CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211488Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

Approval *with Post-Marketing Commitment*

NDA *211488*
Assessment #2

Drug Product Name	Camcevi (Leuprolide mesylate)
Dosage Form	Injectable emulsion
Strength	42 mg
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Foresee Pharmaceuticals Co., Ltd.
US agent, if applicable	NDA Regulatory Development Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original submission 0001	03/28/2019	API, DP, OPMA, Bioph, Micro.
SN#0003	05/20/2019	Bioph
SN#0007	07/27/2020	API, DP, OPMA, Bioph, Micro.
SN#0009	09/21/2020	DP, OPMA. Bioph
SN#0013	12/18/2020	DP, Micro, Bioph
SN#0014	12/21/2020	Bioph
SN#0016	12/22/2020	OPMA, Bioph
SN#0017	12/22/2020	API, Bioph
SN#0019	01/08/2021	OPMA
SN#0021	01/28/2021	Bioph
SN#0023	02/22/2021	DP, OPMA, Bioph
SN#0025	03/30/2021	API, DP, Bioph
SN#0026	03/31/2021	DP, OPMA
SN#0027	04/09/2021	DP
SN#0030	04/19/2021	Bioph
SN#0031	04/20/2021	Bioph
SN#0033	04/27/2021	Bioph
SN#0034	04/27/2021	DP, Bioph
SN#0036	05/03/2021	DP, OPMA, Bioph
SN#0038	05/11/2021	OPMA
SN#0040	05/11/2021	Bioph
SN#0041	05/14/2021	Bioph

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Rohit Tiwari	Paresma Patel
Drug Product	Yang Nan	Anamitro Banerjee
Manufacturing	Steven Hertz	David Anderson
Microbiology	Bethanie Lee	Jesse Wells
Biopharmaceutics	Gerlie Gieser	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	
Laboratory (OTR)		
Environmental	Yang Nan	Anamitro Banerjee

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	4/22/2021	Reviewed by Rohit Tiwari
	III			Adequate	6/3/2020	*Refer to section 2.3.P.7 Container Closure System (CCS)*
	III			Adequate	07/12/2018	*Refer to section 2.3.P.7 CCS*
	III			Adequate	9/6/2019	*Refer to section 2.3.P.7 CCS*
	IV			Adequate	5/5/2021	*Refer to section 2.3.P.7 CCS*
	III			Adequate	5/5/2021	*Refer to section 2.3.P.7 CCS*
	III			Adequate	5/5/2021	*Refer to section 2.3.P.7 CCS*

[1] Adequate, Adequate with Additional Comments, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be assessed).

B. Other Documents: IND, RLD, RS, Approved NDA

Document	Application Number	Description
Syringe needle	510(k)# (b) (4)	The submission of 510K is reviewed by CDRH reviewer.

2. CONSULTS:

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH	Acceptable	Acceptable		Florencia Wilson
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The product quality review team recommends the NDA for Approval with a PMC (#3614-1). The CMC information and all manufacturing and controls facilities are deemed acceptable. The following comments should be included in the action letter:

CAMCEVI is grated the 24 months expiration date when stored at 2°C to 8°C (36°F to 46°F).

PMC 3614-1

Develop a separate, specific, complimentary method to determine the degradant at RRT [redacted] (b) (4) Submit a CBE-30 supplement to update the drug product specifications with the new method for RRT [redacted] (b) (4) In the supplement, provide a description of the new method as well as the validation data.

Final Report Submission

06/2022

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Proposed Indication(s) including Intended Patient Population	CAMCEVI is a gonadotropin-releasing hormone (GnRH) agonist indicated for the treatment of adult patients with advanced prostate cancer.
Duration of Treatment	Once every 24 weeks.
Maximum Daily Dose	The recommended dose of CAMCEVI is 42 mg administered subcutaneously once every 24 weeks.
Alternative Methods of Administration	*N/A*

Leuprolide is a gonadotropin releasing hormone (GnRH) agonist for the palliative treatment of advanced prostate cancer. Leuprolide is a synthetic nonapeptide analog of naturally occurring GnRH that inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. Foresee Pharmaceuticals resubmitted 505(b)(2) NDA for CAMCEVI (leuprolide mesylate injectable emulsion) after refuse to file (RTF) of its original submission dated Mar 28, 2019 based on the deficiencies from the CDRH review of the device. The applicant conducted a Phase 3 study to demonstrate the safety and efficacy of its proposed drug. The applicant will

also rely on the FDA's finding of nonclinical safety of the Listed Drug (NDA 19010) that was approved for marketing in 1985. The proposed product differs from the currently approved leuprolide products in the salt form of the drug substance (proposed drug is leuprolide mesylate vs the marketed leuprolide acetate). The strength of the proposed drug (42 mg of API) is the same as the marketed leuprolide drugs when calculated on free base basis. The proposed product is a depot formulation which releases leuprolide over a 6-month period after a single subcutaneous administration. Unlike currently marketed leuprolide products that require reconstitution and/or mixing prior to administration, the proposed product will be supplied as ready-to-use in a sterile, pre-filled syringe along with a sterile 18 gauge needle. The product quality review team found the CMC information in the NDA acceptable. The manufacturing and controls facilities are deemed acceptable based on Office of Pharmaceutical Manufacturing Assessment (OPMA) review recommendation.

B. Quality Assessment Overview

Drug Substance: *Adequate*

The applicant references DMF # (b) (4) for the entire chemistry manufacturing and control information of leuprolide mesylate drug substance. For more details, refer to DMF # (b) (4) and associated review in support of this NDA for full information regarding the manufacturing process, process parameters, in-process controls, characterization, impurities, analytical methods, method validations, and stability data. The applicant cited DMF# (b) (4) to justify acceptance criteria for individual specification tests and provided the batch analyses data for the drug substance batches from the DMF holder. All tests met their acceptance criteria. The applicant committed to retest the drug substance upon receipt as per the DMF holder's specification prior to the drug product manufacture. All the specified impurities and total impurities were found to be within their proposed limits. The primary packaging component is (b) (4)

The data provided in DMF supports the applicant's retest period of (b) (4) months when stored at (b) (4) °C.

Drug Product: *Adequate*

CAMCEVI leuprolide injectable emulsion is provided as a prefilled syringe for subcutaneous administration to deliver 42 mg leuprolide (equivalent to approximately 48 mg leuprolide acetate) in biodegradable polymer Poly(D,L-Lactide) (PLA) and solvent *N*-methylpyrrolidone (NMP). The target total delivered weight of drug product is (b) (4) mg. The pre-filled and capped syringe is co-packed with a sterile, capped needle and placed in secondary blister packaging consisting of a thermoformed tray and (b) (4) lid. The

blister is placed together with a non-sterile Point-Lok needle protection device and package leaflet in a cardboard carton.

(b) (4)

CAMCEVI specifications ensure adequate control of critical quality attributes of the drug product. The dose accuracy is controlled through (b) (4) . The batch analysis for six drug product batches, including two clinical batches and three registration batches, met the proposed regulatory specifications.

CAMCEVI is temperature and light sensitive. When stored at accelerated conditions (25°C and 60% RH), the drug product shows signs of degradation. The stability data generated at long-term storage condition (2 to 8 °C) from three registration batches do not show sign of degradation for 24 months. Therefore, the proposed 24 month shelf-life may be granted.

