CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205054Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 205054

Original-1 22.5 mg

(b) (4)

Review #2

Drug Name/Dosage Form	Lutrate Depot (leuprolide acetate)/Injection
Strength	22.5 mg (b) (4)
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	GP Pharm., S.A., Spain
US agent, if applicable	Peter Saxon, Summit, NJ

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission (SD-0046)	02/28/2018	API/DP/Process/Biopharm/Facility/CDRH Manufacturing/CDRH Product
Quality Amendment SD-46	02/28/2018	API
Quality Amendment SD-41, 46, 52	08/22/2017 02/28/2018 04/27/2018	Process
Quality Amendment SD-50	04/10/2018	Biopharm
Quality Amendment SD-52	04/27/2018	Process
Quality Amendment SD-53	05/11/2018	DP
Quality Amendment SD-54	05/18/2018	DP
Quality Amendment SD-58	06/07/2018	DP
Quality Amendment SD-59	06/08/2018	DP/Process
Quality Amendment SD-68	07/12/2018	Process
Quality Amendment SD-70	07/18/2018	Biopharm
Quality Amendment SD-76	07/31/2018	CDRH Product
Quality Amendment SD-77	08/03/2018	DP
PMR/PMC-1 SD-81	08/10/2018	CDRH Product
PMR/PMC-1 SD-82	08/14/2018	CDRH Product
PMR/PMC-1 SD-84	08/17/2018	Biopharn

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Chuck Jewell, CDER/OPQ/ONDP/DNDAPI
Drug Product	Amit Mitra	Anamitro Banerjee, CDER/OPQ/ONDP/DNDP1
Process	Steve Rhieu	Maotang Zhou CDER/OPQ/OPF/DPA1
Microbiology	Neal Sweeney	OMPT/CDER/OPQ/OPF/DMA/MA BII
Facility	Steve Rhieu	CDER/OPQ/OPF/DIA
Biopharmaceutics	Parnali Chatterjee,	Banu Zolnik/Angelica Dorantes CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI
Application Technical Lead	Haripada Sarker	CDER/OPQ/ONDP/DNDAPI
Laboratory (OTR)	N/A	
ORA Lead	Caryn McNab	OGROP/ORA/OMPTO/OPQO/DPQ P/PQIB
Environmental	Amit Mitra	Anamitro Banerjee, CDER/OPQ/ONDP/DNDP1

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

MFs:

	Type			Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	7/17/2018	(b) (4)
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type IV			Adequate	No DMF review is needed.	Adequate, and covered under original NDA reviewed (R-1) by Li-Shan Hsieh dated 4/30/2015.
	Type IV			Adequate	No DMF review is needed.	Adequate, and covered under original NDA reviewed (R-1) by Li-Shan Hsieh dated 4/30/2015.
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DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 020517 (b) (4) (b) (4)	Lupron Depot

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH (ODE)	Approved with the PMR	See CDRH ODE Product Review dated 08/14/2018	See review	Jacquie Getz/Carolyn Dargan (secondary), OMPT/CDRH/ODE/DAGID/GHDB
CDRH (Inspection)	Approved with the recommendation for PAI.	See CDRH OC Manufacturing Review dated 08/10/2018	See review	Latoya-Oliver-Powell OMPT/CDRH/OC/DMQ
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA was submitted for (b) (4) 22.5 mg (b) (4) NDA 205054 Original 1 is for the 22.5 mg strength, (b) (4) (b) (4) NDA (Original-1) is recommended for approval for the 22.5 mg strength. There is one PMR regarding the assessment of the break loose and glide force of the syringe from the CDRH ODE product review and one PMC from the Biopharmaceutics review regarding the development of an

(b) (4)

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Proposed Indication(s) including Intended Patient Population	Lutrate Depot is indicated for Palliative treatment of advanced prostate cancer.
Duration of Treatment	The duration of treatment (b) (4) 3-months formulation was 168 d.
Maximum Daily Dose	There is no maximum daily dose. (b) (4) (b) (4) The 3 month is 22.5 mg every 84 days.
Alternative Methods of Administration	There is no alternative method of administration.

B. Quality Assessment Overview

Refer to IQA for NDA 205054 (Original-1)

Application Technical Lead Name and Date:
Haripada Sarker, Ph.D./Xiao Hong Chen Ph.D.

24-August-2018

Xiao Chen

Digitally signed by Xiao Chen
Date: 8/27/2018 10:14:13AM
GUID: 508da7220002a138fcc70fbccbfd08bf

Haripada Sarker

Digitally signed by Haripada Sarker
Date: 8/27/2018 10:15:49AM
GUID: 507d82ab00005f362bcd357373643206

Recommendation: Approval

NDA 205054 (Original 1)
Review #2

Special Note: The NDA is (b) (4) Original 1 is for the 22.5 mg strength (b) (4)

Drug Name/Dosage Form	Lutrate Depot (leuprolide acetate)/Injection
Strength	22.5 mg only
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	GP Pharm., S.A., Spain
US agent, if applicable	Peter Saxon, Summit, NJ

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DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH (ODE)	Approved with the PMR	See CDRH ODE Product Review dated 08/14/2018	See review	Jacquie Getz/Carolyn Dargan (secondary), OMPT/CDRH/ODE/DAGID/GHDB
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Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA was submitted for (b) (4) 22.5 mg (b) (4) NDA 205054 (b) (4) Original 1 is for the 22.5 mg strength, (b) (4) (b) (4) Currently, the NDA (Original 1) is recommended for approval for the 22.5 mg strength. There is one PMR regarding the assessment of the break loose and glide force of the syringe from the CDRH ODE product review and one PMC from the Biopharmaceutics review regarding the development of an in vitro drug release method and acceptance criteria for the drug product regulatory specification. Regarding the details of the PMR/PMC, see below and the documents in DARRTS.

The current NDA 205054 submission (SD-46) is a response to Incomplete Response issued by the Agency dated Nov 3, 2017. The CMC of original NDA was previously reviewed (R-1) by Li-Shan Hsieh dated 4/30/2015. Current CMC information provided for Lutrate Depot have been review by the quality review team in the Office of Pharmaceutical Quality, and is found to be acceptable. The review team recommended approval for NDA from the product quality standpoint.

Since Lutrate Depot is a combination product, CDRH (ODE and Inspection) was consulted to evaluate the updates of the device portion of the NDA. Based on CDRH reviewer, the updated information on device was not available in the resubmission. An IR was sent for the applicant to submit the CDRH information. Applicant responded to IR from CDRH. (b) (4)
From CDRH (ODE) prospective, the NDA is recommended for approval but with a PMR.

(b) (4)

(b) (4)

(b) (4)

Temperature].

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A. Product Overview

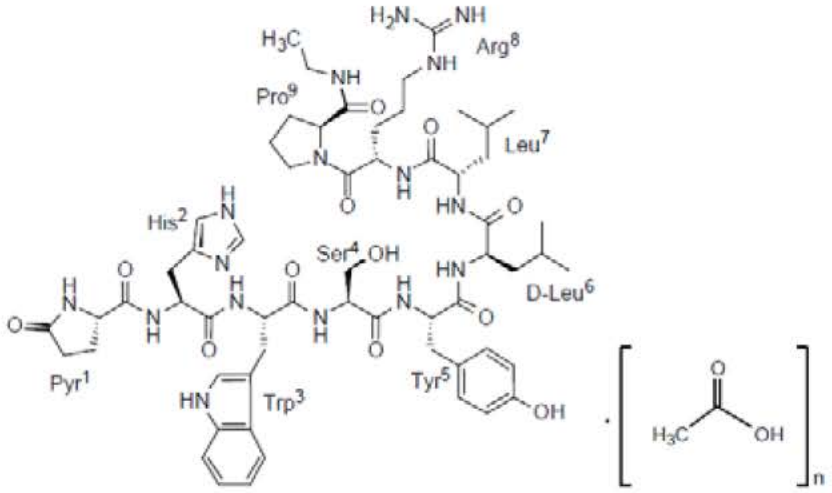
Proposed Indication(s) including Intended Patient Population	Lutrate Depot is indicated for Palliative treatment of advanced prostate cancer.
Duration of Treatment	The duration of treatment for (b) (4) 3-months formulation was 168 d.
Maximum Daily Dose	There is no maximum daily dose. (b) (4) (b) (4) The 3 month is 22.5 mg every 84 days.
Alternative Methods of Administration	There is no alternative method of administration.

B. Quality Assessment Overview

Drug Substance
No DS information is noted in the Resubmission (SD-46); however, following are the summary.

- Chemical Name and Structure:
Name: Leuprolide acetate.

Chemical Name: 5-oxo-L-Prolyl-L-Histidil-L-Tryptophanil-L-Seril-L-Tyrosil-D-Leucil-L- Leucil-L-Arginil-L-Prolil-ethilamide acetate (salt)
Structure:



Molecular Weight: 1209,42 a.m.u (as free base)

The drug substance is an amorphous powder with white to off-white color.

The drug substance leuprolide acetate (leuprorelin) is supplied by [redacted] (b) (4)

Recommended for Approval from the standpoint of drug substance, leuprolide acetate.

Drug Product

Leuprolide is not a new molecular entity. This application was accepted via a 505 (b)2 path since the inactive ingredients for the proposed drug product are different both qualitatively and quantitatively from that of the listed drug (LD) product (Lupron Depot). The active ingredient leuprolide is present as leuprolide acetate salt in both LD and in the 505 (b)2 application. Both the LD and the proposed drug product contain same acetate salt of leuprolide and both are injections for intramuscular administration. However, the quantitative and qualitative compositions of the inactive ingredients are different. The Lupron Depot is supplied as a Kit consisting of a dual chamber syringe, one plunger and two alcohol swabs and it is available in four different strengths: 1) 7.5 mg leuprolide acetate for one month administration; 2) 22.5 mg leuprolide acetate for 3 months administration; 3) 30 mg leuprolide acetate for 4 months administration; 4) 45 mg leuprolide acetate for six months administration. The 505(b)2 application with trademark "Lutrate Depot" is supplied as a kit consisting of a lyophilized formulation of leuprolide acetate in a vial and a pre-filled syringe containing mannitol solution for reconstitution prior to application. Lutrate Depot is proposed to be supplied in [redacted] (b) (4) 22.5 mg for 3 months administration. However, the Clinical Division is proposing to approve [redacted] (b) (4) 22.5 mg for 3 months administration. As indicated above, the drug product is a lyophilized

[redacted]

mannitol: 88.4 mg [redacted] carboxymethyl cellulose: 25.0 mg [redacted] polysorbate 80: 3.8 mg [redacted] The applicant provided data for justification of overfill [redacted] Each vial is supplied with a 2 ml solution of 0.8% mannitol solution in water (with adjusted pH) available in a prefilled syringe. When the mannitol solution is mixed with the lyophilized drug product the mixture becomes a suspension intended for intramuscular injection. The lyophilized drug product is manufactured [redacted]

Each carton contains one sealed plastic holder containing one vial of drug product, one syringe of diluent for reconstitution, one Mixject transfer device and one [redacted] backstop. The MIXJECT® sterile device allows the direct reconstitution of the freeze-dried powder using the solvent contained in the pre-filled syringe and the direct intramuscular injection of the resulting suspension into the patient. The device is fitted on the vial to pierce the stopper, and coupled to the pre-filled syringe containing the diluent, allowing the transfer of the reconstitution diluent into the vial. Once the product suspension is obtained, the device allows drawing the reconstituted product back to the syringe through the device's two-way valve. Throughout this process, the stopper is pierced only once, and the vial, device, syringe and needle stays coupled thereby ensuring the sterility of the drug product injected intramuscularly into the patient. The registration batch size for [redacted] 22.5 mg strength vial is approximately [redacted]

Similarly, two commercial batch sizes are proposed for the 22.5 mg: [redacted] vials. Each unit dose of the Lutrate Depot is packaged in the proposed commercial primary container closure which consists of: 1) [redacted] glass vials; 2) [redacted] rubber stoppers. [redacted] The drug product (Lutrate Depot) quality controls are conducted with the following quality attributes: Appearance, ID (HPLC and UV), pH, Uniformity of dosage unit, Related substances, [redacted] Particle size of reconstituted solution, needle possibility, TEC content, In vitro release, Sterility and Endotoxin. The applicant provided 36 months long term (25oC/60% RH) satisfactory stability data for two batches and 18 months long term stability data of one batch of Lutrate Depot. Based on the stability data the applicant is proposing an expiration date of 36 months. A 0.8% mannitol sterile solution is used as a diluent. After a 0.8% solution is prepared it is sterile [redacted]

filled into sterile syringes and stoppered, (b) (4) The plunger rod is inserted into the syringe followed by packaging. The diluent (0.8% mannitol solution) is controlled by the current USP specification for mannitol injection with additional test for container/closure integrity test. The 0.8% mannitol solution is packaged in (b) (4) (b) (4) syringe system. The current manufacturer of mannitol solution is GP-Pharm. The applicant manufactured the mannitol solution in commercial scale (approximately (b) (4) liters) and placed the batches on primary stability. The applicant also included stability data from previously manufactured batches of mannitol solution. Nine months long term (25°C/60% RH) stability data are available for the 0.8% mannitol solution. The applicant also included 60 months long term stability data for 0.8% mannitol solution from previously manufactured lots from a site which is no longer involved in the manufacturing of 0.8% mannitol. Since the drug product is proposed to be used as a Kit with the Lutrate Depot, the applicant is proposing a shelf life of 36 months under long term conditions for the Kit. Based on the above data, a tentative expiration date of 36 months may be granted when the kit is stored at "20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]".

