒ Verified the following:

1. Completion of the following endorsement tasks, if applicable:
    a. Division of Legal and Regulatory Support Endorsement
    b. Paragraph IV Evaluation
    c. REMS Endorsement
    d. Quality Endorsement
    e. Bioequivalence Endorsement
    f. Clinical-Bioequivalence Endorsement
    g. Labeling Endorsement
    h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates in DARRTS since the Labeling Endorsement
5. No new issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments received since Quality Endorsement
9. No new amendments received since the RPM Team Leader Endorsement

This **ANDA** is ready for **FULL APPROVAL**.

****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL****



(b) (4)

[redacted]

Endorsement Signatures (To be provided by endorsees in the event of Platform unavailability):

- Division of Legal and Regulatory Support Endorsement
  - Sign & Date_____
- Paragraph IV Evaluation
  - Sign & Date_____
- REMS Endorsement
  - Sign & Date_____
- Quality Endorsement
  - Sign & Date_____
- Bioequivalence Endorsement
  - Sign & Date_____
- Clinical-Bioequivalence Endorsement
  - Sign & Date_____
- Labeling Endorsement
  - Sign & Date_____
- RPM Team Leader Endorsement
  - Sign & Date_____
- ORO IO Endorsement
  - Sign & Date_____

REFERENCES / ASSOCIATED DOCUMENTS

Reference Name
4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Author	Role	Version	Change Date	Summary of Changes
Heather Strandberg	Author	1.0	2014-10-01	New Form
Kevin Denny	Reviser	2.0	2017-10-03	Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 Remove content adequately captured in the platform Update information captured in the Division of Legal and Regulatory Support Endorsement section Other minor administrative corrections to format and content
Kevin Denny	Reviser	3.0	2018-01-14	Update Final Decision section
Joe Shin	Reviser	4.0	2019-03-04	Changes made: 1) "No Relevant Patents" checkbox added to patent types; 2) Basis of Submission was updated to include (NDA#/Proprietary Name/Applicant); 3) Removed "(CR)" from the second checkbox in the RPM Evaluation section; 4) Added "Shared BE studies..." and "Shared Labeling..." bullets to the review date section; 5) Added a not applicable checkbox for the MMA question; 6) Sentence revised to include not applicable cases in the OSIS question
John Ibrahim/QM Team	Reviser/QM	5.0	2021-08-18	• Update page 1 (revisted ANDA information section, RPM checklist, and discipline completion dates) • QM Team updated Header, document #, & title to conform to OGD Controlled Documents Program naming conventions & formatting standards • QM Team updated Footer to conform to ISO 8601 – International Time & Date Standards

ANDA 215737

COMPLETE RESPONSE

Akorn Operating Company LLC
1925 West Field Court, Suite 300
Lake Forest, IL 60045
Attention: John Franolic
Vice President, Regulatory Affairs

Dear John Franolic:

This is in reference to your abbreviated new drug application (ANDA) received for review on June 23, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Cetrorelix Acetate for Injection, 0.25 mg/vial, Single-Dose Vial.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

(b) (4)

(b) (4)

PROCESS / MICROBIOLOGY / FACILITY INSPECTION / BIOEQUIVALENCE / LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be reevaluated upon resubmission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure that your ANDA addresses all listed patents and exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE / DRUG PRODUCT

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees

must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Emmanuel Kerry, Regulatory Project Manager, Division of Project Management, at (301) 796 - 7737.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Mandy Kwong

Digitally signed by Mandy Kwong
Date: 5/10/2022 05:07:46PM
GUID: 529372550000cc96a0a98e57d06862e5

M E M O R A N D U M

DATE: 24 February 2022

TO: ANDA 215737

FROM: Erika Pfeiler, Ph.D.

THROUGH: Bethanie Lee, Ph.D.

SUBJECT: Follow-up assessment after Information Request Response dated 01 February 2022

Note: This ANDA transferred ownership from from Calyptus Pharmaceuticals, Inc. to Akorn Operating Company LLC on 31 August 2021. This change was not documented in Microbiology Review 1 of this ANDA.

An information request response was received on 01 February 2022 with responses to IRs from multiple disciplines, including process. The following statement was made in response to a process IR:

(b) (4)

(b) (4)

M E M O R A N D U M

Information Request – 16 February 2022
In your response to process Information Request question #7 (submitted on 01 February 2022) you state the following:

(b) (4)

Assessment: This response is adequate. The microbiology assessment remains as recommending approval.

END

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 2/25/2022 10:12:32AM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

Bethanie Lee

Digitally signed by Bethanie Lee
Date: 2/24/2022 12:53:53PM
GUID: 5a9d84b3000e5ae45e6f6044896c5811

ANDA 215737

DISCIPLINE REVIEW LETTER
QUALITY

Akorn Operating Company LLC
1925 West Field Court
Suite 300
Lake Forest, IL 60045
Attention: John Franolic

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 23, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Cetrorelix Acetate for Injection, Eq. 0.25mg base/vial.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance

(b) (4)

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

If you have any questions, please contact Christina Pleas, Regulatory Business Process Manager, at Christina.Pleas@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Christina Pleas, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Christina Pleas

Digitally signed by Christina Pleas
Date: 12/20/2021 12:01:35PM
GUID: 55686ad0003e26d887d4ceb8cf685131

ANDA 215737

DISCIPLINE REVIEW LETTER
LABELING

Akorn Operating Company LLC
1925 West Field Court Suite 300
Lake Forest, IL 60045 USA
Attention: John Franolic, Ph.D
Vice President, Regulatory Affairs

Dear Dr. Franolic:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 23, 2021, August 05, 2021, August 11, 2021, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetrorelix Acetate for Injection, 0.25 mg/Vial (Single-Dose Vial).