The current analytical method for the determination of impurities in the drug product by (b) (4) cannot resolve a degradant peak at RRT (b) (4) (D) (4) A PMC (#3614-1) has been proposed and agreed by the applicant to develop a separate, specific, complimentary method that is capable of resolving the peak at RRT (b) (4)

Labeling: *Adequate*
The following are the major issues that have been resolved during the review:

- Per USP salt and nomenclature policy, the proposed drug is labeled as 42 mg leuprolide that is equivalent to 48 mg of leuprolide mesylate. The strengths of all marketed drugs of leuprolide acetate are based on the salt form.

- Based on its physicochemical characterization, the proposed drug product establish name is leuprolide injectable emulsion. The currently marketed leuprolide drugs are named as leuprolide acetate for injectable suspension.

- Special handling includes 1). Allow the product to reach room temperature before using. 2). avoid applying heat directly to the site of Camcevi injection.

Special Product Quality Labeling Recommendation

No labeling issue was found.

Manufacturing: *Adequate*

The manufacturing process involves the following steps: (b) (4) All the facilities are acceptable. Both the combination product and drug substance facilities are approved based on the firm's inspection history and manufacturing experience. There are also no major GMP issues raised based on the review of the submitted Exhibit Batch Manufacturing Record. The Applicant also sufficiently responded to identified process deficiencies.

Biopharmaceutics: *Adequate*

The proposed *in vitro* drug release (IVR) method parameters and revised IVR acceptance criteria (as tabulated below) are deemed acceptable for the routine QC testing of LMIE at batch release and during shelf-life/stability testing. Based on the provided data, the proposed IVR method is considered sufficiently discriminating for changes/differences in critical quality attributes ((b) (4) and also has stability-indicating potential.

Overall, adequate *in vitro* and/or *in vivo* PK/PD/efficacy/safety data were submitted to establish the bridge between the pivotal Phase 3 clinical trial/primary (registration) stability lots and the process validation lots (which represent the proposed commercial drug product).

Microbiology: *Adequate*

CAMCEVI is manufactured by (b) (4). The microbiology review assessed sterility assurance of the drug product manufacturing and specifications for sterility and endotoxins. All the information are deemed adequate.

C. 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 parameters • Scale/equipments • Site	H	Refer to Product Quality Microbiology review	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M	Refer to Product Quality Microbiology Review	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L	Controlled via specs	Acceptable	Controls are in place
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Controlled via specs	Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	• Formulation • **Container closure** • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development	Acceptable	Absence is demonstrated through the leachable studies performed during development

***In vitro* release (ER)-Depot forming**	• Formulation • Process parameters • Scale/equipments • Site	H	Controlled via specs	Acceptable	The IVR method is considered sufficiently discriminating for the CQAs (b) (4)), and also has stability-indicating potential.
Appearance (Color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled via specs	Acceptable	Controls are in place

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Xiao Hong Chen May 17, 2021

Xiao Chen

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	211448
Assessment Cycle Number	1
Drug Product Name/ Strength	Leuprolide Mesylate Injectable Suspension (CAMCEVI), 50 mg
Route of Administration	Injection (SC)
Applicant Name	Forsee Pharmaceuticals
Therapeutic Classification/ OND Division	Oncology Products 1
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: Recommended

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 (1) ORIG-1	**03/28/2019**
0007 (7) ORIG-1 Resubmission	**7/27/2020**
IR response (email attachment, not in eCTD at time of review)	**11/16/2020**
IR response (email attachment, not in eCTD at time of review)	**12/1/2020**

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

Remarks: N/A

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- **DMF** (b) (4) **(adequate)**
- **DMF** (b) (4) **(adequate)**

- **DMF** [redacted] **(adequate)**

S DRUG SUBSTANCE

No review was conducted on the drug substance as the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of the drug product –** Sterile, off-white to pale yellow viscous and opalescent solution [redacted] contained in a 1 mL long-barrel colorless to pale-yellow plastic syringe closed with a gray elastomeric tip cap and a plunger.
- **Drug product composition –**
(Section 3.2.P.1 Description and Composition of Drug Product p.1)

Ingredient/Quality	Function	Theoretical Amount Delivered per Syringe (mg/syringe)	LMIS (% w/w)
Poly(D,L Lactide) (PLA), In-house	Biodegradable [redacted] polymer	[redacted]	[redacted]
N-methylpyrrolidone (NMP), NF/Ph.Eur/JP	Solvent		
Total quantity of PLA/NMP*	N/A		
Leuprolide base**	API	42.0**	[redacted]
Total ***	N/A	[redacted]	100.00

[redacted]

- **Description of container closure system –**
(Section 3.2.P.7 Container Closure System, 32p7 - resubmission, p.2)

Primary Package Component	Description	Manufacturer	DMF
Syringe barrel	[redacted]		
Tip cap			
Plunger stopper			
Plunger rod and backstop (no product contact)			
Needle			

Assessment: Adequate
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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Jesse Wells

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Bethanie Lee

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BIOPHARMACEUTICS

Product Background:

NDA: 211488

Drug Product Name / Strength: CAMCEVI® (leuprolide mesylate injectable emulsion/LMIE) containing the equivalent of **42 mg leuprolide free base** in a biodegradable poly(D, L-lactide) PLA polymer dissolved in a biocompatible solvent (N-methyl-2-pyrrolidone, NMP). (b) (4) .

Route of Administration: For subcutaneous injection (once every 24 weeks or ~ 6 months).

Proposed Indication: Palliative treatment of advanced prostate cancer

Applicant Name: Foresee Pharmaceuticals Co., Ltd.

Primary Reviewer: Gerlie Gieser, PhD.
Secondary Reviewer: Banu Zolnik, Ph.D.

EXECUTIVE SUMMARY*:*

Review Recommendation: APPROVAL

Review Summary:
Background
Leuprolide is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH). CAMCEVI® (leuprolide mesylate injectable emulsion/LMIE) is a long-acting injection (LAI) of leuprolide administered via subcutaneous injection once every 6 months. [Note that the Drug Product review team decided that the proposed LAI drug product should be categorized as an emulsion (as opposed to a suspension).] (b) (4) .

CAMCEVI® is supplied as a single dose kit containing a pre-filled, ready-to-use (1 mL) sterile syringe, a sterile 18-gauge needle, and a Point-Lok® needle protection device (for safe disposal of used syringe & needle). The pre-filled syringe contains the equivalent to 42 mg leuprolide free base (from approximately 48 mg leuprolide mesylate salt) in a biodegradable poly (D, L-lactide) (PLA) polymer formulation dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). CAMCEVI® should be stored under refrigeration (2–8°C), and is protected from light by storing in the original package until time of use. The labeling states: "Allow prefilled syringe to sit at room temperature for 30 minutes prior to subcutaneous injection. Do not freeze or shake."

The efficacy, safety, pharmacokinetics and pharmacodynamics of LMIE in advanced prostate cancer patients were evaluated in the pivotal Phase 3 clinical trial (FP01C-13-001).

Putative Mechanism of Extended Drug Release

Per the Applicant, upon subcutaneous injection of the LMIE, a solid drug delivery depot [i.e., an *in situ* implant] forms and the drug release process occurs over approximately 6 months. The drug release process (b) (4)

In Vitro Drug Release (IVR) Method and Acceptance Criteria

The proposed *in vitro* drug release (IVR) method parameters and revised IVR acceptance criteria (as tabulated below) are recommended to be approved for the routine QC testing of LMIE at batch release and during shelf-life/stability testing.