(b) (4)

Microbiology

(b) (4)

4/27/2015) of NDA 205054 recommended approval. The NDA was resubmitted 8/22/2017, and an Information Request (IR) requesting confirmation that drug product manufacturers were ready for inspection was subsequently issued 9/20/2017. The resulting 10/9/2017 IR response stated that (b) (4) (proposed in the original NDA submission) would not be manufacturing the Mannitol 0.8% pre-filled syringe diluent for Lutrate Depot® (leuprolide acetate) Injectable, and that GP Pharm would internalize the manufacturing (b) (4) processes within its own GP

Pharm (Sant Quintí de Mediona, Spain) facility. (b) (4) validation information for Mannitol 0.8% pre-filled syringes manufactured at GP Pharm was included in the original NDA or NDA resubmission, and the applicant maintained that the corresponding sterilization process validation information would not become available until late February 2018, the 8/22/2017 resubmission was determined to be an incomplete response to the 5/29/2015 Complete Response Letter. The current (2/28/2018) Complete Response to the Acknowledge Incomplete Response Letter of 11/3/2017 provides for the mannitol pre-filled syringe (b) (4) sterilization process validation at the GP-Pharm facility.

Recommended for Approval from the standpoint of product quality microbiology.

Facility

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application.

The manufacturing facilities for NDA 205054 are found to be acceptable.

Biopharmaceutics

Biopharmaceutics review evaluated **1)** proposed accelerated in vitro release methods and acceptance criteria for the (b) (4) 22.5 mg strengths, and **2)** the need for (b) (4) (b) (4) manufacturing process and site changes throughout product's development, (b) (4) between the proposed drug product and Listed Drug products.

➢ ***In Vitro Drug Release Method and Acceptance Criteria for the 22.5 mg strength***

The proposed accelerated in vitro drug release method B and acceptance criteria for the 22.5 mg strength drug product are acceptable on an **interim basis** as described in Table 1 below.

TABLE 1. Interim Basis Accelerated In Vitro Release Method B for Lutrate Depot® 22.5 mg

Parameters	In-Tube Method
Apparatus/Speed	The content of the vials transferred to **propylene tubes**
Media/Volume	Hydrolysis buffer (10 mM citric acid buffer, pH 4) /**30 mL**
Bath temperature	60.0±0.5° C
Sampling Time Points/Sample	4 hours: Supernatant* Day 1: Pellets Day 4: Pellets It should be noted sample analysis was done on the supernatant (i.e. released drug) at 4 hour time point, and on Day 1 and Day 4, reported drug release value was based on back-calculation on what is remaining in the microspheres (referred as pellets) by collecting the pellets and solubilizing the remaining polymer in IPA/H20 solution.
Analytical Method	HPLC/UV at 220 nm

Acceptance Criteria	
Time	Percent (%) Leuprolide Released
4 hours Day 1 Day 4	(b) (4)

Although the proposed accelerated method and acceptance criteria are acceptable on an interim basis, there were several concerns regarding the method's sample preparation and methodology procedures. Therefore, the Applicant was requested to provide additional information/data and submit their proposal for the final in vitro drug release method and acceptance criteria under a Post-Marketing Commitment for specifics refer to PMC Document # 3463-2 in DARRTS) described below:

PMC #1 No:	**3463-2**
PMC #1 Description:	Development and validation of an accelerated in vitro drug release method and setting of the drug release acceptance criteria for Lutrate Depot® (leuprolide acetate), 22.5 mg product.
PMC Schedule	Interim Report: 02/2019 (submit as

(b) (4)

(b) (4)

Bridging between the Proposed and Listed Drug Products:

This application is a 505(b)(2) submission, partly relying on the FDA's previous nonclinical toxicology findings from approved [redacted] (b) (4) NDA 020517 for Lupron Depot®, [redacted] (b) (4) 22.5 mg strengths, respectively, and published literature. For bridging information refer to Pharmacology and Toxicology Review in DARRTS by Drs. E. Zahalka, T. Palmy, and J. Leighton dated 04/25/2015.

REVIEW RECOMMENDATION for NDA 205054-ORIG-1 for 22.5 mg

Based on the review of the overall in vitro drug release information, the proposed accelerated in vitro release method and acceptance criteria for the 22.5 mg strength are

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[redacted] (b) (4)

(b) (4)

CDER requested the consult for review of the device constituent of the combination product on 05/30/2018.

The consult product review will cover the following review areas, and to provide a recommendation of the approvability of the device constituent of the combination product.

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent

The consult review will not cover the following review areas:

• Compatibility of the drug with the device materials (Refer to the drug product review)
• Human Factors (DMEPA reviewed risk analysis and concluded that no HF studies were required)
• Sterility of the device constituent (refer to the microbiology review)

Based on the information submitted to the NDA, CDRH ODE product review recommends that the device constituent of the combination product is **Approvable** with the following **PMR** agreed by the applicant:

Assess the break loose and glide force necessary for the safe administration of Lutrate Depot 22.5 mg with syringes that are at the beginning and end of their shelf life and submit a final study report. Develop a standing protocol to control the essential performance characteristics and regular testing of the break loose and glide force, and dose accuracy for the combination product, pre-filled syringe containing 2 mL mannitol for injection.

Final Report Submission: 02/2019

CDRH OC Manufacturing Consult Review
The consult manufacturing review for the combination product was conducted to evaluate manufacturing sites needing inspections and to review the 21 CFR 820 requirements of the combination product. The CDRH OC review provides the following recommendation:

CDRH OC noted that CDER has made the decision to approve NDA 205054/Original -1 = 22.5 mg formulation (b) (4) With that, CDRH has determined that NDA 205054 is approvable from the perspective of the Medical Device Regulations.

CDRH OC recommends that compliance to the 21 CFR 820 requirements for management controls, design controls, CAPA, and purchasing controls be verified during a post-approval inspection. CDRH also recommends a review of the final validation data collected on the final combination product post-approval.

C. Special Product Quality Labeling Recommendations (NDA only)
N/A.

D. Final Risk Assessment (see Attachment)
Attachment-1 (Lutrate Depot)

Table. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Sterility	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	H	(b) (4)	H	Continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		M	Continue stability monitoring post approval
Assay (API)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		M	Continue stability monitoring post approval
Physical Stability (solid state)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	H		M; The applicant has submitted evidence that leuprolide acetate remains in amorphous state throughout the shelf life. Since this is a resubmission application and this item was not part of the CR. The applicant is not being requested to adopt a control strategy throughout the life-cycle.	None

Table. Risk Assessment (contd.)

Uniformity of dose (Fill volume/deliverable volume)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M	(b) (4)	M	Monitor dose uniformity
Assay (plasticizer-triethyl citrate)	• Formulation • Container/closure • Scale/equipment • Site	M		M	Monitor stability data
Osmolality	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		L	N/A
pH (high)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		L; Controlled by specification	Monitor stability data
pH (low)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		L; Controlled by specification	Monitor stability data
Particulate matter	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		M; Controlled by specification	Monitor stability
Leachable Extractable	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L		L; Not monitored routinely	Not monitored
Redispersibility/reconstitution time	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		M	Forms a suspension after reconstitution

Table. Risk Assessment (contd.)

			(b) (4)		
In-vitro release (ER-depot forming)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	H		H	Controlled by specification
Appearance (caking)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		M; Monitor the lyophilization primary and secondary drying process	Monitor stability and change in process.
Appearance(color /turbidity)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L		L	Monitor stability

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

0.8% mannitol solution is used as a diluent for the Kit. The mannitol solution is supplied in a pre-filled syringe. The quality of the diluent is controlled by its specification.

Application Technical Lead Name and Date:
Haripada Sarker, Ph.D.

10-August-2018

Updated and signing by Xiao Hong Chen for Haripada Sarker

16-August-2018

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Product Quality Microbiology Review

04 MAY 2018

NDA: 05054

Drug Product Name
Proprietary: Lutrate Depot
Non-proprietary: Leuprolide Acetate

Review Number:

Dates of Submission(s) Covered by this Review

Submit	eceived	eview Request	Assigned to Reviewer
28 Feb 2018	8 Feb 2018		01 March 2018

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
31 July 2014	1	27 April 2015
22 August 2017	2	26 October 2017

Applicant/Sponsor
Name: P Pharm, S.A.
Address: oligono Industrial ELS VINYETS-FOGARS
Sector 2 CRTA 244 KM 22
Sant Quintí de Mediona, Barcelona, Spain 08777

US Agent: AXON INTERNATIONAL ASSOCIATES
10 DeBary Place
Summit NJ 07901

Representative: Peter Saxon
Telephone: -908-273-1303

Name of Reviewer: Neal J. Sweeney, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505 (b) (2) Original NDA (resubmission)

2. SUBMISSION PROVIDES FOR: New drug product. Complete Response to the Acknowledge Incomplete Response Letter of November 3, 2017.

3. MANUFACTURING SITES: GP-Pharm, S.A.
POLIGONO INDUSTRIAL ELS VINYETS-

Manufacturing of Leu (b) (4)

(b) (4)

(b) (4)

4. DOSAGE FORM, R (b) (4)
STRENGTH/POTEN
mg (3-month dose) ly
dose vials, co-packaged with a 2-mL prefilled mannitol diluent syringe, for intramuscular injection. The kit also includes a commercially available MIXJECT® polycarbonate/HDPE transfer device containing a sterile (20 gauge) needle.

5. METHOD(S) OF STERILIZATION:

(b) (4)

6. PHARMACOLOGICAL CATEGORY: Gonadotropin-releasing hormone agonist indicated for palliative treatment of advanced prostate cancer.

B. SUPPORTING/RELATED DOCUMENTS:
510(k) 122023 (MIXJECT® polycarbonate/HDPE transfer device)
DMF (b) (4)

C. REMARKS: A Complete Response Letter dated 5/29/2015 was issued for NDA 205054 Lutrate Depot® (leuprolide acetate) Injectable. However, Microbiology Review #1 (dated 4/27/2015) of NDA 205054 recommended approval. The NDA was resubmitted 8/22/2017, and an Information Request (IR) requesting confirmation that

drug product manufacturers were ready for inspection was subsequently issued 9/20/2017. The resulting 10/9/2017 IR response stated that (b) (4) (b) (4) (proposed in the original NDA submission) would not be manufacturing the Mannitol 0.8% pre-filled syringe diluent for Lutrate Depot® (leuprolide acetate) Injectable, and that GP Pharm would internalize the manufacturing and te (b) (4) sterilization processes within its own GP Pharm (Sant Quintí de Mediona, Spain) facility. As no (b) (4) sterilization process validation information for Mannitol 0.8% pre-filled syringes manufactured at GP Pharm was included in the original NDA or NDA resubmission, and the applicant maintained that the corresponding sterilization process validation information would not become available until late February 2018, the 8/22/2017 resubmission was determined to be an incomplete response to the 5/29/2015 Complete Response Letter. The current (2/28/2018) Complete Response to the Acknowledge Incomplete Response Letter of 11/3/2017 provides for the mannitol pre-filled syringe (b) (4) sterilization process validation at the GP-Pharm facility.

(See additional details on pages 7-8 of this review)

filename: N205054MR03.doc

Executive Summary

I. ecommendations

A. Recommendation on Approvability - Recommended for Approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The leuprolide drug product vial is

ic lly roce e i i (b) (4)

B. Brief Description of Microbiology Deficiencies – Based upon the information provided, no microbiology deficiencies were identified.

