CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208956Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
APPROVAL
(This Recommendation includes the Manufacturing Inspection Recommendation)

NDA 208956
Review #1
Review Date (see last page)

Drug Name/Dosage Form	triptorelin for extended release suspension
Strength	22.5 mg
Route of Administration	intramuscular injection
Rx/OTC Dispensed	Rx
Applicant	Arbor Pharmaceuticals

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	8/29/16
0002	9/2/16
0003	9/27/16
0007	3/8/17
0009	3/24/17
0010	4/20/17

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Xavier Ysern/Donna Christner	New Drug API/ONDP
Drug Product	Christopher Galliford/ Danae Christodoulou	New Drug Products II/ONDP
Process	Yong Hu/Zhigang Sun	Process Assessment II/OPF
Facility	Michael Klapal/Vidya Pai	Inspectional Assessment/OPF
Biopharmaceutics	Suneet Shukla/Haritha Mandula	Biopharmaceutics/ONDP
Microbiology	Denise Miller/Neal Sweeney	Process Assessment II/OPF

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**

   A. **DMFs: Adequate** (see the drug product review of DMF (b) (4))

   B. **Other Documents:** not applicable

2. **CONSULTS:** not applicable

Executive Summary

I. Recommendation and Conclusion on Approvability

The final OPQ recommendation is for Approval, including the overall manufacturing inspection recommendation.

II. Summary of Quality Assessment

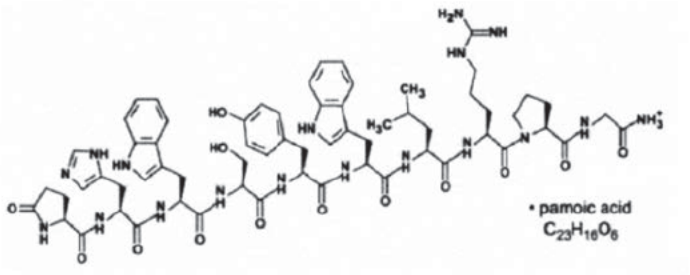
This is a 505(b)(1) application, but it is NOT for an NME because there are three approved NDAs for the same active ingredient, and the applicant has the right of reference to the approved NDAs.

Specifically, the applicant has the right of reference to the approved NDA 22437 for the same 22.5 mg product, approved for prostate cancer. This new NDA subject of this review is for a new indication, treatment of precocious puberty.

- DMF (b) (4) is referenced for all CMC information on the drug substance.
- DMF (b) (4) is referenced for all CMC information on the drug product. The information is identical to that in the referenced NDA 22437.
- DMF (b) (4) is referenced for all CMC information on the co-packaged diluent, Sterile Water for Injection USP. The manufacturer/DMF holder is different from the one supporting the referenced NDA 22437.

Proposed Indication(s)	treatment of children with central precocious puberty; see CDTL's memo
Duration of Treatment	[not finalized by GRMP goal; see CDTL's memo]
Maximum Daily Dose	not applicable; the product is extended release over 24 weeks
Alternative Methods of Administration	not applicable

Drug Substance



The drug substance is triptorelin pamoate.
molecular weight = 1699.9

The drug substance is a small synthetic peptide with DMF (b) (4) being referenced for all CMC information. The DMF is currently adequate.

Drug Product

The drug product is a sterile, lyophilized powder, 22.5 mg triptorelin free base (equivalent to 31 mg triptorelin pamoate), to be reconstituted with the co-packaged pre-filled syringe containing 2 mL of Sterile Water for Injection. The reconstituted product is an extended release suspension for IM injection.

Excipients: (b) (4) mg poly-d,l-lactide-co-glycolide (b) (4) (b) (4) 4 mg mannitol, 26 mg carboxymethylcellulose sodium, and 1.7 mg polysorbate 80.
Sterile Water for Injection is co-packaged in a pre-filled syringe.

DMF (b) (4) is referenced for all CMC information on the drug product. The DMF is currently adequate (including information on sterility assurance).