Apparatus	Shaking Speed	Medium/ Temperature	Volume	Sampling Times	Acceptance criteria
500 mL glass bottle with cap; Reciprocal shaking water bath	50 rpm	23.25 mM morpholino-ethanesulfonic acid (MES) buffer with 10 mM zinc acetate and 10% IPA at pH 6.00 ± 0.05; 60˚C	200 mL	For IVR profiling: 6, 22, 30, 46, 54, 70, 78, 94, 102 hours	6 h: NMT (b) (4)% **54 hours:** (b) (4)% 102 hours: NLT (b) (4)%

Allow the refrigerated LMIE to sit at room temperature for at least 30 minutes. The entire LMIE content of the pre-filled syringe (with 18G 5/8" needle and plunger attached) is introduced into the IVR medium as 6 droplets. The plunger rod is marked to enable transfer of LMIE sample as 6 equal portions. Drug quantification is accomplished by reversed-phase HPLC with UV detection at (b) (4) nm.

Based on the provided data, the proposed IVR method is considered sufficiently discriminating for changes/differences in critical quality attributes (b) (4) and also has stability-indicating potential.

Formulation/Drug Product Bridging

Overall, adequate *in vitro* and/or *in vivo* PK/PD/efficacy/safety data were submitted to establish the bridge between the pivotal Phase 3 clinical trial/primary (registration) stability lots and the supporting stability/process validation lots (which represent the proposed commercial drug product). Specifically, two of the 3 primary stability LMIE lots were evaluated in the pivotal Phase 3 clinical trials; the third primary stability lot was used in toxicology studies. The final proposed commercial drug product will have the same/similar "theoretical" batch formula, manufacturing process steps including

(b) (4) process type, and API & PLA suppliers as the pivotal clinical trial lots, but will be marketed with additional secondary packaging (blister) anticipated to improve long-term physicochemical stability. One of the two pivotal clinical trial lots was manufactured by the proposed commercial/process validation drug product manufacturer. Evidence of comparable *in vitro* drug release profile data between the pivotal clinical/primary stability and the process validation/supporting stability lots supported qualification of the proposed commercial (b) (4) site, and the proposed commercial PLA grade.

Of note, future commercial LMIE drug product lots will be manufactured using the proposed theoretical batch formula (b) (4) to provide the label claim of 42 mg leuprolide free base per pre-filled syringe]. Note also that the two pivotal Phase 3 clinical/primary stability lots were manufactured using (b) (4); the toxicology/primary stability lot, (b) (4) retest), whereas the three process validation lots were manufactured using API with an assay value of either (b) (4)%. Thus, to minimize commercial product composition variations from those LMIE formulations used in pivotal clinical trials, FDA recommended further tightening of the leuprolide mesylate peptide content acceptance range from "NLT (b) (4)%" to "(b) (4) %".

***This 505(b)(2) NDA relies for approval, in part, on the FDA's findings of PK, efficacy and safety for the Listed Drug (LD) product, LUPRON® (leuprolide *acetate* injectable *solution in multi-dose vial*) 1.0 mg/0.2 mL daily via subcutaneous injection (NDA 019010). Based on the 'in silico' relative bioavailability results of Study FSEE-CSC-100, as well as the pharmacokinetics, pharmacodynamic, efficacy & safety findings for the proposed drug product (leuprolide *mesylate* injectable *emulsion*/LMIE *in single-dose/use pre-filled syringe*) in the pivotal Phase 3 clinical trial (FP01C-13-001), the Clinical Pharmacology and the Medical Review teams determined that the scientific reliance to the clinical and non-clinical safety information for the Listed Drug product is justified.

In Vitro Drug Release (IVR) in the Presence of Extrinsic Factors (Applied Pressure or Applied Heat)

The impact of applied pressure on *in vitro* or *in vivo* drug release of LMIE was not formally investigated. However, it is noted that *the proposed labeling already warns against injecting LMIE in tissues or locations that can be rubbed or compressed (i.e., with a belt or clothing waistband).*

Based on the results of a small 5-month *in vitro* drug release study, intermittent applications of higher heat (40℃) to the medium for 1 to 2 weeks consistently resulted in approximately NMT (b) (4)% higher cumulative drug release over the duration of the heating period, as compared to when the medium was maintained at 37°C. The clinical relevance of such increases in IVR with heat application is unclear, and the impact of applied heat on *in vivo* drug release was not investigated. *Thus, per FDA*

recommendation, a labeling statement was added which recommends that directly applied heat to the site of LMIE injection be avoided.

List of Submissions reviewed:

SN-1, 3/28/2019 (Original NDA)
SN-3, 5/20/2019 (Response to Early Quality Information Request/IR)
SN-7, 7/27/2020 (NDA Resubmission)
SN-9, 9/21/2020 (Response to DMEPA Information Request – fill & deliverable volumes/weights)
SN-13, 12/18/2020 (Responses to Quality/Drug Product (DP) IRs dated 10/16/20, 11/13/20, 11/20/20 – (b) (4))
SN-14, 12/21/2020 (Response to Quality/Biopharmaceutics IR dated 10/26/2020
SN-16, 12/22/2020 (Response to Quality/Biopharmaceutics IR dated 12/1/2020)
SN-17, 12/22/2020 (Response to Quality/Drug Substance IR – peptide content)
SN-23, 02/22/2021 (Response to DP IR -- (b) (4))
SN-21, 1/28/2021 (Response to Biopharmaceutics IR – Lot P99996 IVR profile data at Month 24
SN-25, 3/30/2021 (Response to Biopharm/DP IR) to be sent – (b) (4) e
SN-30, 4/19/2021 (Response to Biopharm IR – supplementary IVR method temperature robustness study)
SN-31, 04/20/2021 (Response to Biopharm IR - IVR acceptance criteria, labeling statement regarding applied heat)
SN-32, 4/21/2021 (Revised Labeling/Package Insert)
SN-33, 4/xx/2021 (Response to Biopharm IR – IVR acceptance criteria, medium temperature control)
SN-34, 4/27/2021 (Response to DP IR- including deliverable weight)
SN-36, 5/3/2021 (Response to follow-up DP IR – deliverable weight)
SN-40, 5/11/2021 (Response to IR – sample preparation video; revised IVR standard test procedure)
SN-41, 5/14/2021 (Response to IR – revised IVR standard test procedure, etc.)

Concise Description Outstanding Issues Remaining:
None

BCS Designation

Reviewer's Assessment: *BCS Designation Not Applicable*

BCS Designation is not applicable to LMIE because it is not a solid oral immediate release dosage form. The following information was submitted in the NDA and is being provided below for a complete understanding of the drug substance/active pharmaceutical ingredient (API), and the proposed drug product's *in vitro* drug release and other quality attributes.

Solubility: *Freely soluble*
Table 1 of the solubility report shows that leuprolide mesylate exhibits high solubility (i.e., freely soluble per USP definition) in water, pH 1, pH 2, pH 4, pH 6, and pH 7 buffer solutions. Approximately 150 mg/mL of leuprolide mesylate dissolves in aqueous media regardless of pH, when kept at 25 °C for 10 minutes.

Leuprolide mesylate is also *freely soluble in* dimethylsulfoxide (DMSO), and *n-methyl-2-pyrrolidone (NMP; 263.5 mg/mL) at 25°C*. The drug substance is insoluble in tetrahydrofuran, acetone, acetonitrile, n-hexane and ethyl acetate. (b) (4) Of note, the Appearance test in the finished product QC specifications describes LMIE as "a viscous and opalescent product free from particles [visible to the naked eye], (b) (4)

Note that per the Applicant, the use of the mesylate salt of leuprolide enhanced the drug product's stability, which enabled the formulation to be pre-filled into a single-dose, ready-to-use syringe with a proposed shelf-life of least 2 years when stored under refrigerated conditions at 5 °C.