C. Contains Potential Precedent Decision(s)- ☐ Yes ☒ No
(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

Leuprolide Vials

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3,4,5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)						(b) (4)

(b) (4)

(b) (4)

Mannitol Diluent Prefilled Syringes

		Occ. (O)	O[3,4,5]	Effect (S)		Number[6] (RPN)	based on Risk (in addition to normal review process)
Ster.	(b) (4)						(b) (4)

(b) (4)

Leupro (b) (4)

(b) (4)

Mann

(b) (4)

IV. Administrative

A. Reviewer's Signature _____
Neal J. Sweeney, Ph.D.

B. Endorsement Block _____
Bryan S. Riley, Acting Branch Chief

C. CC Block
N/A

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Bryan Riley

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Neal Sweeney

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LABELING

NDA 205054

R Regional Information

1.14 Labeling

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: N/A Established Name: leuprolide acetate for depot suspension	Per recommendation of USP <1121>, the established name should be **leuprolide extended release injectable suspension**. The LD "Lupron Depot" established name is "leuprolide acetate for depot suspension". Therefore, the Lupron depot and Lutrate depot labels are recommended to be changed at the same time to avoid confusion among practitioners. The LNC is in the process of writing a guidance on this subject.
Dosage form, route of administration	Dosage: 1) Injection Route: Intramuscular	Satisfactory
Controlled drug substance symbol (if applicable)	None	N/A ***
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	(b) (4) 22.5 mg injection in a kit with a vial, a prefilled syringe and a MIXJECT transfer device.	Satisfactory

(b) (4)

(b) "Full Prescribing Information" Section
3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

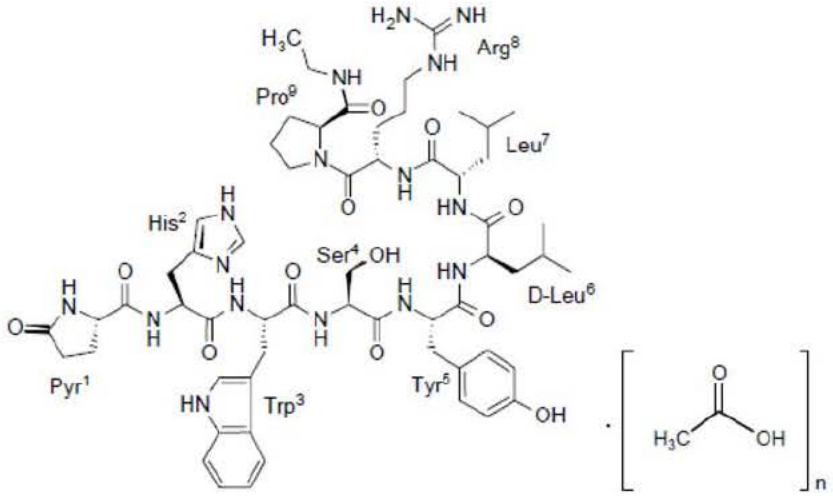
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Not provided	Include:" sterile and single dose". Satisfactory after revision.
Strengths: in metric system	LUTRATE DEPOT (b) (4) (b) (4) 22.5 mg for 3-month administration are each supplied as a kit with a vial, a syringe and a MIXJECT transfer device.	Satisfactory after revision
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Sterile is not mentioned, single-dose not mentioned. Satisfactory after revision

Reviewer's Assessment: The applicant was requested to revise the statement from: "LUTRATE DEPOT (b) (4) 22.5 mg for 3-month administration (b) (4) (b) (4) 22.5 mg for 3-month administration are each supplied as a kit with a vial, a syringe and a MIXJECT transfer device for sterile single dose application". (b) (4) (b) (4) the applicant revised the Dosage forms and strengths as follows: "For Injection: 22.5 mg of leuprolide acetate for 3-month administration as lyophilized microspheres in a single dose vial as a kit with a prefilled syringe containing 2 mL 0.8% mannitol solution and a MIXJECT transfer device for a single dose injection". The revised statement is satisfactory.

#11: Description (21CFR 201.57(c)(12))

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:

Replace the structure on the label with stereochemistry (added to the PI)



n=1 or 2

(b) (4)

(b) (4)

[redacted]

LUTRATE DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration is available in a vial containing sterile lyophilized microspheres together with the corresponding reconstitution diluent in a pre-filled syringe. When mixed together, become a suspension intended as an intramuscular injection to be given **ONCE EVERY 12 WEEKS** as a single dose.

Each vial of LUTRATE DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration delivers leuprolide acetate (22.5 mg), polylactic acid (PLA) (188.4 mg), triethylcitrate (TEC) (10.4 mg), polysorbate 80 (3.8 mg), mannitol (88.4 mg) and carmellose sodium (25 mg). The prefilled syringe containing the reconstitution diluent (2 mL) contains mannitol (16 mg), water

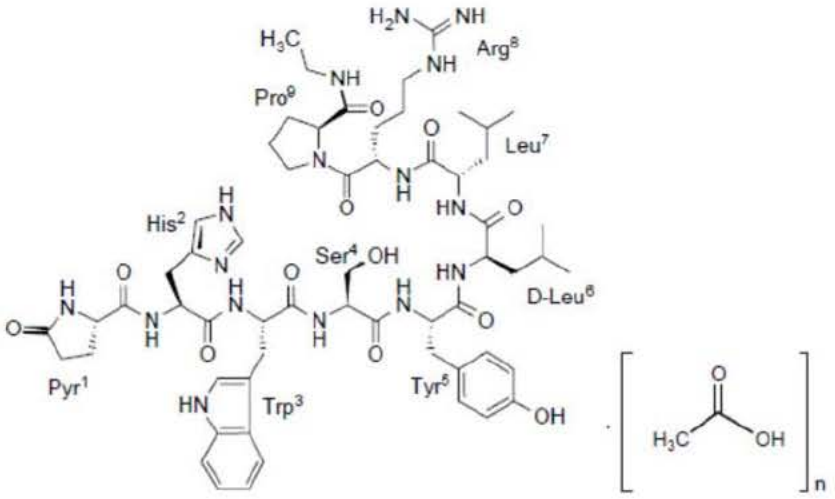
(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: Lutrate Depot Established name: leuprolide acetate for depot suspension	Satisfactory Not satisfactory per USP/FDA salt nomenclature policy. However, it is consistent with Lupron Depot established name (see the Reviewer's Assessment of "Highlights" Section).
Dosage form and route of administration	Injection, intramuscular	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	Strength on the basis of leuprolide acetate. Salt equivalence statement not included	Not satisfactory. However, consistent with Lupron Depot label (see the Reviewer's Assessment of "Highlights" Section).
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See the text above under description section	Satisfactory
Statement of being sterile (if applicable)	No mention	The revised statement is satisfactory
Pharmacological/ therapeutic class	Analog of GnRH	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Solubility added	Satisfactory.

Reviewer's Assessment: The yellow highlighted section above is added to the PI for

(b) (4)



Where: n=1 or 2

Leuprolide acetate has a molecular weight of 1209.41 as free base". Leuprolide is freely soluble in water.

LUTRATE DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration is available in a vial containing white to off white sterile lyophilized microspheres together with the corresponding sterile reconstitution diluent in a pre-filled syringe. When LUTRATE DEPOT and the diluent are mixed together they become a suspension intended as an intramuscular injection to be given **ONCE EVERY 12 WEEKS** as a single dose.

Each vial of LUTRATE DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration delivers leuprolide acetate (22.5 mg), polylactic acid (188.4 mg), triethylcitrate (10.4 mg), polysorbate 80 (3.8 mg), mannitol (88.4 mg) and carmellose sodium (25 mg). The prefilled syringe containing the clear reconstitution diluent (2 mL) contains mannitol (16 mg), water for injections, and sodium hydroxide and hydrochloric acid to control pH.

Leuprolide acetate for depot suspension is an extended release sterile, single dose injection in suspension form for intramuscular administration.

Reviewer's Assessment: The revised "Description" section is satisfactory.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17)) before revision

Lutrate Depot is supplied as a kit consisting of a Lutrate Mixjet single dose delivery system consisting of a vial with a flip-off seal containing sterile lyophilized leuprolide acetate microspheres incorporated into a biodegradable polymer, a Mixject vial adapter containing the needle, and a pre-filled syringe containing sterile mannitol injection, 2 ml, pH 4.5-7.0.

(b) (4)

Lutrate Depot 22.5 mg- NDC 69112-002-02

Store at 25° C (77°F) excursions permitted (b) (4) 30°C (b) (4) 86°F)

Handling and Disposal: None included.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Strengths provided but does not comply with the USP salt nomenclature policy but corresponds to Lupron Depot	Satisfactory (see Reviewer's Assessment in "Highlights" section).
Available units (e.g., bottles of 100 tablets)	Single unit as a kit	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See the description above. NDC number is provided	NDC number provided. Satisfactory after revision (see Reviewer's Assessment below)
Special handling (e.g., protect from light, do not freeze)	None	Satisfactory
Storage conditions	Storage conditions are inaccurate it is recommended to be revised to correspond to USP controlled storage conditions.	Satisfactory after revision

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributor's name and address included: (b) (4) Manufactured For: (b) (4)	Satisfactory

Reviewer's Assessment: The reviewer recommends the following revisions to the "How Supplied" Section: 1) Change the statement from: "LUTRATE DEPOT is supplied as a LUTRATE MIXJECT single-dose delivery system consisting of a vial with a Flip-Off seal containing sterile lyophilized leuprolide acetate microspheres incorporated in a biodegradable polymer, a MIXJECT vial adapter containing the needle, and a pre-filled syringe containing sterile mannitol for injection, USP, 2 mL, pH 4.5 to 7.0" to " Lutrate Depot is supplied as a kit consisting of a Lutrate Mixjet single dose delivery system consisting of a vial with a flip-off seal containing sterile lyophilized leuprolide acetate microspheres incorporated into a biodegradable polymer, a Mixject vial adapter containing the needle, and a pre-filled syringe containing sterile mannitol injection, 2 ml, pH 4.5-7.0"; 2) Change the storage statement from: "Store at 25° C (77°F) excursions permitted to 2 – 30°C (35.6 – 86°F)" to "Store at controlled room temperature at 20°- 25° C (68°–77°F) excursions permitted between 15 ° and 30 ° C (59 ° and 86°F)".

(b) (4)

clinical division's request. The revised How Supplied/Storage and Handling is provided below: "LUTRATE DEPOT (leuprolide acetate for depot suspension) is supplied as a kit consisting of a LUTRATE MIXJECT single-dose delivery system consisting of a vial with a Flip-Off seal containing sterile, white to off white lyophilized leuprolide acetate microspheres incorporated in a biodegradable polymer, a MIXJECT vial adapter containing the needle, and a pre-filled syringe containing clear sterile mannitol solution for injection, USP, 2 mL, pH 4.5 to 7.0.

LUTRATE DEPOT 22.5 mg – NDC 69112-002-02

Storage: Store at controlled room temperature at 20°-25°C (68°-77°F) [*see USP Controlled Room Temperature*]".

Reviewer's Assessment: The revised "How Supplied" section is satisfactory.

2. Labels

1) Immediate Container Label

Reviewer's Assessment: The applicant was requested to revise the label as follows:

Sterile Mannitol Solution (0.8% w/v)

2 ml

Solvent for reconstitution of Lutrate Depot.

Prescription only

Lot #

Expiration date

Storage conditions.

abel after revision:

Reviewer's Assessment: The revised syringe label is satisfactory.

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Lutrate Depot Established name: Not Satisfactory. Change from [redacted] (b) (4) to "Leuprolide acetate for depot suspension" to be consistent with PI	Satisfactory Satisfactory after revision
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per	None	Satisfactory
Storage (not required)	Storage condition not included	Satisfactory after revision
NDC number (per 21 CFR 201.2)	Included	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Reviewer's Assessment: Based on the review of the label applicant was requested to include the word "sterile" and storage conditions to the immediate container label. The applicant revised the label and the revised label (see below) is satisfactory to the reviewer. The revised 22.5 mg container label is provided below:

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
"Keep out of reach of children" (optional for Rx, required for OTC)	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	Referenced	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name: Satisfactory	Satisfactory after revision

	Established name: Satisfactory	See immediate container label comment
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	None	Satisfactory.
Sterility Information (if applicable)	Included	Satisfactory
Storage Conditions	Not Satisfactory	Satisfactory after revision
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory

Reviewer's Assessment: Based on the review the applicant was requested to make the following changes to the carton (outer packaging) of 22.5 mg strength: 1) Change the storage statement from: [redacted] (b) (4) to "Store at controlled room temperature at 20°- 25° C (68°–77°F) excursions permitted between 15° and 30°C (59° and 86°F)", since the primary long term stability studies for the drug product and the diluent were conducted at 25°C/60% RH; 2) Revise the statement from: "The vial contains: leuprolide acetate 22.5 mg, carmelose sodium 25 mg, mannitol 88.4 mg, poly lactic acid [redacted] (b) (4) mg, polysorbate 80 3.8 mg, triethyl citrate [redacted] (b) (4) mg" to "The vial

contains the following ingredients to deliver: leuprolide acetate 22.5 mg, carmelose sodium 25 mg, mannitol 88.4 mg, polylactic acid 188.4 mg, polysorbate 80 3.8 mg, triethyl citrate 10.4 mg" to be consistent with Component/Composition table in Section P.1 of the submission and the Section 11 of the package insert". The applicant revised the outer packaging. The

(b) (4)

(b) (4)

List of Deficiencies: None

Amit Mitra

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Thomas Oliver

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Date: 8/08/2018 03:09:21PM
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CHAPTER VII: BIOPHARMACEUTICS

Application: Resubmission of NDA 205054-ORIG-1 for 22.5 mg dated 2/28/2018 (SDN-46) (b) (4)

Drug Product Name/Strength: Lutrate Depot® (leuprolide acetate), (b) (4) 22.5 mg
Route of Administration: Intramuscular Injection
Applicant Name: GP Pharm, SA

Biopharmaceutics ReviewTeam:
Primary Reviewer: Parnali Chatterjee, Ph.D. Date: 08/16/2018
Secondary Reviewer: Banu Zolnik, Ph.D. Date: 08/16/2018
Tertiary Reviewer: Angelica Dorantes, Ph.D. Date: 08/16/2018

REVIEW SUMMARY:

Background: NDA 205054-ORIG-1 (b) (4) 05/29/2015, due to Clinical and Drug Product Quality deficiencies identified in the application. (b) (4)

The Applicant conducted (b) (4) (b) (4) GP/C/05/PRO study with 22.5 mg administered at 84-days (3-month) interval in patients with prostate cancer to support the approval of their application. (b) (4) studies evaluated the pharmacokinetic and pharmacodynamics of leuprolide.