- Information on the drug product in DMF (b) (4) is confirmed to be identical to the currently approved information in the referenced NDA 22437.
- The same In Vitro In Vivo Relationship (IVIVR) report submitted to the referenced NDA 22437 was submitted to NDA 208956 and DMF (b) (4). As this information was found not adequate to support post-approval changes for the referenced NDA 22437, the same conclusion applies to NDA 208956 and DMF (b) (4) that there is no valid IVIVR to support post-approval changes.
- Expiration Date & Storage Conditions: 36 months at room temperature (b) (4) for the product (b) (4)

DMF (b) (4) s referenced for all CMC information on the co-packaged pre-filled syringe containing 2 mL of Sterile Water for Injection USP for reconstitution. The DMF is currently adequate for CMC information on the diluent (including information on sterility assurance). Reference is made to the separate CDRH reviews of the syringe and other device-related information.

A. Special Product Quality Labeling Recommendation: not applicable

B. Life Cycle Knowledge Information/ Final Risk Assessment:

API	none
Drug product	none
Process	none
Facilities	Page 11 of Chapter VI
Biopharmaceutics	none
Microbiology	none

Application Technical Lead Signature:

Suong T. Tran -S Digitally signed by Suong T Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T Tran -S, 0.9.2342.19200300.100.1.1=1300101829 Date: 2017.05.30 09:50:38 -04'00'

Suong (Su) Tran, Ph.D.
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CHAPTERS: Primary Quality Assessment

Chapter I: Drug Substance
Chaper II: Drug Product
Chapter III: Environmental Assessment
Chapter IV: Labeling
Chapter V: Process
Chapter VI: Facilities
Chapter VII: Biopharmaceutics
Chapter VIII: Microbiology
Attachment I: Final Risk Assessment (see last page of Executive Summary)

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CHAPTER III: Environmental Analysis

see chapter II

CHAPTER IV: Labeling

see chapter II

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CHAPTER VII: Biopharmaceutics

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 208956

Drug Product Name / Strength: Triptorelin Pamoate for (b) (4) suspension/22.5 mg

Route of Administration: Intramuscular injection

Applicant Name: ARBOR PHARMACEUTICALS

Review Summary:

This application is a new NDA for triptorelin for (b) (4) suspension 22.5 mg, for the treatment of children with central precocious puberty (CPP). This product is already marketed as Trelstar 6-Month and is approved under NDA 022437 for the palliative treatment of advanced prostate cancer by maintaining chemical castration.

Triptorelin pamoate microgranules 22.5 mg is a sterile, lyophilized, biodegradable microgranule formulation which is supplied as a single-dose vial intended for single use. The drug product is provided in a kit that contains sterile water for injection for reconstitution which is provided in a pre-filled syringe. Upon reconstitution, a suspension is formed which is administered as an intramuscular injection every 168 days (i.e., every 24 weeks).

The current NDA 208956 does not contain any drug substance or drug product manufacturing information. Instead, the information for the drug substance **triptorelin pamoate**, the drug product **triptorelin pamoate microgranules 22.5 mg** and the **sterile water for injection** is provided in **DMF** (b) (4), **DMF** (b) (4) and **DMF** (b) (4), respectively.

This review is focused on reviewing the current NDA 208956 from Biopharmaceutics perspective.

The drug substance **DMF** (b) (4) for triptorelin pamoate has been recently reviewed by the Division of New Drug API/ONDP on 12 Sep, 2016 and has been found to be 'adequate'.

The biopharmaceutics aspects of drug product **DMF** (b) (4) for triptorelin pamoate microgranules 22.5 mg has been reviewed recently for dissolution specifications and is found to be acceptable.

Therefore, no additional review is necessary and the current NDA 208956 is 'adequate' from Biopharmaceutics perspective.