Permeability: *Undefined/Not Available*
Absolute bioavailability and human mass balance studies were not conducted with LMIE.

Drug Release: *Extended-Release/Long-Acting*
The conducted clinical pharmacokinetic (PK) and pharmacodynamic (PD) studies in rats and human patients demonstrated that a single subcutaneous injection of LMIE produces prolonged/sustained systemic (serum) exposures to leuprolide that are sufficient to reduce serum testosterone levels to below castrate threshold values (≤ 50 ng/dL) within 3 to 4 weeks post-injection which then lasts over a period of 6 months post-injection (refer to Figure 1 of the proposed labeling).

In Vitro Drug Release Method and Acceptance Criteria

Reviewer's Assessment:

IN VITRO DRUG RELEASE METHOD – *Acceptable*

The originally proposed parameters for accelerated *in vitro* drug release (IVR) testing of LMIE is summarized in Reviewer Table 1. Per FDA request, the standard test procedure was updated in SN-41 to include a more detailed procedure for test sample preparation and handling.

Reviewer Table 1. Proposed *In Vitro* Drug Release Method for QC testing of LMIE

Apparatus	500 mL glass bottle with cap; Reciprocal shaking water bath agitated at 50 rpm (b) (4)
Dissolution Medium Composition/ Volume Temperature	23.25 (b) (4) mM morpholino-ethanesulfonic acid (MES) buffer with 10 mM zinc acetate and 10% (b) (4) isopropyl-alcohol (IPA, by vol%), isopropyl alcohol/IPA (10%), pH 6.0 (b) (4) 200 mL maintained at (60˚C (b) (4)
Sample introduction	The entire content of the LMIE in pre-filled syringe is transferred into the dissolution medium by adding dropwise above the surface of the dissolution media (6 drops (b) (4) The weights of the syringe before and after dispensing the contents are determined.
Sampling Time points	6, 22, 30, 46, 54, 70, 78, 94 h and 102 h
Analytical Method/Assay	Reversed-phase HPLC with UV detection at (b) (4) nm
Sample preparation	After removing from the refrigerator, the LMIE pre-filled syringes are allowed to sit at room temperature for at least 30 minutes prior to dispensing into the medium. One LMIE, ~42 mg sample product syringe with an 18G 5/8" needle attached is weighed. The plunger rod is marked into 6 (b) equal portions, and the portions are transferred dropwise to the dissolution medium, taking care to empty the syringe. The weight is recorded to calculate the LMIE sample mass added to the dissolution medium. Calculations for the total mcg of leuprolide in the implant, the amount of leuprolide released at each sampling time point (and cumulatively) are as described in the standard test procedure.
Special Notes	(b) (4)

Sources: Table 6 of 3.2.P.5.2 Analytical Procedures, and mono_cmc_2741 (Resubmission); mth-disso-release-0623.pdf (initial submission); mono_cmc_4116 (final)

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(b) (4)

[redacted]

Discriminating Power

The proposed accelerated IVR method has the ability to discern changes/differences in potentially critical quality attributes (b) (4) [redacted] In some cases, small variations in IVR are produced, but the anticipated rank-order relationship of the changes to IVR are observed. Larger deviations from the quality attributes of the target product than those studied are expected to produce larger profile separations and thus, lower calculated profile similarity (f_2) values relative to the target/reference product. *The evaluation of the adequacy of the proposed acceptance values/ranges for these quality attributes is deferred to the Drug Product and Process Reviewers.*

Reviewer Figure 1

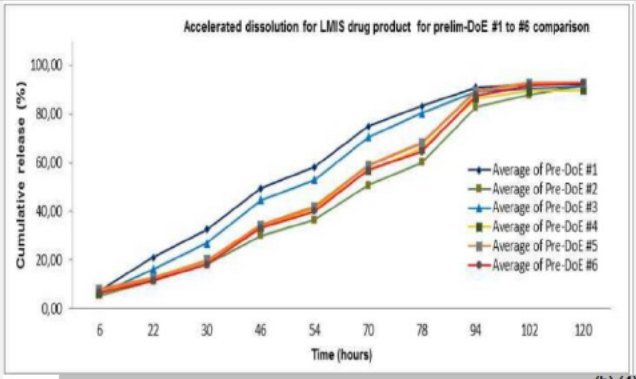


Figure 4. (b) (4)

(b) (4) [redacted]

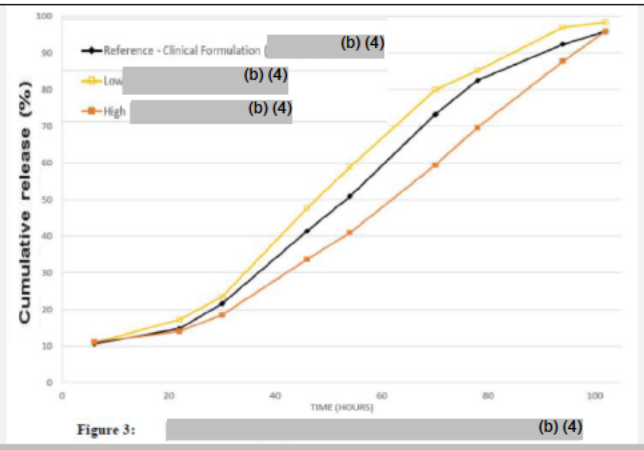


Figure 3: (b) (4)

(b) (4)

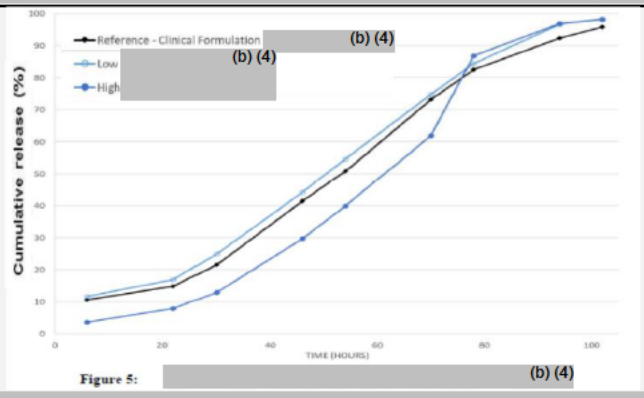


Figure 5: (b) (4)

(b) (4)

(b) (4)

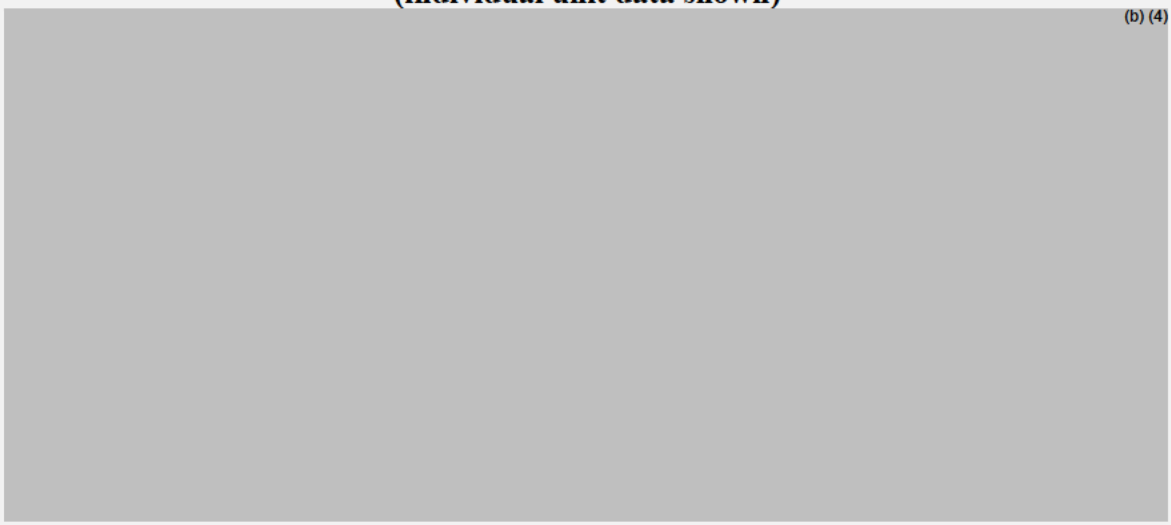
(b) (4)