Review: This Biopharmaceutics review evaluated **1)** proposed accelerated in vitro release methods and acceptance criteria for the 22.5 mg (b) (4) and **2)** the need for (b) (4) (b) (4) manufacturing process and site changes throughout product's development, (b) (4) (b) (4) between the proposed drug product and Listed Drug products.

- ***In Vitro Drug Release Method and Acceptance Criteria***

Lutrate Depot® (leuprolide acetate), 22.5 mg: The proposed accelerated in vitro drug release method and acceptance criteria for the 22.5 mg strength drug product are acceptable on an **interim basis** as described in Table 1 below.

TABLE 1. Accelerated In Vitro Release Method for Lutrate Depot® 22.5 mg

Parameters	In-Tube Method
Apparatus/Speed	The content of the vials transferred to **propylene tubes**
Media/Volume	Hydrolysis buffer (10 mM citric acid buffer, pH 4) /30 mL
Bath temperature	60.0±0.5° C
Sampling Time Points/Sampling Method	4 hours: Supernatant Day 1: Pellets Day 4: Pellets It should be noted sample analysis was done on the supernatant (i.e. released drug) at 4-hour time point, and on Day 1 and Day 4, reported drug release value was based on back-calculation on what is remaining in the microspheres (referred as pellets) by collecting the pellets and solubilizing the remaining polymer in IPA/H_20 solution.
Analytical Method	HPLC/UV at 220 nm
Acceptance Criteria	
Time	Percent (%) Leuprolide Released
4 hours Day 1 Day 4	(b) (4)

Although the proposed accelerated method and acceptance criteria are acceptable on an interim basis, there were several concerns regarding the method's sample preparation and methodology

(b) (4)

(b) (4)

Proposed and Listed Drug Products: This application is a 505(b)(2) NDA submission partly relying on the FDA's previous nonclinical toxicology findings from approved (b) (4)

(b) (4) NDA 020517 for Lupron Depot® (b) (4) 22 mg strengths, respectively, and published literature. For bridging information refer to Pharmacology and Toxicology Review in DARRTS by Drs. E. Zahalka, T. Palmy, and J. Leighton dated 04/25/2015.

REVIEW RECOMMENDATION for NDA 205054-ORIG-1 for 22.5 mg

Based on the review of the overall in vitro drug release information, the proposed accelerated in vitro release method and acceptance criteria for the 22.5 mg strength are acceptable on **an interim**

(b) (4)

(b) (4)

SIGNATURES

Primary Reviewer:
Parnali Chatterjee, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

Secondary Reviewer:
Banu Zolnik, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

Tertiary Reviewer:
Angelica Dorantes, Ph.D.
Branch Chief
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

BIOPHARMACEUTICS ASSESSMENT

1. SUBMISSIONS REVIEWED

Documents	Date Received
SDN 41 - Resubmission/Incomplete	08/22/2017
SDN 46 - Resubmission/ (b) (4) NDA ORG 1 (b) (4)	02/28/2018
SDN 70 - Response to Information Request Comment	07/18/2018

2. BACKGROUND

GP Pharm, SA is seeking approval for Lutrate Depot® (leuprolide acetate), (b) (4) 22.5 mg strengths to be administered by intramuscular injection to patients (b) (4) (b) (4) quarterly (Lutrate Depot®, 22.5 mg) for palliative treatment of patients with advanced prostate cancer *via* the 505 (b) (2) regulatory path.

Lutrate Depot® (leuprolide acetate), (b) (4) 22.5 mg strengths are extended-release suspensions that are supplied as freeze-dried powders to be reconstituted with sterile 0.8% mannitol as diluent supplied in prefilled syringe for intramuscular injection. (b) (4) (b) (4) (b) (4) For 22 mg strength, the Applicant identified NDA 20517 for Lupron Depot®, 22 mg strength as the Listed Drug.

NDA 205054 for Lutrate Depot® (leuprolide acetate), (b) (4) 22.5 mg strengths for intramuscular injection was originally submitted for regulatory approval on July 31, 2014. The Application received a Complete Response Letter (CRL, **Appendix I**) on 05/29/2015 due to number of Clinical and Drug Product Quality deficiencies identified in the application.

In response to the deficiencies listed in the CRL, the Applicant updated the Drug Product Quality sections in the eCTD and resubmitted the NDA 205054 on 08/22/2017, which was subsequently found to be incomplete because all the manufacturing sites were not ready for inspection on the submission date. The Applicant resubmitted the NDA 205054 on 02/28/2018. The information provided in the eCTD 0037 SDN 41 Resubmission/Incomplete, eCTD 0042 SDN 46 Resubmission/Class 2, and eCTD 0066 SDN 70 Response to Information Request Comment was assessed in this review.

3. DRUG SUBSTANCE:

The drug substance is white to off-white amorphous powder and highly hygroscopic. Leuprolide is a synthetic analog of human luteinizing hormone-releasing factor that is composed of a non-glycosylated polypeptide chain containing nine amino acids.

Solubility: The drug substance is a synthetic polypeptide that is composed of nine amino acids. The Applicant noted that the drug substance is freely soluble in water with solubility approaching 160 mg/ml.

Permeability: Per the Applicant, the synthetic nonapeptide is completely inactivated by proteolytic enzymes in the gastrointestinal tract. Therefore, the drug substance is not orally active.

4. DRUG PRODUCT:

The Applicant developed (b) (4) extended-release Lutrate Depot® (leuprolide acetate) (b) (4) (b) (4) 22.5 mg strength microspheres of leuprolide acetate to be reconstituted with sterile diluent.

Each vial is packaged along with a 20G syringe assembly that is prefilled with 0.8% mannitol as reconstitution diluent along with a sterile transfer device (MIXJECT®) for administration of the drug products, intramuscularly.

(b) (4)

Lutrate Depot® (leuprolide acetate), 22.5 mg drug product is encapsulated in microspheres of poly(D,L-lactide) (PLA) and TEC that releases leuprolide over three-month period (approximately 84 da lide a (b) (4) (b) (4) **2b,** (b) (4)

(b) (4)

Table 2b. Qualitative and Quantitative Composition of Lutrate Depot® (leuprolide acetate),

INGREDIENT	QUANTITY FINISHED DOSAGE FORM		QUANTITY MANUFACTURING BATCH FORMULA			FUNCTION	REFERENCE TO STANDARDS
	PER DOSE	PER VIAL	PER	PER	PER	(b) (4)	
Active Ingredient							
Leuprolide Acetate[7]	22.5 mg	(b) (4)					USP*
Excipients							
PLA[7]	188.4 mg						In - House
Triethyl citrate (b) (4)	10.4 mg						NF*
	---						NF*
	---						NF*
	---						In - House
	---						NF*
	88.4 mg						USP*
	25.0 mg						NF*
Polysorbate 80	3.8 mg						NF*
Water for injections	--						USP*

5. *PROPOSED IN VITR*

a) Accelerated In Vitro Drug Release Method for 22.5 mg Strength:

The accelerated in vitro drug release method was found acceptable for batch release and stability testing of the 22.5 mg strength drug product during the original NDA review cycle, as described below (see **Table 3**).

However, upon further evaluation of this method, several concerns regarding the sample preparation and testing methodology were identified for the in vitro drug release method and acceptance criteria of the 22.5 mg strength. Therefore, the proposed accelerated method and acceptance criteria are acceptable only on **an interim basis** for release and on stability. The Applicant is being requested to provide additional information/data and submit their proposal for the final in vitro drug release method and acceptance criteria under a Post-Marketing Commitment (for specifics refer to PMC document # 3463-2). The Biopharmaceutics comments/request for information listed in the PMC commitment conveyed to the Applicant in an Email correspondence dated 08/13/2018, will be addressed by the Applicant at a future time under a Prior Approval Supplement.

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Parnali Chatterjee

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Date: 8/16/2018 03:07:54PM
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Banu Zolnik

Digitally signed by Banu Zolnik
Date: 8/16/2018 03:56:03PM
GUID: 508da7270002a568e175a2c0dd90f334

Angelica Dorantes

Digitally signed by Angelica Dorantes
Date: 8/16/2018 04:51:54PM
GUID: 502d0913000029d59f1c87e0a380c7f7

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date:	
To:	ICCR Lead-Center Contact, Office, Location, E-mail:
CC:	Office of Combination Product at: combination@fda.gov Regulatory Business Program Manager (RBPM)/Regulatory Progra Manager (RPM): Name, Office, E-Mail: Kristine.Leahy@fda.hhs.gov
Through:	Nazia Rahman, /OC, CDRH, WO 66, Rm 3458, E-mail: Combination Product Team Lead, DMQ/OC, CDRH, WO 66, Rm 3458, E-mail: Nazia.Rahman@fda.hhs.gov
From:	Latoya Oliver-Powell, ASDB/DMQ/OC, CDRH, WO 66, Rm 3458, E-mail:Nazia.Rahman@fda.hhs.gov
Applicant/Licensure:	GP PHARM, S.A. Polígon Industrial Els Vinyets - Els Fogars, Sector 2Carretera Comarcal C-244, Km. 22 Sant Quintí de Mediona, Barcelona, SPAIN 08777 FEI: 3008345811
Submission (Type & Number):	NDA 205054/Original -1 = 22.5 mg formulation (b) (4)
Combination Product Name:	Leuprolide acetate
Combination Product Intended Use:	Palliative treatment of advanced prostate cancer
Device Constituent (Type):	re-filled syringe- Injectable
CTS ICCR Number:	CC1800227
Sharepoint ICCR Number:	CCR2018-02542
ICCR Instruction (ICCR Form):	Site Inspection Review, 21 CFR 820 Requirements Review
Pre-Approval Facility Inspection:	**No** **Post Approval Inspection Recommended**
CDRH/OC Recommendation:	**Approvable; Post Approval Inspection Recommended**

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205054 to identify manufacturing sites needing inspections and to review the 21 CFR 820 requirements of the combination product.

Sites Requiring Inspections

Post approval device inspection recommended:

The following site is recommended for a post approval device inspection.

GP PHARM, S.A.
Polígon Industrial Els Vinyets - Els Fogars, Sector 2
Carretera Comarcal C-244, Km. 22
Sant Quintí de Mediona, Barcelona, SPAIN 08777

FEI: 3008345811

Activities performed at site: Leuprolide vial manufacture (b) (4) Mannitol 0.8% syringe manufacture; Control (release and stability) of Leuprolide vial and Mannitol 0.8% syringe; Primary &Secondary Packaging; Product Release; Warehouse for Product storage; Excipient testing and release.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 205054 (b) (4) has the following recommendations:

CDRH notes that CDER has made the decision to approve NDA 205054/Original -1 = 22.5 mg formulation (b) (4) With that, CDRH has determined that NDA 205054 is approvable from the perspective of the Medical Device Regulations.

CDRH recommends that compliance to the 21 CFR 820 requirements for management controls, design controls, CAPA, and purchasing controls be verified during a post-approval inspection. CDRH also recommends a review of the final validation data collected on the final combination product post-approval.