The following possible deficiencies have been identified by LABELING:

Labeling deficiencies based on your submissions received June 23, 2021, August 05, 2021 and August 11, 2021:

1. GENERAL COMMENTS
    a. Comment as to whether text appears on your cap/ferrule overseal. Ensure your proposed cap/ferrule overseals are in compliance with the requirements of the USP, General Chapter <7> Labeling for Ferrules and Cap Overseals.
    b. We note per your Quality submission and the HOW SUPPLIED section of proposed labeling that your drug product is supplied in a carton of one packaged tray that includes “...one 20-gauge needle (yellow) and one 27 gauge needle (grey).” If accurate and you intend to include these needles in the packaging, submit the labeling for the needles under Module 1.14 for our review.

2. CONTAINER LABEL
    a. Drug Product Vial: Revise the presentation of the established name to appear in title case (i.e., Cetrorelix Acetate for Injection). If space permits, present "Cetrorelix Acetate" to appear in one line followed by "for Injection 0.25 mg".
    b. Drug Product Vial: Include the National Drug Code (NDC) number and a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Ensure the bar code appears in a vertical orientation to ensure accurate scanning to minimize medication error.

Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

3. CARTON LABELING
    a. Tray Label and Outer Carton label: Revise the presentation of the established name to appear in title case (i.e., Cetrorelix Acetate for Injection).
    b. Tray Label and Outer Carton label: Ensure to complete the National Drug Code (NDC) number and a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

4. PRESCRIBING INFORMATION
    a. ADVERSE REACTIONS: Include the statement "To report SUSPECTED ADVERSE REACTIONS, contact..." as required per 21 CFR 201.57(a)(11). Include your contact information and the FDA toll free number and website.
    b. HOW SUPPLIED/ STORAGE AND HANDLING: See GENERAL comment. We note your HOW SUPPLIED section includes packaging components of “one 20 gauge needle (yellow) and one 27 gauge needle (grey).” If accurate and you intend to market these packaging components, submit the remaining labeling pieces under Module 1.14 for our review.

    c. HOW SUPPLIED/ STORAGE AND HANDLING: Ensure to include the NDC number. If the NDC numbers are not available at the time of approval, consider stating “NDC numbers pending”. We remind you that the NDC numbers must accurately be reflected in your labeling prior to marketing.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than November 08, 2021. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

[1] GDUFAD Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi, PharmD, PMP
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Juliette Larmie-Gyamfi

Digitally signed by Juliette Larmie-Gyamfi
Date: 10/25/2021 01:39:50PM
GUID: 5508755d000926ebceca6d5de2d276c5

ANDA 215737

TRANSFER OF OWNERSHIP

Akorn Operating Company LLC
1925 West Field Court, Suite 300
Lake Forest, IL 60045
Attention: John Franolic, PhD
Vice President, Regulatory Affairs

Dear Sir:

We acknowledge receipt of your communication on August 31, 2021, submitted as required by the provisions of 21 CFR 314.72(a) for notifying the Food and Drug Administration of the change of ownership of the following abbreviated new drug application (ANDA):

Name of Drug Product: Cetrorelix Acetate for Injection, 0.25 mg (base)/vial

Name of New Owner: Akorn Operating Company LLC

Name of Former Owner: Calyptus Pharmaceuticals, Inc.

Your correspondence notes that the date that the change in ownership is effective on August 31, 2021. Under 21 CFR 314.72(b), the new owner shall advise us about any change in the conditions of the approved application.

We request that you notify your suppliers and contractors who have Drug Master Files (DMFs) referenced by your application of the change in ownership so that they can submit new letters of authorization to their DMFs.

We remind you that you must comply with the requirements for an approved ANDA in 21 CFR 314.80 and 21 CFR 314.81. In addition, you are responsible for any correspondence that is outstanding as of the effective date of the transfer.

If the drug that is the subject of an ANDA requires a risk evaluation and mitigation strategy (REMS), the change in ownership must also be reflected in the approved REMS and submitted as described below. Because the change is made to the REMS supporting document, it is not considered a REMS revision.

1. Submit the updated REMS supporting document to the application or communicate with the DMF holder to submit the updated REMS supporting document to the DMF as follows:

ANDA or DMF ######
General Correspondence—REMS Supporting Document

2. Submit a redline (using Track Changes) version and a clean version of the revised REMS supporting document with the new corporate name and address to reflect the change in ownership of the application.

3. Follow the procedures outlined in the guidance for industry *Use of a Drug Master File for Shared System REMS Submissions*[1] and the Technical Conformance Guide for Shared System REMS Drug Master File Submissions.[2]

4. If the approved REMS contains a Medication Guide, you must also revise the Medication Guide to reflect the change in ownership. As described in the guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*, a REMS change of this kind is considered a REMS revision. Submit the revised Medication Guide as a REMS revision as described in the guidance, prominently identifying the submission with the following wording in bold capital letters at the top of the first page of the submission:

   ANDA ######
   REMS REVISION

5. You should also describe this REMS revision in the next annual report.

The communication you submitted will be retained as part of your application.

If you have any questions, contact CAPT Aaron Sigler, Deputy Director, Division of Project Management at (240) 402-8786.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] The Technical Conformance Guide for Shared REMS Drug Master File Submissions is available on the eCTD Resources web page at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm535180.htm#Technical_Conformance_Guide.

Megan Tychinski

Digitally signed by Megan Tychinski
Date: 10/21/2021 10:27:51AM
GUID: 556dc3e3004eeaee540b388a26735dfb