Stability Indicating Potential

There is strong evidence indicating that the accelerated *in vitro* drug release method is able to reject LMIE lots that exhibit significantly increased drug release due to aging of the formulation ((b) (4)). Reviewer Figure 2 shows that when the process validation/supporting stability lots were stored at room temperature/accelerated stability conditions (instead of under refrigeration/long-term storage conditions), there were notable signs of increased drug release as early as 3 months of accelerated stability testing.

Likewise, as shown in Figure 13 of the droplet size distribution report (excerpted as Reviewer Figure 3 below), older samples of the toxicology/primary stability Lot CC0442 exhibited faster drug release than their newer stability sample counterparts. That the rate of the *later* drug release (b) (4)) phase changed in a storage-time dependent manner supports the involvement of changes affecting (b) (4) degradation in aged stability samples. Note that although Lot CC0442 is one of three primary stability lots of LMIE, it was not used in the pivotal Phase 3 clinical trial.

Reviewer Figure 2
In Vitro Drug Release Profiles of Supporting Stability Lots P99996 and P99997 During Long-Term and Accelerated Stability Storage (0 – 6 months) (individual unit data shown)



Reviewer Figure 3
Accelerated in vitro drug release of Toxicology/Primary Stability Lot CC0442 during long-term storage

Sink conditions

Based on the pH-solubility data provided for the drug substance in various pH aqueous media, it is anticipated that sink conditions will be achieved and maintained during the course of accelerated in vitro dissolution testing of the LMIE depot.

Analytical Method Validation

Reversed-phase HPLC with UV detection at (b) (4) nm is used for assay of drug in the IVR samples. The analytical method validation evaluated precision, accuracy, linearity, quantitation and detection limits, specificity, solution stability, and robustness. The API was reported to be stable in the dissolution medium at 60°C for 120 hours. The 102-hr and 120-hr sample solutions and the standard solutions were stable in refrigerated conditions for 67 hours, 28 hours, and 169 hours, respectively. Per the Applicant, the HPLC analytical

finish was adapted from the HPLC assay for determination of LMIE impurities. Per the Applicant, the IVR method was successfully transferred to (b) (4) (the proposed commercial IVR testing site). Of note, the pre-specified acceptance criterion of %RSD = NMT (b) (4)% between labs was achieved for the final specification time point. Also, the mean IVR profiles of the two labs were almost superimposable, consistent with the very low absolute difference in IVR values at all 3 specification time points. Note that the Drug Product Reviewer deferred to the FDA Office of Testing and Research (OTR) for the evaluation of the adequacy of the analytical method validation for *in vitro* drug release testing.

Method Verification:
The FDA's Office of Testing and Research (OTR) evaluated and found the proposed IVR method standard test procedure (with recommended modifications) acceptable for quality control and regulatory purposes. Refer to the IVR Method Verification Report for details.

(b) (4)

IN VITRO DRUG RELEASE ACCEPTANCE CRITERIA – *Tightened Acceptance Criteria Adequate)*

Based on the IVR profile data of the three registration batches with 36-months of long-term stability data including two that were used in clinical studies (Batches P99999 and CL0080) and one used in preclinical toxicology study (Batch CC0442), and (as part of the NDA resubmission) three additional batches, (Batches P99997, P99996, and P00001 with 18 months, 12 months and 3 months stability data, respectively), as summarized in 3.2.P.5.6 Justification of Specifications, the Applicant's originally proposed IVR acceptance criteria are tabulated below. However, in the IR response in SN-14, the Applicant decided to tighten the tolerance limits of (b) (4)

Note that the stability samples of the latest three (process validation/PV) batches were analyzed using the fully validated analytical method (V03) whereas the Months 0 – 24 or 0 – 18 stability samples of the earlier (e.g., primary stability) batches were analyzed using a "partially validated" method (V02). In SN-14, the Applicant confirmed that the three newer/PV LMIE lots were manufactured using the same formulation and manufacturing process type, and possess the same/comparable quality attributes, as the pivotal clinical trial lots. (b) (4)

Originally Proposed *In Vitro* Drug Release Acceptance Criteria

Timepoint	Average Value	Individual Values [a]
6 hours	(b) (4)	
54 hours		
102 hours		

(b) (4)

Refer to Reviewer Table 2 below for the FDA recommended In Vitro Drug Release Acceptance Criteria. Based mainly on the drug release profile data of the clinical lots (generated as close as possible to the time of their use in the pivotal clinical trial) by the *fully validated* IVR method (V03), and additionally based on the understanding of the observed impact of long-term storage (b) (4) degradation and in vitro drug release, as well as based on potential to reject drug product batches with unacceptable quality, this Reviewer recommended tightening of the acceptance range (b) (4) (Reviewer Figure 4). This Reviewer determined that it is justified to shift the recommended (b) (4) IVR acceptance range from an ideal tightened range of (b) (4)

(b) (4)

Reviewer Table 2
Reviewer's Recommended *In Vitro* Drug Release Acceptance Criteria

Timepoint	Acceptance Range (b) (4)
6 hours	
54 hours	
102 hours	

(b) (4)

Reviewer Figure 4
***In Vitro* Drug Release Profiles of the Two Pivotal Clinical Trial Lots**
(generated using the fully validated IVR Method)

(b) (4)

Reviewer Note: Age of clinical lots at time of pivotal clinical trial use: CL0080 (~8 to 11.5 months); P99999 (~9.5 – 20 months). Note that based on the unacceptable IVR profile data of Lot CL0080 at 36 months, the proposed expiration dating period of LMIE is 24 months when stored under refrigeration.

Note that the proposed labeling indicates that androgen deprivation therapy [like the proposed drug product] may prolong the QT/QTc interval. The Applicant reported that clinically significant changes in ECG were observed and correlated with testosterone levels rather than leuprolide concentrations. Thus, this Reviewer considers reasonable the proposal to use for the earliest IVR specification time point a not-to-exceed (NTE or NMT) tolerance limit, i.e., determined based mainly on the clinical lot data, as the means to control for premature rapid or higher than optimum drug release from the LMIE depot, especially in consideration of the substantially higher Day 1 $AUC_{0\text{-}24h}$ of CAMCEVI 42 mg as compared to Lupron 1 mg (as reported in Table 4.3 of FSEE-CSC-100). Based on the IVR profile data of Pivotal Clinical Lot P99999, an upper tolerance limit of (b) (4) % cumulative drug release for the first of three IVR specification time points is justified (refer also to Reviewer Figure 8 in the Bridging Assessment section of this review).