Latoya Oliver-powell -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000354592, cn=Latoya Oliver-powell -S
Date: 2018.08.10 12:58:10 -04'00'

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Latoya Oliver-Powell

Nazia Rahman -S
2018.08.10 11:32:37 -04'00'

_____

Nazia Rahman

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

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Date	August 7, 2018
To	Kristine Leahy Kristine.Leahy@fda.hhs.gov OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI 240-402-5834
Requesting Center/Office	*CDER/OPQ*
OND Review Division	*N/A*
From	Jacqueline Gertz CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Carolyn Dorgan, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # NDA205054 ICCR # 2018-02992 ICC# 1800459
Final Recommendation	*Recommendation Date:* *Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, Section 12.2*

Digital Signature Concurrence Table	
Reviewer	Jacqueline Gertz -S Digitally signed by Jacqueline Gertz -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001948760, cn=Jacqueline Gertz -S Date: 2018.08.14 15:04:27 -04'00'
Team Lead	Carolyn C. Dorgan -S Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2018.08.14 15:19:26 -04'00'
Branch Chief	Geeta K. Pamidimukkala -S 2018.08.14 15:21:35 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	2018-02992
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=3279
ICC tracking # (Lead)	1800459
Submission Number	NDA 205054/Original -1 = 22.5 mg formulation (Approvable) [redacted] (b) (4)
Sponsor	GP Pharma SA
Drug/Biologic	Leuprolide Acetate
Indications for Use	Prostate Cancer
Device Constituent	Syringe and reconstitution assistant
Related Files	ICCR2017-01639 ICCR2018-02542 ICCR2017-01722 ICC1400553 - compliance ICC1800227 - compliance ICC1700747 - compliance

Table 2. Review Team		
Were other disciplines consulted?	☐ **Yes**	☒ **No**

Table 3. Important Dates	
Interim Due Dates	**Due Date**
Primary Review	August 1, 2018
PDUFA/GDUFA Due Date	

TABLE OF CONTENTS

Update TOC

2. PURPOSE/BACKGROUND

2.1. Scope

GP Pharma SA is requesting approval of the Leuprolide Depot injection. The device constituent of the co ination product is a syringe filled with diluent and a reconstitution assistant

CDER has requested the following consult for review of the device constituent of the combination product on 05/30/2018:

Review the device constituents of the combination product.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors
- Sterility of the device constituent

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

CDRH has interacted previously regarding compliance issues under the following ICC numbers:

- ICC1400553
- ICC1800227
- ICC1700747

The NDA was originally submitted July 31, 2014 and received a complete response letter on May 29, 2015.

2.2.1. Related Files

Related compliance consults:

- ICC1400553
- ICC1800227
- ICC1700747

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use
Leuprolide Acetate	palliative treatment of advanced prostate cancer
Syringe with reconstitution assistant Mixject - K963583	Reconstitute drug product and drug delivery
Route of administration	Intramuscular injection

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
lut-1-3-a-gp-us-comb-prod-report-v02-rs-feb2018	Sequence 0042/3.2.r – combination product
lut-1-3-gp-us-cover-v42-rs-s0042-feb2018	Sequence 0042/1.2 cover letter
inner-packaging-syringe-label-v01-jun2018.pdf	Sequence 0061/1.14.1.1
LUT(1-3)-GP-US-5.3.5.4-HF studies-v00-May2018.pdf	0051/5.3.5.4- unassigned
stability summary-annex2-valassay-srt	Sequence 0042/3.2.p.8-stability
IR Response received 7/31	
Design history file	

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Is the syringe part of a kit?

The following information is from the combination product document in 0042/3.2.r.

As commented above, Lutrate Depot is an extended release formulation consisting on lyophilized microspheres, intended for intramuscular injection. Before being administered to the patient, the product should be reconstituted in 2 mL of Mannitol 0.8% solution. The method of administration should guarantee the injection

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CHAPTER VII: BIOPHARMACEUTICS

Application: Resubmission of NDA 205054-ORIG-1 for 22.5 mg dated 2/28/2018 (SDN-46) (b) (4)

Drug Product Name/Strength: Lutrate Depot® (leuprolide acetate) (b) (4) 22.5 mg
Route of Administration: Intramuscular Injection
Applicant Name: GP Pharm, SA

Biopharmaceutics ReviewTeam:
Primary Reviewer: Parnali Chatterjee, Ph.D. Date: 08/16/2018
Secondary Reviewer: Banu Zolnik, Ph.D. Date: 08/16/2018
Tertiary Reviewer: Angelica Dorantes, Ph.D. Date: 08/16/2018

REVIEW SUMMARY:

Background: NDA 205054-ORIG-1 (b) (4) Complete Response Action on 05/29/2015, due to Clinical and Drug Product Quality deficiencies identified in the application. (b) (4)

The Applicant conducted (b) (4) pivotal Phase III safety and efficacy studies (b) (4) GP/C/05/PRO study with 22.5 mg administered at 84-days (3-month) interval in patients with prostate cancer to support the approval of their application. (b) (4) studies evaluated the pharmacokinetic and pharmacodynamics of leuprolide.

Review: This Biopharmaceutics review evaluated **1)** proposed accelerated in vitro release methods and acceptance criteria for the 22.5 mg (b) (4) and **2)** the need for (b) (4) (b) (4) manufacturing process and site changes throughout product's development, (b) (4) (b) (4) between the proposed drug product and Listed Drug products.

- ***In Vitro Drug Release Method and Acceptance Criteria***

Lutrate Depot® (leuprolide acetate), 22.5 mg: The proposed accelerated in vitro drug release method and acceptance criteria for the 22.5 mg strength drug product are acceptable on an **interim basis** as described in Table 1 below.

TABLE 1. Accelerated In Vitro Release Method for Lutrate Depot® 22.5 mg

Parameters	In-Tube Method
Apparatus/Speed	The content of the vials transferred to **propylene tubes**
Media/Volume	Hydrolysis buffer (10 mM citric acid buffer, pH 4) /30 mL
Bath temperature	60.0±0.5° C
Sampling Time Points/Sampling Method	4 hours: Supernatant Day 1: Pellets Day 4: Pellets It should be noted sample analysis was done on the supernatant (i.e. released drug) at 4-hour time point, and on Day 1 and Day 4, reported drug release value was based on back-calculation on what is remaining in the microspheres (referred as pellets) by collecting the pellets and solubilizing the remaining polymer in IPA/H_20 solution.
Analytical Method	HPLC/UV at 220 nm
Acceptance Criteria	
Time	Percent (%) Leuprolide Released
4 hours Day 1 Day 4	(b) (4)

Although the proposed accelerated method and acceptance criteria are acceptable on an interim basis, there were several concerns regarding the method's sample preparation and methodology procedures. Therefore, the Applicant was requested to provide additional information/data

(b) (4)

(b) (4)

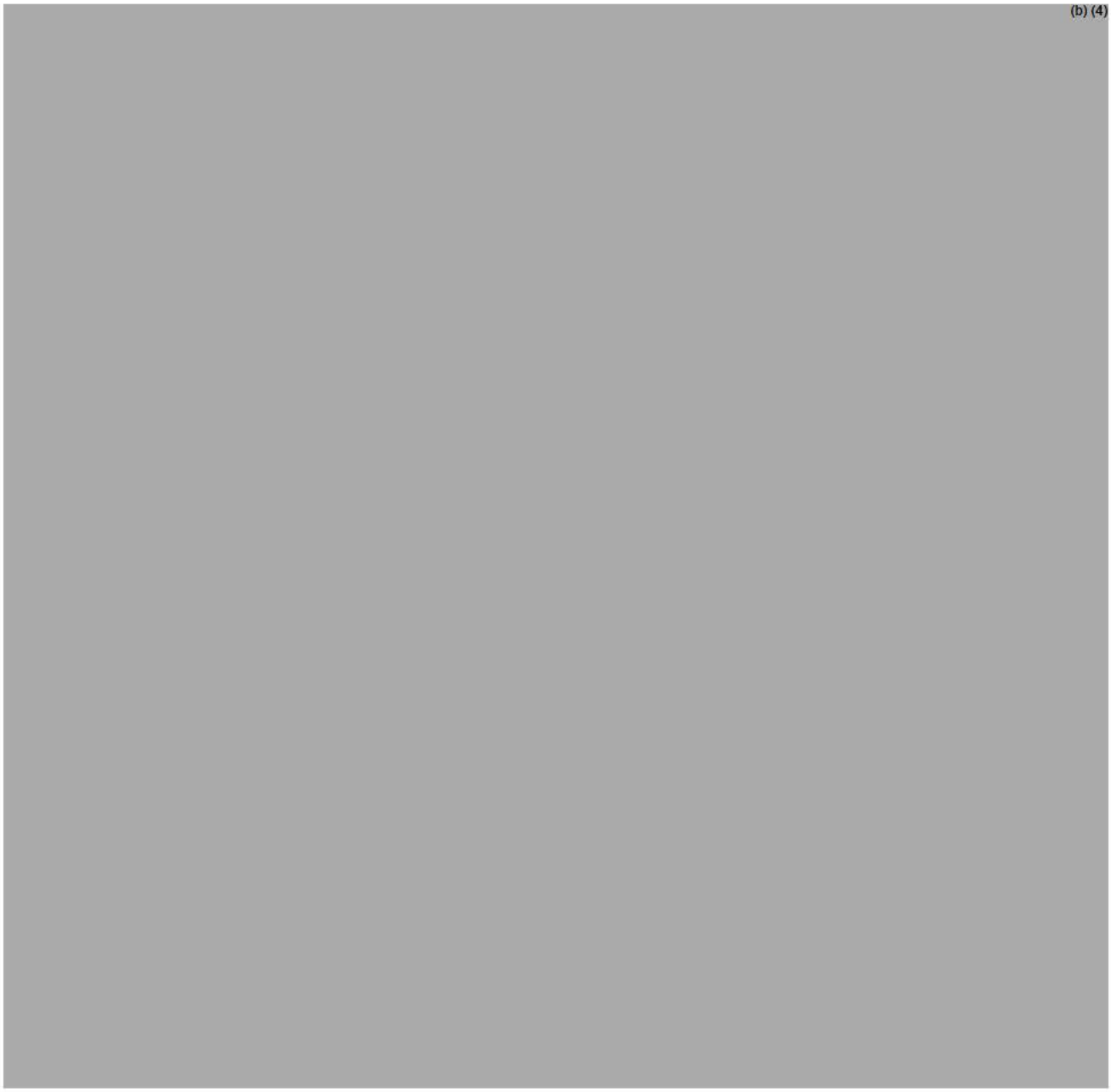
Proposed and Listed Drug Products: This application is a 505(b)(2) NDA submission partly relying on the FDA's previous nonclinical toxicology findings from approved (b) (4)

(b) (4) NDA 020517 for Lupron Depot®, (b) (4) 22 mg strengths, (b) (4) and published literature. For bridging information refer to Pharmacology and Toxicology Review in DARRTS by Drs. E. Zahalka, T. Palmy, and J. Leighton dated 04/25/2015.

REVIEW RECOMMENDATION for NDA 205054-ORIG-1 for 22.5 mg

Based on the review of the overall in vitro drug release information, the proposed accelerated in vitro release method and acceptance criteria for the 22.5 mg strength are acceptable on **an interim**

(b) (4)



(b) (4)

SIGNATURES

Primary Reviewer:
Parnali Chatterjee, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

Secondary Reviewer:
Banu Zolnik, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

Tertiary Reviewer:
Angelica Dorantes, Ph.D.
Branch Chief
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

BIOPHARMACEUTICS ASSESSMENT

1. SUBMISSIONS REVIEWED

Documents	Date Received
SDN 41 - Resubmission/Incomplete	08/22/2017
SDN 46 - Resubmission (b) (4) NDA ORG 1 (b) (4)	02/28/2018
SDN 70 - Response to Information Request Comment	07/18/2018

2. BACKGROUND

GP Pharm, SA is seeking approval for Lutrate Depot® (leuprolide acetate (b) (4) 22.5 mg strengths to be administered by intramuscular injection to patients (b) (4) (b) (4) quarterly (Lutrate Depot®, 22.5 mg) for palliative treatment of patients with advanced prostate cancer *via* the 505 (b) (2) regulatory path.

Lutrate Depot® (leuprolide acetate (b) (4) 22.5 mg strengths are extended-release suspensions that are supplied as freeze-dried powders to be reconstituted with sterile 0.8% mannitol as diluent supplied in prefilled syringe for intramuscular injection. (b) (4) (b) (4) (b) (4) 22 mg strength, the Applicant identified NDA 20517 for Lupron Depot®, 22 mg strength as the Listed Drug.

NDA 205054 for Lutrate Depot® (leuprolide acetate) (b) (4) 22.5 mg strengths for intramuscular injection was originally submitted for regulatory approval on July 31, 2014. The Application received a Complete Response Letter (CRL, **Appendix I**) on 05/29/2015 due to number of Clinical and Drug Product Quality deficiencies identified in the application.

In response to the deficiencies listed in the CRL, the Applicant updated the Drug Product Quality sections in the eCTD and resubmitted the NDA 205054 on 08/22/2017, which was subsequently found to be incomplete because all the manufacturing sites were not ready for inspection on the submission date. The Applicant resubmitted the NDA 205054 on 02/28/2018. The information provided in the eCTD 0037 SDN 41 Resubmission/Incomplete, eCTD 0042 SDN 46 Resubmission (b) (4) and eCTD 0066 SDN 70 Response to Information Request Comment was assessed in this review.

3. DRUG SUBSTANCE:

The drug substance is white to off-white amorphous powder and highly hygroscopic. Leuprolide is a synthetic analog of human luteinizing hormone-releasing factor that is composed of a non-glycosylated polypeptide chain containing nine amino acids.

Solubility: The drug substance is a synthetic polypeptide that is composed of nine amino acids. The Applicant noted that the drug substance is freely soluble in water with solubility approaching 160 mg/ml.

Permeability: Per the Applicant, the synthetic nonapeptide is completely inactivated by proteolytic enzymes in the gastrointestinal tract. Therefore, the drug substance is not orally active.