List Submissions being reviewed (table):

Document(s) Reviewed (eCTD #)	Comment	Date Received	Review Cycle #
eCTD # 0001	Original application	8/29/2016	1

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer's Assessment:

Solubility: Refer to Biopharmaceutics review of DMF (b) (4)

Permeability: N/A

Dissolution: see below

Dissolution Method and Acceptance Criteria

The in-vitro dissolution test conditions, the sampling time points, and acceptance criteria proposed in the current NDA 208956 are identical to the DMF (b) (4) as follows.

The In-Vitro Dissolution Test Conditions:

Dissolution Apparatus:	USP Type 2 Paddle
Dissolution Medium:	50 mL of methanol to 950 mL of water
Stirring Speed:	75 rpm
Temperature:	Gradient from 37 to 61°C over 48 hours, (b) (4)
Sampling Points:	1, 8, 24, 96, and 168 hours
Dissolution Analysis:	HPLC

The sampling time points and acceptance criteria:

Time (hr)	% Released
1	(b) (4)
8	
24	
96	
168	

Reviewer's Assessment: Dissolution method and specifications are adequate.

The dissolution method and specifications were developed and approved in the DMF (b) (4). The current NDA 208956 refers to this DMF for information related to dissolution method development and the specifications. The reviewer compared the in vitro dissolution test specifications and the dissolution method development provided in the DMF (b) (4) with the current NDA 208956 and confirmed that they are identical as shown below Table 1 and 2:

Table 1: Drug product (Triptorelin for (b) (4) Suspension 22.5 mg) quality control specifications for NDA 208956

Parameter	Analytical Method	Release Criteria	Shelf Life Criteria
In vitro dissolution	USP<711> Apparatus 2 USP<621>	(b) (4)	

Table 2: Drug product (Triptorelin for (b) (4) Suspension 22.5 mg) quality control specifications for DMF (b) (4)

Parameter	Analytical Method	Release Criteria	Shelf Life Criteria
In vitro dissolution	USP<711> Apparatus 2 USP<621>	(b) (4)	

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: IVIVR is not established and is inadequate.

The IVIVR studies in the current NDA 208956 refers to the studies that are included in DMF (b) (4).

The IVIVR report submitted in this NDA 208956 (same IVIVR report in DMF (b) (4)) is recommended as 'inadequate' and cannot be used to support any future post-approval changes for the current NDA 208956 (refer to DMF (b) (4) Biopharmaceutics review).

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: N/A

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: N/A

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: N/A

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: N/A

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: N/A

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: N/A

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: Refer to DMF (b) (4) review.

Bridging of Formulations

Reviewer's Assessment: N/A

Biowaiver Request

Reviewer's Assessment: N/A

R Regional Information

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

List of Deficiencies:

IVIVR is inadequate and cannot be used to support any future post-approval changes.

Primary Biopharmaceutics Reviewer Name and Date:

Suneet Shukla, Ph.D. 5/11/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Haritha Mandula, Ph.D. 05/12/2017

Suneet Shukla

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Haritha Mandula

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CHAPTER VIII: Microbiology

MICROBIOLOGY

Product Background: This is a granulated powder product co-packaged with the diluent (sterile water for injection). The drug product is currently an FDA approved product marketed under other NDAs. This current NDA was submitted by a different NDA holder but has the right of reference to the information for the currently marketed NDA products. The same manufacturer of the currently approved product will be manufacturing this product. The manufacturer of the co-packaged diluent is not the same as the referenced NDAs.

NDA: 208-956/N000

Drug Product Name / Strength: TRIPTODUR (Triptorelin pamoate for (b) (4) suspension)

Route of Administration: Intramuscular

Applicant Name: Arbor Pharmaceuticals, LLC

Manufacturing Site:
Product: Debiopharm Research & Manufacturing S.A., Martigny Valais Switzerland
Diluent: (b) (4)

Method of Sterilization:
(b) (4)

Review Summary: Recommendation is to APPROVE from a quality microbiology perspective.
This drug product is currently an approved marketed drug product under the following NDAs; N20-715, N22-437, and N21-288. There is no difference in the manufacturing process from the currently approved products; however this is a different NDA holder for a new indication. The sponsor of the subject NDA has the right of reference to the supporting information found in the above mentioned NDAs. There were no changes in the manufacturer, the manufacturing process, (b) (4), or the release specifications proposed for this drug product. The co-packaged diluent (sterile water for injection - SWFI) is not the same manufacturer. Information for the SWFI was submitted to the Agency in a Drug Master File (DMF (b) (4)).