IVR on Stability

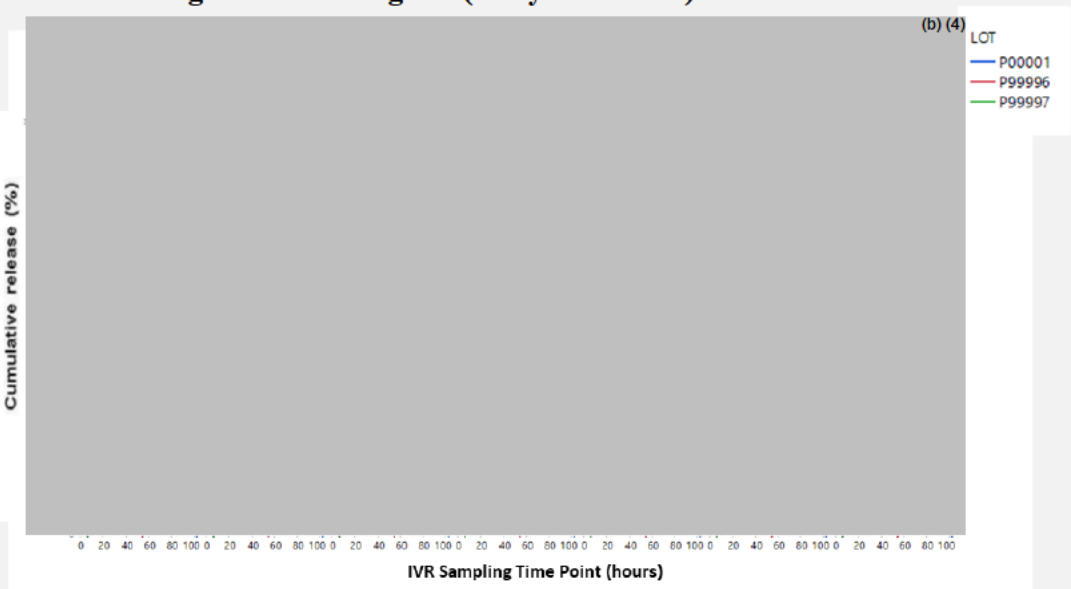
Based on 36 months of long-term stability testing (refrigerated, 5°C ± 3°C) and 6 months of accelerated (25±2°C/60%±5%RH) stability testing of the primary stability lots, the proposed expiration dating period for CAMCEVI is 24 months when stored at 5°C (which is acceptable to the Drug Product Reviewer). (b) (4)

(b) (4)

(b) (4) The Applicant committed to provide the previously requested IVR on stability data as soon as available.]

Based on the results of the photostability, temperature excursion, and freeze-thaw studies, the Applicant reported that light exposure of the product in the pre-filled syringe, higher temperature exposures of up to 6 days at 25°C, or up to 48 hours at T ≤ 40°C, or three cycles of freeze-thaw conditions did not impact the *in vitro* drug release characteristics of the proposed drug product relative to the non-stressed controls. Refer to Figure 3 of the photostability study report, Figures 4, 5, 6 and of the temperature excursion stability report, and Figure 1 of the freeze-thaw study report.

Reviewer Figure 5
Mean IVR on Stability Profile Data of Three Process Validation Lots, generated using the (Fully Validated) Method V03



(b) (4)

Other Critical Quality Attributes of the Pivotal Clinical Trial Lots
As shown in Tables 66, 68 and 69 of the Pharmaceutical Development Report/PDR), the pivotal clinical trial lots (CL0080 and P99999) were manufactured with critical quality attributes that are within the Applicant's proposed specifications, as shown below.

(b) (4)

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(b) (4)

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim, and Impact of Extrinsic Factors on Drug Release

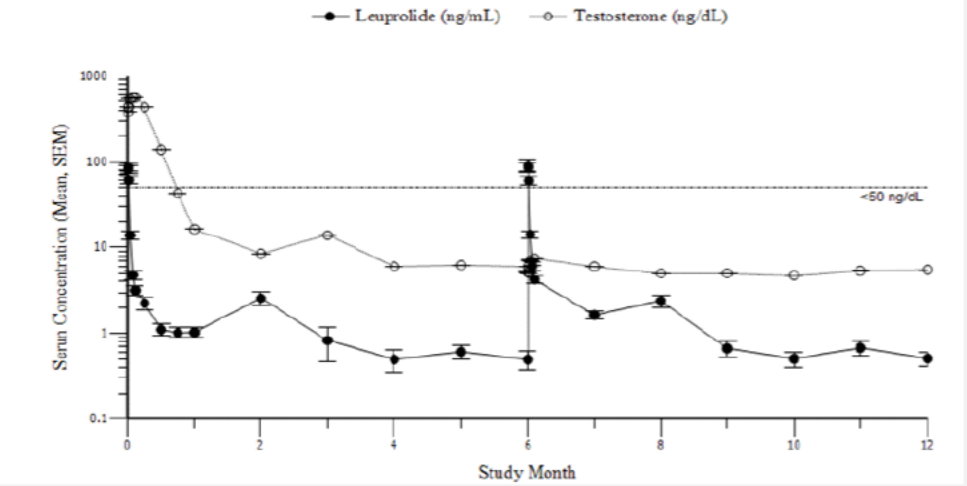
Reviewer's Assessment: ***Adequate***

Extended-Release Claim:

The Clinical Pharmacology Reviewer confirmed that the clinical pharmacokinetic (PK) and pharmacodynamic (PD) profile data which showed attainment of sustained therapeutic leuprolide concentrations over 6 months post-injection support the extended or controlled drug release claim of LMIE; (b) (4) . Specifically, per the Clinical Pharmacology Reviewer (Dr. Lili Pan), at steady state (~6 months), Lupron exposure is ~5 times higher for $AUC_{0\text{-}6month}$ and ~50% higher for $C_{max,ss}$, compared to LMIS 50 mg; refer to Table 4.3 of the Study FSEE-CSC-100 report.

Reviewer Figure 6

(b) (4)



Reviewer Note:
Table 4.3 of the FSEE-CSC-100 study report also shows that CAMCEVI 42 mg ("LMIS 50 mg") once every six months produced a significantly higher leuprolide $AUC_{0\text{-}24h}$ on Day 1 post-injection as compared to LUPRON 1 mg once daily. However, based on the results of pivotal Phase 3 Study FP01C-13-001 and the extension Study FP01C-13-001-EX submitted to support registration of CAMCEVI, as well as the FAERS and EDVAS reports of overdose associated with leuprolide products, the FDA Clinical Team indicated that there were no safety concerns regarding the significantly higher Day 1 leuprolide exposures to CAMCEVI.

Impact of Extrinsic Factors (e.g., applied pressure/applied heat) on the *In vitro* and *In vivo* Drug Release From the Depot:

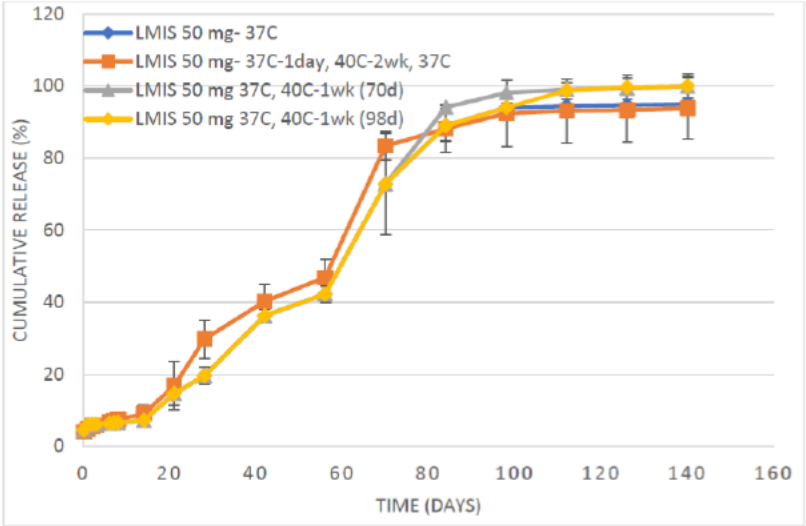
Applied Pressure
To address the concern about potential influence of applied pressure on the *in vivo* drug release profile of LMIE, the proposed label includes directions to mitigate the likelihood of such extrinsic factor. The assessment of the adequacy/acceptability of the following labeling statement was deferred to the DMEPA Labeling Reviewer: (b) (4)