4. DRUG PRODUCT:

The Applicant developed two extended-release Lutrate Depot® (leuprolide acetate) drug products as freeze-dried powder for suspension in a vial containing (b) (4) 22.5 mg strength microspheres of leuprolide acetate to be reconstituted with sterile diluent.

Each vial is packaged along with a 20G syringe assembly that is prefilled with 0.8% mannitol as reconstitution diluent along with a sterile transfer device (MIXJECT®) for administration of the drug products, intramuscularly.

(b) (4)

Lutrate Depot® (leuprolide acetate), 22.5 mg drug product is encapsulated in microspheres of poly(D,L-lactide) (PLA) and TEC that releases leuprolide over three-month period (approximately 84

lide

(b) (4) (b) (4) (b) (4) **2b,**

(b) (4)

Table 2b. Qualitative and Quantitative Composition of Lutrate Depot® (leuprolide acetate), 22.5 mg Strength

INGREDIENT	QUANTITY FINISHED DOSAGE FORM		QUANTITY MANUFACTURING BATCH FORMULA			FUNCTION	REFERENCE TO STANDARDS
	PER DOSE	PER VIAL	PER	PER	PER		
Active Ingredient							
Leuprolide Acetate[7]	22.5 mg	(b) (4)				(b) (4)	USP*
Excipients							
PLA[7]	188.4 mg						In - House
Triethyl citrate (b) (4)	10.4 mg						NF*
	---						NF*
	---						NF*
	---						In - House
	---						NF*
	88.4 mg						USP*
	25.0 mg						NF*
Polysorbate 80	3.8 mg						NF*
Water for injections	--						USP*

5. *PROPOSED IN VITR*

a) Accelerated In Vitro Drug Release Method for 22.5 mg Strength:

The accelerated in vitro drug release method was found acceptable for batch release and stability testing of the 22.5 mg strength drug product during the original NDA review cycle, as described below (see **Table 3**).

However, upon further evaluation of this method, several concerns regarding the sample preparation and testing methodology were identified for the in vitro drug release method and acceptance criteria of the 22.5 mg strength. Therefore, the proposed accelerated method and acceptance criteria are acceptable only on **an interim basis** for release and on stability. The Applicant is being requested to provide additional information/data and submit their proposal for the final in vitro drug release method and acceptance criteria under a Post-Marketing Commitment (for specifics refer to PMC document # 3463-2). The Biopharmaceutics comments/request for information listed in the PMC commitment conveyed to the Applicant in an Email correspondence dated 08/13/2018, will be addressed by the Applicant at a future time under a Prior Approval Supplement.

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APPENDIX II

DR. SANDRA SUAREZ-SHARP'S BIOPHARMACEUTICS REVIEW FOR NDA 205054:

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205054	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Submission Date:	Jul 31, 2014		
Division:	DOP1	**Branch Chief (acting):** Angelica Dorantes, Ph.D.	
Applicant:	GP Pharm, S.A.	**Acting Division Director:** Paul Seo, Ph.D.	
Trade Name:	(b) (4) Lutrate Depot 22.5 mg	**Date Assigned:**	Aug 20, 2014
Generic Name:	Leuprolide acetate	**Date of Review:**	April 13, 2015
Indication:	Use in the palliative treatment of advanced prostate cancer	**PRIMARY REVIEW DUE DATE:** April 20, 2015	
Dosage form/ strengths:	Injectable Suspension, (b) (4) 22.5 mg	**Type of Submission:** 505 (b) (2)	
Route of Administration:	Intramuscular		

SUMMARY OF BIOPHARMACEUTICS FINDINGS

GP-Pharm S.A is seeking approval of (b) (4) sustained release (b) (4) leuprolide (Lutrate Depot) proposed for the treatment of prostate cancer. The products (suspension) are intended to be administered intramuscular (i.m.) to the patient (b) (4) in a three month (Leuprolide Depot 22.5 mg) basis. This 505 (b)(2) application makes reference to Lupron® Depot and Eligard® on their previous established non-clinical and safety findings.

The Applicant conducted the clinical trials with target patients (prostate cancer) to support the efficacy and safety of (b) (4) Lutrate. (b) (4) (b) (4) The submission also included other PK/PD studies (e.g., population PK and multiple dose PK studies). All these clinical pharmacology studies including PD information are being reviewed by the Clinical Pharmacology team at OCP.

The biopharmaceutics review is focused on the evaluation and acceptability of:

1. The data provided to support the in vitro drug release method and acceptance criteria
2. (b) (4) VIVCs (b) (4) for the 22.5 mg strengths.
3. The data supporting appropriate bridging throughout the phases of product development

1. In Vitro Release Method and Acceptance Criteria

(b) (4)

1

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APPENDIX V

Biopharmaceutics Post-Marketing Commitment Comments Conveyed to the Applicant on 08/13/2018

The proposed accelerated in vitro release method B and acceptance criteria for the 22.5 mg strength are acceptable on **an interim basis** for release and on stability. The following comments/request for information need to be addressed in the Post-Marketing Commitment (PMC).

a) (b) (4) proposed for the in vitro drug release testing of leuprolide for your drug product may not be optimal. USP Apparatus IV or dialysis bags may be more amenable for the in vitro drug release testing of your product than the proposed (b) (4) We consider that you have not adequately justified the reasons for why you selected (b) (4) (b) (4) over dialysis membrane for the proposed accelerated in vitro drug release method. Provide a justification with supportive data.

b) It is noted that a relationship should be established between the "accelerated" and "real-time" drug release methods. We recommend that you collect samples at frequent sampling time-points for accelerated and "real-time" testing. Provide complete release profile data (individual, mean, SD, profiles) for both methods.

c) The calculation for cumulative percent (%) leuprolide acetate release is based on the amount of leuprolide released in the supernatant for early timepoints and based on the retained drug in the pellets for the remaining time points for both "real-time" and accelerated release method. It is recommended that first you determine the mass balance of leuprolide released in the supernatant and retained in the pellets by measuring the amount of drug on the same samples, then select the most appropriate sampling method i.e., supernatant *vs*. amount remaining in the microspheres by both methods. Provide in vitro leuprolide release data from both the supernatant and pellets at frequent sampling time-points.

d) From the information provided in the submission, we could not determine if the pH of the proposed in vitro release medium is maintained throughout the course of in vitro release testing. Provide pH data for the release medium throughout the in vitro release testing time-frame.

e) It is stated in the method description report that three vials of Lutrate Depot are combined, and then grinded and homogenized prior to testing. We recommend that only one vial of Lutrate Depot be used without any alterations on the sample for testing.

f) Once the in vitro drug release method for Lutrate Depot, 22.5 mg is deemed acceptable by FDA as the final method, collect in vitro drug release data from a minimum of six commercial batches using the new method and provide in the final PMC-report your proposal for the acceptance criteria of your product, which should be based on the complete drug release profile data generated using the final drug release method.

Parnali Chatterjee

Digitally signed by Parnali Chatterjee
Date: 8/16/2018 03:07:54PM
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Banu Zolnik

Digitally signed by Banu Zolnik
Date: 8/16/2018 03:56:03PM
GUID: 508da7270002a568e175a2c0dd90f334

Angelica Dorantes

Digitally signed by Angelica Dorantes
Date: 8/16/2018 04:51:54PM
GUID: 502d0913000029d59f1c87e0a380c7f7

OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

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Date	August 7, 2018
To	Kristine Leahy Kristine.Leahy@fda.hhs.gov OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI 240-402-5834
Requesting Center/Office	*CDER/OPQ*
OND Review Division	*N/A*
From	Jacqueline Gertz CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Carolyn Dorgan, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # NDA205054 ICCR # 2018-02992 ICC# 1800459
Final Recommendation	*Recommendation Date:* *Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, Section 12.2*

Digital Signature Concurrence Table	
Reviewer	Jacqueline Gertz -S Digitally signed by Jacqueline Gertz -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001948760, cn=Jacqueline Gertz -S Date: 2018.08.14 15:04:27 -04'00'
Team Lead	Carolyn C. Dorgan -S Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2018.08.14 15:19:26 -04'00'
Branch Chief	Geeta K. Pamidimukkala -S 2018.08.14 15:21:35 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	2018-02992
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=3279
ICC tracking # (Lead)	1800459
Submission Number	NDA 205054/Original -1 = 22.5 mg formulation (Approvable) (b) (4) These NDA's were submitted together and we split in 8/2018 at the end of the review cycle
Sponsor	GP Pharma SA
Drug/Biologic	Leuprolide Acetate
Indications for Use	Prostate Cancer
Device Constituent	Syringe and reconstitution assistant
Related Files	ICCR2017-01639 ICCR2018-02542 ICCR2017-01722 ICC1400553 - compliance ICC1800227 - compliance ICC1700747 - compliance

Table 2. Review Team		
Were other disciplines consulted?	☐ **Yes**	☒ **No**

Table 3. Important Dates	
Interim Due Dates	**Due Date**
Primary Review	August 1, 2018
PDUFA/GDUFA Due Date	

TABLE OF CONTENTS

Update TOC

2. PURPOSE/BACKGROUND

2.1. Scope

GP Pharma SA is requesting approval of the Leuprolide Depot injection. The device constituent of the combination product is a syringe filled with diluent and a reconstitution assistant

CDER has requested the following consult for review of the device constituent of the combination product on 05/30/2018:

Review the device constituents of the combination product.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors
- Sterility of the device constituent

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

CDRH has interacted previously regarding compliance issues under the following ICC numbers:

- ICC1400553
- ICC1800227
- ICC1700747

The NDA was originally submitted July 31, 2014 and received a complete response letter on May 29, 2015.

2.2.1. Related Files

Related compliance consults:

- ICC1400553
- ICC1800227
- ICC1700747

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use
Leuprolide Acetate	palliative treatment of advanced prostate cancer
Syringe with reconstitution assistant Mixject - K963583	Reconstitute drug product and drug delivery
Route of administration	Intramuscular injection

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
lut-1-3-a-gp-us-comb-prod-report-v02-rs-feb2018	Sequence 0042/3.2.r – combination product
lut-1-3-gp-us-cover-v42-rs-s0042-feb2018	Sequence 0042/1.2 cover letter
inner-packaging-syringe-label-v01-jun2018.pdf	Sequence 0061/1.14.1.1
LUT(1-3)-GP-US-5.3.5.4-HF studies-v00-May2018.pdf	0051/5.3.5.4- unassigned
stability summary-annex2-valassay-srt	Sequence 0042/3.2.p.8-stability
IR Response received 7/31	
Design history file	

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Is the syringe part of a kit?

The following information is from the combination product document in 0042/3.2.r.

As commented above, Lutrate Depot is an extended release formulation consisting on lyophilized microspheres, intended for intramuscular injection. Before being administered to the patient, the product should be reconstituted in 2 mL of Mannitol 0.8% solution. The method of administration should guarantee the injection

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/s/

KRISTINE F LEAHY
08/14/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date:	
To:	ICCR Lead-Center Contact, Office, Location, E-mail:
CC:	Office of Combination Product at: combination@fda.gov Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Name, Office, E-Mail: Kristine.Leahy@fda.hhs.gov
Through:	Nazia Rahman, /OC, CDRH, WO 66, Rm 3458, E-mail: Combination Product Team Lead, DMQ/OC, CDRH, WO 66, Rm 3458, E-mail: Nazia.Rahman@fda.hhs.gov
From:	Latoya Oliver-Powell, ASDB/DMQ/OC, CDRH, WO 66, Rm 3458, E-mail:Nazia.Rahman@fda.hhs.gov
Applicant/Licensure:	GP PHARM, S.A. Polígon Industrial Els Vinyets - Els Fogars, Sector 2Carretera Comarcal C-244, Km. 22 Sant Quintí de Mediona, Barcelona, SPAIN 08777 FEI: 3008345811
Submission (Type & Number):	NDA 205054/Original -1 = 22.5 mg formulation (b) (4) [redacted]
Combination Product Name:	Leuprolide acetate
Combination Product Intended Use:	Palliative treatment of advanced prostate cancer
Device Constituent (Type):	Pre-filled syringe- Injectable
CTS ICCR Number:	ICC1800227
Sharepoint ICCR Number:	ICCR2018-02542
ICCR Instruction (ICCR Form):	Site Inspection Review, 21 CFR 820 Requirements Review
Pre-Approval Facility Inspection:	**No** **Post Approval Inspection Recommended**
CDRH/OC Recommendation:	**Approvable; Post Approval Inspection Recommended**

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205054 to identify manufacturing sites needing inspections and to review the 21 CFR 820 requirements of the combination product.

Sites Requiring Inspections

Post approval device inspection recommended:

The following site is recommended for a post approval device inspection.

GP PHARM, S.A.
Polígon Industrial Els Vinyets - Els Fogars, Sector 2
Carretera Comarcal C-244, Km. 22
Sant Quintí de Mediona, Barcelona, SPAIN 08777

FEI: 3008345811

Activities performed at site: Leuprolide vial manufacture (b) (4) Mannitol 0.8% syringe manufacture; Control (release and stability) of Leuprolide vial and Mannitol 0.8% syringe; Primary &Secondary Packaging; Product Release; Warehouse for Product storage; Excipient testing and release.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 205054 (including injectable strength (b) (4) 22.5 mg) and has the following recommendations:

CDRH notes that CDER has made the decision to approve NDA 205054/Original -1 = 22.5 mg formulation, (b) (4) (b) (4) With that, CDRH has determined that NDA 205054 is approvable from the perspective of the Medical Device Regulations.

CDRH recommends that compliance to the 21 CFR 820 requirements for management controls, design controls, CAPA, and purchasing controls be verified during a post-approval inspection. CDRH also recommends a review of the final validation data collected on the final combination product post-approval.

Latoya Oliver-powell -S

Digitally signed by Latoya Oliver-powell -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000354592, cn=Latoya Oliver-powell -S
Date: 2018.08.10 12:58:10 -04'00'

Latoya Oliver-Powell

Nazia Rahman -S
2018.08.10 11:32:37 -04'00'

Nazia Rahman

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/s/

KRISTINE F LEAHY
08/14/2018

LABELING

NDA 205054

R Regional Information

1.14 Labeling

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: N/A Established Name: leuprolide acetate for depot suspension	Per recommendation of USP <1121>, the established name should be **leuprolide extended release injectable suspension**. The LD "Lupron Depot" established name is "leuprolide acetate for depot suspension". Therefore, the Lupron depot and Lutrate depot labels are recommended to be changed at the same time to avoid confusion among practitioners. The LNC is in the process of writing a guidance on this subject.
Dosage form, route of administration	Dosage: 1) Injection Route: Intramuscular	Satisfactory
Controlled drug substance symbol (if applicable)	None	N/A ***
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	(b) (4) 22.5 mg injection in a kit with a vial, a prefilled syringe and a MIXJECT transfer device.	Satisfactory

(b) (4)

(b) "Full Prescribing Information" Section
3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

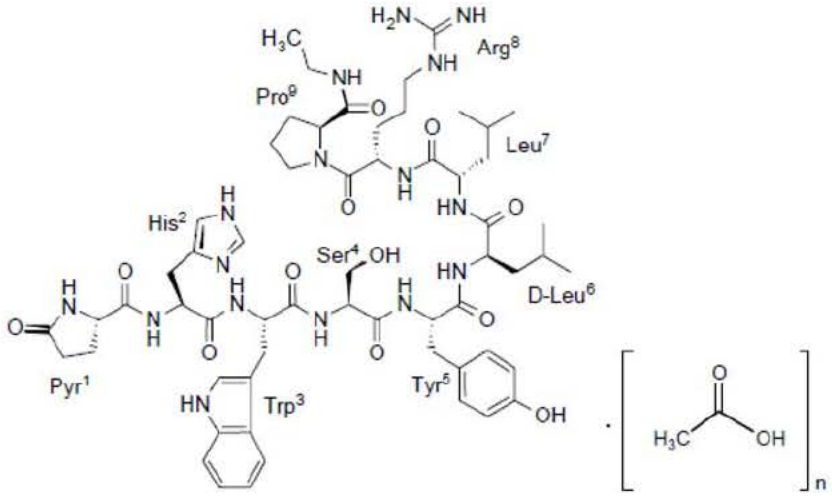
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Not provided	Include:" sterile and single dose". Satisfactory after revision.
Strengths: in metric system	LUTRATE DEPOT (b) (4) (b) (4) 22.5 mg for 3-month administration are each supplied as a kit with a vial, a syringe and a MIXJECT transfer device.	Satisfactory after revision
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Sterile is not mentioned, single-dose not mentioned. Satisfactory after revision

Reviewer's Assessment: The applicant was requested to revise the statement from: "LUTRATE DEPOT (b) (4) 22.5 mg for 3-month administration (b) (4) (b) (4) 22.5 mg for 3-month administration are each supplied as a kit with a vial, a syringe and a MIXJECT transfer device for sterile single dose application". (b) (4) (b) (4) the applicant revised the Dosage forms and strengths as follows: "For Injection: 22.5 mg of leuprolide acetate for 3-month administration as lyophilized microspheres in a single dose vial as a kit with a prefilled syringe containing 2 mL 0.8% mannitol solution and a MIXJECT transfer device for a single dose injection". The revised statement is satisfactory.

#11: Description (21CFR 201.57(c)(12))

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:

Replace the structure on the label with stereochemistry (added to the PI)



n=1 or 2

[redacted]

(b) (4)

[redacted]

(b) (4)

LUTRATE DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration is available in a vial containing sterile lyophilized microspheres together with the corresponding reconstitution diluent in a pre-filled syringe. When mixed together, become a suspension intended as an intramuscular injection to be given **ONCE EVERY 12 WEEKS** as a single dose.

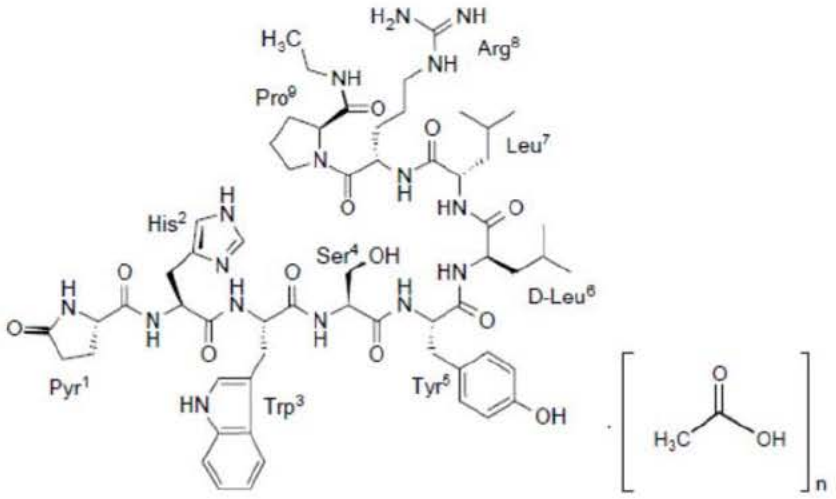
Each vial of LUTRATE DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration delivers leuprolide acetate (22.5 mg), polylactic acid (PLA) (188.4 mg), triethylcitrate (TEC) (10.4 mg), polysorbate 80 (3.8 mg), mannitol (88.4 mg) and carmellose sodium (25 mg). The prefilled syringe containing the reconstitution diluent (2 mL) contains mannitol (16 mg), water

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: Lutrate Depot Established name: leuprolide acetate for depot suspension	Satisfactory Not satisfactory per USP/FDA salt nomenclature policy. However, it is consistent with Lupron Depot established name (see the Reviewer's Assessment of "Highlights" Section).
Dosage form and route of administration	Injection, intramuscular	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	Strength on the basis of leuprolide acetate. Salt equivalence statement not included	Not satisfactory. However, consistent with Lupron Depot label (see the Reviewer's Assessment of "Highlights" Section).
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See the text above under description section	Satisfactory
Statement of being sterile (if applicable)	No mention	The revised statement is satisfactory
Pharmacological/ therapeutic class	Analog of GnRH	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Solubility added	Satisfactory.

Reviewer's Assessment: The yellow highlighted section above is added to the PI for

(b) (4)



Where: n=1 or 2

Leuprolide acetate has a molecular weight of 1209.41 as free base". Leuprolide is freely soluble in water.

LUTRATE DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration is available in a vial containing white to off white sterile lyophilized microspheres together with the corresponding sterile reconstitution diluent in a pre-filled syringe. When LUTRATE DEPOT and the diluent are mixed together they become a suspension intended as an intramuscular injection to be given **ONCE EVERY 12 WEEKS** as a single dose.

Each vial of LUTRATE DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration delivers leuprolide acetate (22.5 mg), polylactic acid (188.4 mg), triethylcitrate (10.4 mg), polysorbate 80 (3.8 mg), mannitol (88.4 mg) and carmellose sodium (25 mg). The prefilled syringe containing the clear reconstitution diluent (2 mL) contains mannitol (16 mg), water for injections, and sodium hydroxide and hydrochloric acid to control pH.

Leuprolide acetate for depot suspension is an extended release sterile, single dose injection in suspension form for intramuscular administration.

Reviewer's Assessment: The revised "Description" section is satisfactory.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17)) before revision

Lutrate Depot is supplied as a kit consisting of a Lutrate Mixjet single dose delivery system consisting of a vial with a flip-off seal containing sterile lyophilized leuprolide acetate microspheres incorporated into a biodegradable polymer, a Mixject vial adapter containing the needle, and a pre-filled syringe containing sterile mannitol injection, 2 ml, pH 4.5-7.0.

(b) (4)

Lutrate Depot 22.5 mg- NDC 69112-002-02

Store at 25° C (77°F) excursions permitted (b) (4) 30°C (b) (4) 36°F)

Handling and Disposal: None included.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Strengths provided but does not comply with the USP salt nomenclature policy but corresponds to Lupron Depot	Satisfactory (see Reviewer's Assessment in "Highlights" section).
Available units (e.g., bottles of 100 tablets)	Single unit as a kit	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See the description above. NDC number is provided	NDC number provided. Satisfactory after revision (see Reviewer's Assessment below)
Special handling (e.g., protect from light, do not freeze)	None	Satisfactory
Storage conditions	Storage conditions are inaccurate it is recommended to be revised to correspond to USP controlled storage conditions.	Satisfactory after revision

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributor's name and address included: (b) (4) Manufactured For: (b) (4)	Satisfactory

Reviewer's Assessment: The reviewer recommends the following revisions to the "How Supplied" Section: 1) Change the statement from: "LUTRATE DEPOT is supplied as a LUTRATE MIXJECT single-dose delivery system consisting of a vial with a Flip-Off seal containing sterile lyophilized leuprolide acetate microspheres incorporated in a biodegradable polymer, a MIXJECT vial adapter containing the needle, and a pre-filled syringe containing sterile mannitol for injection, USP, 2 mL, pH 4.5 to 7.0" to " Lutrate Depot is supplied as a kit consisting of a Lutrate Mixjet single dose delivery system consisting of a vial with a flip-off seal containing sterile lyophilized leuprolide acetate microspheres incorporated into a biodegradable polymer, a Mixject vial adapter containing the needle, and a pre-filled syringe containing sterile mannitol injection, 2 ml, pH 4.5-7.0"; 2) Change the storage statement from: "Store at 25° C (77°F) excursions permitted to 2 – 30°C (35.6 – 86°F)" to "Store at controlled room temperature at 20°- 25° C (68°–77°F) excursions permitted between 15 ° and 30 ° C (59 ° and 86°F)".

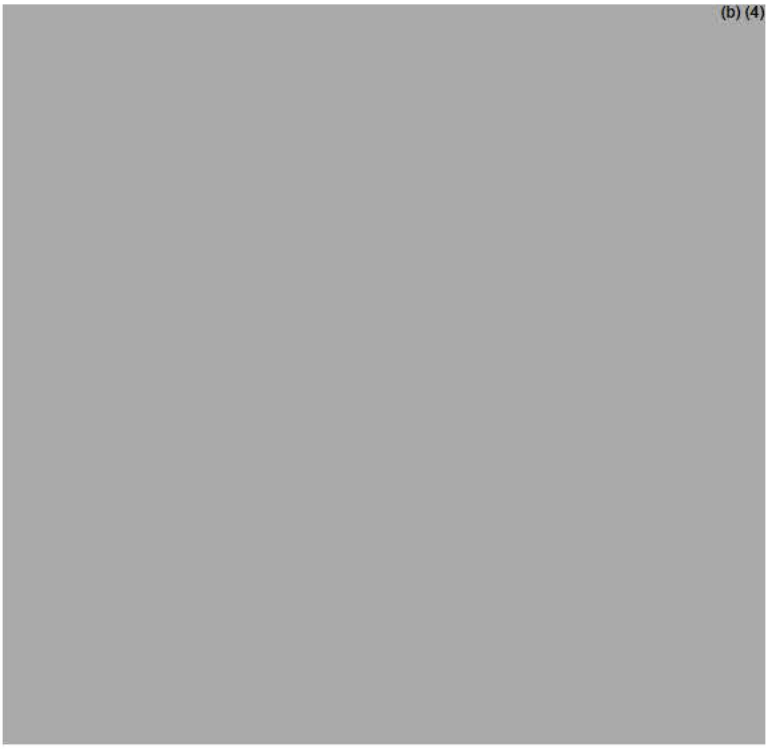
(b) (4)

clinical division's request. The revised How Supplied/Storage and Handling is provided below: "LUTRATE DEPOT (leuprolide acetate for depot suspension) is supplied as a kit consisting of a LUTRATE MIXJECT single-dose delivery system consisting of a vial with a Flip-Off seal containing sterile, white to off white lyophilized leuprolide acetate microspheres incorporated in a biodegradable polymer, a MIXJECT vial adapter containing the needle, and a pre-filled syringe containing clear sterile mannitol solution for injection, USP, 2 mL, pH 4.5 to 7.0.