.... ***Do NOT*** *inject in areas with brawny or fibrous subcutaneous tissue or locations that can be rubbed or compressed (i.e., with a belt or clothing waistband)".*

Applied Heat
The Applicant conducted an *in vitro* 5-month drug release study to simulate the effect of increased bodily temperature from 37°C to ~40°C lasting a few days or 1 - 2 weeks on the different phases of LMIE drug release including the early and the later (b) (4) phases; refer to Figure 1 of the IR Response in SN-25. As shown in the excerpted figure below, increasing the medium temperature from 37°C to ~40°C for 1 - 2 weeks consistently resulted in (b) (4) higher cumulative drug release over the duration of heat application. Based on the results of this small *in vitro* drug release study (and given that there was no corresponding in vivo PK study, as well as considering the input of the Clinical/Medical Review Team), it was deemed prudent by this Biopharmaceutics Reviewer to recommend that a labeling statement be added to warn against use of directly applied heat on the site of the in-situ implant to prevent alterations in the sustained drug release profile of LMIE over 6 months post-injection. Note that it was not feasible to directly evaluate the impact of simulated higher bodily temperature on *in vitro* drug release rate using the accelerated IVR method proposed for routine QC testing of CAMCEVI because the medium in such *in vitro* test system is maintained at a temperature of 60 °C (rather than 37 °C). In SN-32, per FDA recommendation, the Applicant added a labeling statement which recommends that direct heat application to the injection site be avoided; per the

DMEPA Reviewer (Dr. Sarah Thomas), the additional labeling statement is acceptable from a medication safety perspective.

Real time in vitro release of LMIS 50 mg at 37°C and with temperature excursions to 40°C



"Real-time" *in vitro* drug release method parameters: (b) (4) [redacted] The analytical method was reported to be specific, linear, accurate, repeatable in the range tested (i.e. 12.5 to 150 µg/mL).

Bridging of Formulations/Drug Products

Reviewer's Assessment: ***Adequate***

The proposed to-be-marketed leuprolide mesylate injectable emulsion (LMIE) product has the same ***theoretical formula**** and ***manufacturing process*** steps, and will be produced [(b) (4) [redacted] from the same ***raw material manufacturers*** (b) (4) [redacted] at a similar ***batch size/scale*** as the Phase 3 clinical trial/primary registration (stability) lots (b) (4) [redacted]). Note that the proposed commercial ***drug product manufacturer*** ((b) (4) [redacted]) is the same as that which produced one of the two Phase 3 clinical trial/primary registration lots (i.e., Batch P99999), and there is evidence of comparable PK/PD/efficacy/safety (as well as primary stability) data between this Phase 3 clinical lot P99999 and the other Phase 3 clinical lot CL0080, produced by the original drug product manufacturer ((b) (4) [redacted]; refer to Figures 5.4.3 and 5.5.4 of the FSEE-CSC-101 Study Report, excerpted as Reviewer Figure 7 below).

(b) (4) [redacted]

(b) (4) will be the same as used for the filling of the clinical trial/toxicology (primary registration/stability) batches. During stability testing, the pre-filled syringes of one of the three process validation (PV) lots used the same ***packaging configuration*** (carton without blister packaging) as the pivotal clinical trial/primary stability lots.

Overall, the provided data/information in the NDA are adequate to justify additional noted changes/differences in quality attributes (b) (4)) between the drug product evaluated in clinical/stability studies and the final proposed to-be-marketed drug product, as discussed in detail below.

(b) (4)

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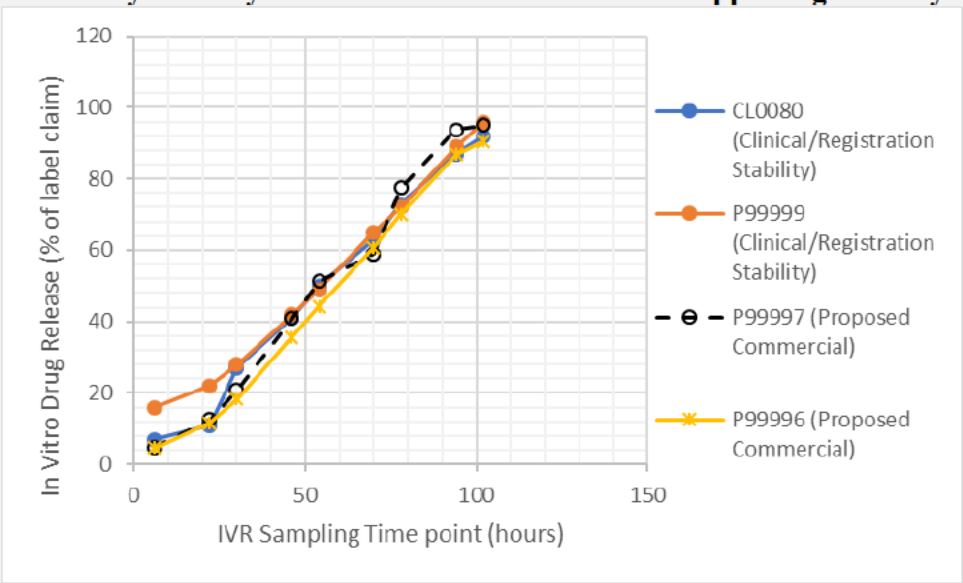
(b) (4)

Reviewer Figure 8
Comparative *In Vitro* Drug Release Profiles of the LMIE: Pivotal Clinical Trial/Primary Stability Lots versus Process Validation/Supporting Stability Lots



The profile similarity (f_2) values of the proposed commercial lots to clinical/registration stability lots: range from 57 to 68, suggesting in vitro drug release profile similarity

(b) (4)

REVIEWER NOTE (CROSS-PRODUCT BRIDGING):
The Applicant investigated LMIE's PK, efficacy and safety in a Phase 3 clinical trial (FP01C-13-001), as well as nonclinical safety. This NDA for LMIE relies for approval, in part, on the FDA's previous findings of nonclinical safety (as well as clinical pharmacology and clinical safety) for the Listed Drug, Lupron Injection 1 mg/0.2 mL (NDA 019010), administered subcutaneously once daily. The Clinical Pharmacology Reviewer (Dr. Hisham Qosa) confirmed that the reliance is justified based on the *in silico* demonstration of *lower steady state* leuprolide exposures from LMIE 42 mg relative to daily Lupron 1 mg injections (Study FSEE-CSC-100). Additionally, the Medical Officer (Dr. Michael Brave) confirmed that based on the results of the pivotal (single-arm) Phase 3 clinical trial (Study FP01C-13-001), the substantially *higher Day 1* leuprolide exposures for CAMCEVI than for Lupron in Study FSEE-CSC-100 raise no significant clinical safety (and efficacy) concerns.