LUTRATE DEPOT 22.5 mg – NDC 69112-002-02

Storage: Store at controlled room temperature at 20°-25°C (68°-77°F) [*see USP Controlled Room Temperature*]".

Reviewer's Assessment: The revised "How Supplied" section is satisfactory.



<u>Reviewer's Assessment:</u> The applicant was requested to revise the label as follows:

Sterile Mannitol Solution (0.8% w/v)

2 ml

Solvent for reconstitution of Lutrate Depot.

Prescription only

Lot #

Expiration date

Storage conditions.

el after revision:

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Lutrate Depot Established name: Not Satisfactory. Change from [redacted] (b) (4) to "Leuprolide acetate for depot suspension" to be consistent with PI	Satisfactory Satisfactory after revision
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per	None	Satisfactory
Storage (not required)	Storage condition not included	Satisfactory after revision
NDC number (per 21 CFR 201.2)	Included	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Reviewer's Assessment: Based on the review of the label applicant was requested to include the word "sterile" and storage conditions to the immediate container label. The applicant revised the label and the revised label (see below) is satisfactory to the reviewer. The revised 22.5 mg container label is provided below:


(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
"Keep out of reach of children" (optional for Rx, required for OTC)	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	Referenced	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name: Satisfactory	Satisfactory after revision

	Established name: Satisfactory	See immediate container label comment
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	None	Satisfactory.
Sterility Information (if applicable)	Included	Satisfactory
Storage Conditions	Not Satisfactory	Satisfactory after revision
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory

Reviewer's Assessment: Based on the review the applicant was requested to make the following changes to the carton (outer packaging) of 22.5 mg strength: 1) Change the storage statement from: (b) (4) to "Store at controlled room temperature at 20°- 25° C (68°–77°F) excursions permitted between 15° and 30°C (59° and 86°F)", since the primary long term stability studies for the drug product and the diluent were conducted at 25°C/60% RH; 2) Revise the statement from: "The vial contains: leuprolide acetate 22.5 mg, carmelose sodium 25 mg, mannitol 88.4 mg, poly lactic acid (b) (4) mg, polysorbate 80 3.8 mg, triethyl citrate (b) (4) mg" to "The vial

contains the following ingredients to deliver: leuprolide acetate 22.5 mg, carmelose sodium 25 mg, mannitol 88.4 mg, polylactic acid 188.4 mg, polysorbate 80 3.8 mg, triethyl citrate 10.4 mg" to be consistent with Component/Composition table in Section P.1 of the submission and the Section 11 of the package insert". The applicant revised the outer packaging. The outer packaging label is satisfactory.

(b) (4)

(b) (4)

List of Deficiencies: None

Amit Mitra

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Thomas Oliver

Digitally signed by Thomas Oliver
Date: 8/08/2018 03:09:21PM
GUID: 508da71f00029ed4697700cee3d31ca0

U.S. FOOD & DRUG ADMINISTRATION

DATE: 26 October 2017

TO: NDA 205054

FROM: Neal J. Sweeney, Ph.D.
Quality Assessment Lead (acting)
CDER/OPQ/OPF/Division of Microbiology Assessment

THROUGH: Bryan S. Riley, Ph.D.
Branch Chief (acting)
CDER/OPQ/OPF/Division of Microbiology Assessment

CC: Janice Kim PharmD, MS
Regulatory Project Manager
CDER/OND/OHOP/DOPI

SUBJECT: Product Quality Microbiology review of NDA 205054 Resubmission (8/22/2017)

Background Information: A Complete Response Letter dated 5/29/2015 was issued for NDA 205054 Lutrate Depot® (leuprolide acetate) Injectable. However, Microbiology Review #1 (dated 4/27/2015) of NDA 205054 recommended approval.

The NDA was resubmitted 8/22/2017, and an Information Request (IR) requesting confirmation that drug product manufacturers are ready for inspection was subsequently issued 9/20/2017. The resulting 10/9/2017 IR response stated that (b) (4) (proposed in the original NDA submission) would not be manufacturing the Mannitol 0.8% pre-filled syringe diluent for Lutrate Depot® (leuprolide acetate) Injectable, and that GP Pharm would internalize the manufacturing (b) (4) sterilization processes within its own GP Pharm facility.

(b) (4) sterilization process validation information for Mannitol 0.8% pre-filled syringes manufactured at the GP Pharm was included in the original NDA or NDA resubmission, the following Product Quality Microbiology IR was issued on 10/5/17:

> "According to the October 2, 2017 additional information submitted regarding manufacturing facilities, GP Pharm will perform the (b) (4) sterilization process for the Mannitol 0.8% prefilled syringes. Please submit a complete (b) (4) sterilization process validation package for the Mannitol 0.8% prefilled syringes. Please refer to the 1994

M E M O R A N D U M

"Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" describing the information and data to be submitted in support of the efficacy of the (b) (4) sterilization process. Please respond to Microbiology comments by COB October 18, 2017."

In an October 9, 2017 e-mail correspondence from Mayte Vazquez (Director of Regulatory Affairs, GP Pharm) to Kristine Leahy (RBPM, CDER/OPQ/OPRO) the applicant explained that the newly proposed GP Pharm manufacturing/sterilization facility for the Mannitol 0.8% prefilled syringes has yet to receive the (b) (4) the prefilled syringes. Furthermore, the applicant stated that in an optimal scenario (b) (4) would be installed, qualified, and validation studies would be performed by late February 2018. As a partial response to the 10/5/2017 IR, the applicant proposed to submit an updated Module 3 containing a description of (b) (4) as well as the protocols describing the qualification and validation studies that will be conducted to confirm the suitability of the (b) (4) process. Additionally, the applicant requested that the FDA review timeline be extended by six months.

Reviewer Conclusion: The applicant's proposal for submitting sterilization process validation studies for the (b) (4) sterilization process is inadequate, as there would be insufficient time for FDA to review the corresponding data. In the optimal scenario, the data would be available late February 2018, while the PDUFA date is February 22, 2018.

INADEQUTE

The following Product Quality Microbiology deficiency should be included in the NDA 205054 Incomplete Response Letter:

According to the additional information submitted October 2, 2017 regarding manufacturing facilities, GP Pharm will perform the (b) (4) sterilization process for the Mannitol 0.8% prefilled syringes.

a. In your October 9, 2017 correspondence, you outlined a plan to initially submit a description of the Mannitol 0.8% syringe (b) (4) sterilization process and a description of the sterilization process validation studies that will eventually be performed once the (b) (4) has been received, installed, and qualified, and subsequently submit the corresponding sterilization process validation study data. However, based on the presented timeline for (b) (4) receipt, installation, qualification and (b) (4) validation, it does not appear that the Mannitol 0.8% prefilled syringe sterilization process validation study results would be available for review until late February 2018. Considering the February 22, 2018 PDUFA review goal date, there would be insufficient (if any) time to review the

(b) (4) sterilization process validation data. Therefore, the October 9, 2017 proposal is not acceptable.

b. Please submit a complete (b) (4) sterilization process validation package for the Mannitol 0.8% prefilled syringe manufacturing process at the proposed GP Pharm facility. Please refer to the 1994 "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" describing the information and data to be submitted in support of the efficacy of the (b) (4) sterilization process.

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/s/

NEAL J SWEENEY
10/27/2017

BRYAN S RILEY
10/27/2017
I concur.

NDA 205054

LUTRATE DEPOT
(Leuprolide Acetate) Injection

GP Pharm. S. P.

Li-Shan Hsieh
Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

CMC REVIEW OF NDA 205054
For the Division of Oncology Drug Products I
Office of Hematology and Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 205054

2. REVIEW #: 1

3. REVIEW DATE: 23-Apr-2015

4. REVIEWER: Li-Shan Hsieh, Ph. D.

5. PREVIOUS DOCUMENTS:

(b) (4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date
Original NDA Submission	000	31-Jul-2014
Amendment (BC) (Response to FDA 10/10/14 CMC IR)	012	21-Oct-2014
Amendment (Response to 10/10/14 CMC IR)	014	23-Dec-2014
Amendment (Response to 12/16/14 and 23-Dec-14CMC IR)	016	15-Jan-2015
Amendment (Response to 02/22/15 CMC IR)	017	06-Feb-2015

7. NAME & ADDRESS OF APPLICANT:

Name: GP PHARM, S.A.

Address: POLIGONO INDUSTRIAL ELS VINYETS-FOGARS, SECTOR 2
CRTA 244 KM 22Sant Quinti de MedionaBarcelona, SPAIN 08777
Tel: +34 938 192 210

Representative: Julia Valentine
ELC GROUP. 1500 Market Street, 12th floor, East Tower,
Philadelphia, PA 19102,

Telephone: 1-347-809-3434
juliav@elc-group.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lutrate Depot
b) Non-Proprietary Name: Leuprolide acetate
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY:

A synthetic nonapeptide luteinizing hormone releasing hormone (LHRH) analogue which induces down regulation of LHRH receptor and a post-receptor desensitisation, resulting in reversible biochemical castration

11. DOSAGE FORM: Lyophilized Powder

12. STRENGTH/POTENCY:

(b) (4)

• <LEUPROLIDE DEPOT> 22.5 mg: over a three month period.

13. ROUTE OF ADMINISTRATION: Intramuscular

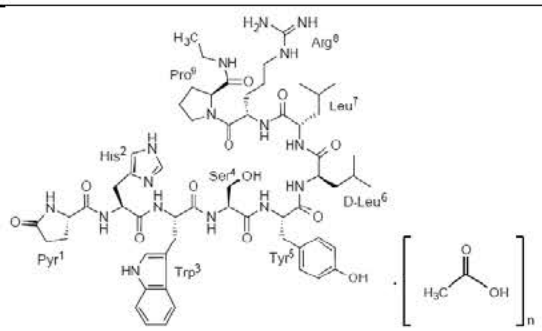
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

This nonapeptide has molecular formula $C_{59}H_{84}N_{16}O_{12}$ $(C_2H_4O_2)_n$ n=1 or 2 Molecular weight of 1209,42 a.m.u (as free base).	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	1	Adequate	06-Nov-2013	Reviewed by CDRH
	III			4	Adequate		Has been approved in (b) (4)
	II			1	Inadequate	23-Apr-2015	Reviewed by Li-Shan Hsieh
	IV			1	adequate	08-Aug-2014	Under DMF (b) (4) by Xavier Ysern
	IV			1	Adequate	16-Feb-2010	Reviewed by William M Adams
	III			1	Adequate	20-Feb-2015	Reviewed by Eric Edeeku
	III			4	Adequate		NDA contains the testing per USP <381> and <88>,
	III			1	Adequate	08-Nov-2014	Reviewed by CDRH for (b) (4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

(b) (4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Approval	4/27/2015	Elias A. Zahalk
Biopharm	Complete Response (CR)	4/21/2015	Sandra Suarez,
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA*	N/A		
EA	Categorical exclusion (see review)	10/25/2014	Li Shan Hsieh
Microbiology	Approval	4/24/2015	Neal Sweeney
CDRH	Approval is deferred until the time when a satisfactory preapproval inspection	3/25/2015	Bleta Vuniqi

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 205054

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is not recommended for approval from Chemistry, Manufacturing and Controls Perspective. In addition, the final recommendation of Office of Compliance is pending.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The drug substance is supplied [(b) (4)]

(2) Drug Product

<LEUPROLIDE DEPOT> [(b) (4)] 22.5 mg are prolonged-release suspensions for injection supplied as freeze-dried powder together with the corresponding reconstitution diluent. The formulations allow the release of the drug substance over a long period of time [(b) (4)] 3 month [(b) (4)]). In the formulations, the active substance, leuprolide acetate, is entrapped inside microspheres constituted by [(b) (4)] PLA for <LEUPROLIDE DEPOT> 22.5 mg), and triethyl citrate (TEC). These polymers are slowly biodegraded after i.m. administration, allowing the release of the active substance. Triethyl citrate [(b) (4)] of drug substance release.

The drug product is supplied with the corresponding reconstitution diluent (0.8% mannitol prefilled syringe), and a transfer device (MIXJECT) which is coupled to 20G needle and provided in a sterile blister.

The device allows direct reconstitution of the powder using the solvent contained in the prefilled syringe and the direct injection of the resulting suspension into the patient. The device is fitted on the vial to pierce the stopper, allows the entrance of the reconstitution diluents and the outflow of the suspension content into the syringe due to the device's two-way valve. With this process the stopper is only pierced once, and the vial, device, syringe and needle are kept coupled throughout injection process to ensure the sterility of the drug product.

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

Palliative treatment of locally advanced or metastatic prostate cancer.

C. Basis for Approvability or Not-Approval Recommendation

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Li-Shan Hsieh, Ph.D. Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Ali Al Hakim, Ph.D. Branch Chief, ONDQA

C. CC Block: entered electronically in DFS

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

/s/

LI SHAN HSIEH
04/30/2015

ALI H AL HAKIM
04/30/2015