Note that the proposed LMIE product differs from the currently approved leuprolide products in that the salt used for the proposed drug product is *mesylate* whereas that used in the currently approved products is *acetate*. Per the Applicant, the use of the mesylate salt enhanced product stability which enabled the formulation to be pre-filled into syringes with a proposed shelf-life of at least 2 years when stored under refrigeration.

Per the Applicant, based mainly on the lower steady state drug exposures to CAMCEVI vs LUPRON in the 'in silico' PK bridging study, reliance on the following PK and safety-related information of the relied upon LD is justified: nonclinical secondary pharmacology, safety pharmacology, repeat dose toxicity, genotoxicity/mutagenicity, carcinogenicity, reproductive and developmental toxicity, as well as certain clinical pharmacology information in the approved labeling including distribution, metabolism, excretion, PK in organ impairment and drug interaction. Refer to the submitted NDA Assessment Aid for details.

Biowaiver Request

Reviewer's Assessment: *Not Applicable*

A biowaiver request for non-bio-strengths is not needed because the strength (42 mg leuprolide) of the proposed drug product evaluated in clinical PK/PD/efficacy/safety and stability studies is the lone strength proposed for commercialization.

Post-Approval Commitments

None

List of Deficiencies:

None

Banu Zolnik

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Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 5/17/2021 02:06:47PM
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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	FDA accepted Applicant's proposed proprietary name CAMCEVI. Recommended revision: *CAMCEVI (leuprolide) injectable emulsions, for subcutaneous use* The Applicant accepted and implemented our recommendations.
Established name(s)	Leuprolide	Acceptable
Route(s) of administration	Injection	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	(b) (4) Recommended revision: *Injectable emulsion: 42 mg* The Applicant accepted recommendation.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not provided	DMEPA reviewer Sarah Thomas recommended the following language included under DOSAGE AND ADMINISTRATION: *See Full Prescribing Information for instructions on the preparation and administration of the injectable emulsion in a pre-filled syringe* The Applicant accepted recommendation.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Refer to Section 2 of the USPI (Version 2, the draft labeling dated December 22, 2020, SD#18) for details.	(b) (4) [redacted] The Applicant agreed to remove the statement after revision.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4) [redacted]	Not acceptable. The dosage form should be emulsion. See below recommended revision.
Strength(s) in metric system	42 mg	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	See above	Recommend revising the salt equivalency, see below.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	The applicant did not provide a description of identifying characteristics for the drug product	Recommended revision for section 3: *Injectable emulsion: 42 mg leuprolide (equivalent to approximately 48 mg leuprolide mesylate) as a sterile, off-white to pale yellow, viscous, and opalescent emulsion in a single-dose, pre-filled syringe for subcutaneous injection.* The Applicant accepted and implemented our recommendations.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not provided	See the above recommendation including the word "single-dose".

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Proprietary name: CAMCEVI; Established name: leuprolide	Acceptable
Dosage form(s) and route(s) of administration	(b) (4)	Not acceptable. (b) (4) . Recommended revision to "injectable emulsion".
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	See above	The Applicant applied USP Salt Policy.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	Recommended revision: *CAMCEVI is supplied as a kit with a pre-filled, single-dose, sterile syringe for subcutaneous injection. Each pre-filled syringe delivers 42 mg leuprolide (equivalent to approximately 48 mg leuprolide mesylate), poly(D, L-lactide) (184 mg) polymer and N-methyl-2-pyrrolidone (136 mg).* The Applicant accepted the recommendations.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	See above	See above recommendations.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	See above	Acceptable
Pharmacological/ therapeutic class	(b) (4)	(b) (4) the drug substance name should be leuprolide mesylate. The revised statement reads: *Leuprolide mesylate is a synthetic nonapeptide analog of*

		naturally occurring GnRH and is a GnRH agonist. The analog possesses greater potency than the natural hormone. The Applicant accepted the recommendations.
Chemical name, structural formula, molecular weight	(b) (4)	The chemical name is correct; however, the counter ion number "n" is not defined and abbreviation "MSA" for methanesulfonic acid is not formal. Recommended revision of the nMSA as follows: n CH_3SO_3H n = 1.5-1.8 The Applicant accepted the recommendations.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Not provided	Recommend inclusion of pKa or pH in this section. The Applicant included the following acceptable language: The pH of 50 mg/mL solution of leuprolide mesylate in water is about (b) (4) this is acceptable.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Not provided	Recommended the following language: *CAMCEVI 42 mg is a sterile, off-white to pale yellow, viscous and opalescent emulsion supplied in a kit as a single-dose, pre-filled syringe.* The Applicant accepted the above recommendation.
Strength(s) in metric system	42 mg	Acceptable
Available units (e.g., bottles of 100 tablets)	(b) (4) [redacted]	The kit contents were revised by DMEPA reviewer Sarah Thomson as follows: *Injectable emulsion in a pre-filled syringe containing 42 mg leuprolide for subcutaneous injection, a sterile 18 gauge needle, a Point-Lok® needle protection device, and Instructions for Use.* The Applicant accepted the revision.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not provided	See above recommendation
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not provided	See above recommendation including the word "single-dose".

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4)	Recommended revision for storage condition: *Store CAMCEVI at 2°C–8°C (36°F–46°F). Protect CAMCEVI from light by storing in the original package until time of use. Do not freeze or shake.* The Applicant accepted the recommendation.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above	Acceptable
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Not provided.	Recommend including the following sentence: *The rubber used in syringe tip cap and plunger stopper is not made of natural rubber latex.* The Applicant accepted the recommendation.
Include information about child-resistant packaging	N/A	Healthcare practitioners will administer CAMCEVI.

1.2.5 Other Sections of Labeling

NA

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Not provided	Requested applicant to include manufacturing information after section 17. In the revised USPI, the Applicant included the following manufacturing information: *Manufactured for:* *Foresee Pharmaceuticals Co., Ltd.* *9F-2, No. 19-3, Sanchong Rd.,* *Nangang Dist., Taipei City 115,* *Taiwan* *By:* *Fareva Pau 1* *Avenue du Bearn, 64320 Idron,* *France* This is acceptable.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

There is no patient labeling included in USPI.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4)	Recommend revision of dosage form as follows: CAMCEVI™ (leuprolide mesylate) injectable emulsions The Applicant accepted the recommendation.
Dosage strength	42 mg	Acceptable
Route of administration	Subcutaneous injection	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not included	Recommend applicant include salt equivalency statement in the labeling. The Applicant included the salt statement in the revised carton label, this is acceptable.
Net contents (e.g. tablet count)	N/A	
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	NDC 72851-042-01	Acceptable
Lot number and expiration date	Included	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Refrigerate at 2–8°C (35.6–46.4°F). Protect from light by storing in the original package until time of use. Do not freeze or shake. (b) (4)	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Yes, single dose is on the blister lid.	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	M/A	
Bar code	Yes	Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Foresee Pharmaceuticals Co. Ltd., Taipei City 115 (b) (4) Taiwan	Acceptable
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	(b) (4)	Recommend removal of this statement. The Applicant accepted the recommendation.

Assessment of Carton and Container Labeling: ***Adequate***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

The label sections covered in this review are adequate and recommended for approval.

Primary Labeling Assessor Name and Date: Yang Nan, Ph.D.

Secondary Assessor Name and Date: Anamitro Banerjee, Ph.D., Branch Chief

Yang Nan

Digitally signed by Yang Nan
Date: 4/29/2021 11:30:20AM
GUID: 520bd6c90002b3b0320380334e69a817

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 4/29/2021 12:04:24PM
GUID: 5075764700003844b7bc89632228509f

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIAOHONG CHEN
05/17/2021 04:42:51 PM