List Submissions being reviewed:

Submit	Received	Review Request	Assigned to Reviewer
29 August 2016	29 August 2016	N/A	08 September 2016

Highlight Key Outstanding Issues from Last Cycle: NA

Concise Description Outstanding Issues Remaining: None

Referenced Supporting Documents:
DMF (b) (4): Type II DMF for Triptorelin pamoate Microgranules LOA Dated March 11, 2016 for the manufacturing process of triptorelin pamoate microgranules. The information submitted to DMF (b) (4) is identical to the information submitted in NDAs 20-715, 22-437, and 21-288 and covers the manufacturing, sterility assurance, and testing/specifications of the final drug product. DMA review of DMF (b) (4) (review (b) (4)) was completed on 05 April 2017 and concluded that the DMF was **ADEQUATE** in support of NDA 208-956.
DMF (b) (4)**:** Type II DMF for Sterile water for Injection, (b) (4) LOA dated April 4, 2016. DMA review of DMF (b) (4) (review (b) (4)) was completed on 24 March 2017 and concluded that the DMF was ADEQUATE in support of NDA 208-956.
DMF (b) (4)**:** (b) (4) LOA dated May 17, 2016 This (b) (4) syringe is used in DMF (b) (4) for the diluent (sterile water for injection). Since the LOA for DMF (b) (4) is located in this NDA, the acceptability of DMF (b) (4) is discussed here. The diluent is (b) (4) is the critical (b) (4) This was reviewed on 2 June 2016 by DMA and was ADEQUATE.

S Drug Substance - NA

Reviewer's Assessment:
A microbiology review of the drug substance is not required as the drug substance is not sterile.

P Drug Product (Triptorelin pamoate) – All information concerning the manufacturing, sterilization, testing, and stability for the drug product was provided in DMF (b) (4).

P Drug Product (Diluent – Sterile Water for Injection) – All information concerning the manufacturing, sterilization, testing, and stability for the co-packaged drug product diluent was provided in DMF (b) (4).

R Regional Information

Executed Batch Records: The executed batch records were provided in DMF (b) (4) for the drug product and DMF (b) (4) for the diluent.

Reviewer's Assessment: NA

Comparability Protocols: None

Reviewer's Assessment: NA

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert: The package insert states that the injection is to occur without delay once the powdered product is reconstituted.

Reviewer's Assessment: Acceptable; There are no post reconstitution hold times proposed. The label and injection instructions state that the administration is to occur immediately after reconstitution is complete.

Post-Approval Commitments: None

Reviewer's Assessment: NA

Lifecycle Management Considerations: None

Reviewer's Assessment: NA

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Denise A. Miller 06 April 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Neal J. Sweeney, Ph.D. 17 May 2017

Denise Miller

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Neal Sweeney

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CHAPTER IX: Additional Quality Discipline

n/a

ATTACHMENT I: Final Risk Assessments

See Executive Summary

Su (Suong) Tran

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Office of Pharmaceutical Quality

NDA FILING REVIEW

Suong Tran, PhD
Application Technical Lead

NDA 208956	**Established/Proper Name:** **triptorelin**
Applicant **Arbor Pharmaceuticals**	**Dosage Form:** **powder for injectable suspension (to be reconstituted with the co-packaged Sterile Water for Injection)**
Submission Type: **505(b)(1)**	**Strength:** **22.5 mg**
Chemical Type **6**	**Cross Referenced Applications** **NDA 22437**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			n/a
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		x	

B. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS

This is a 505(b)(1) application , but it is NOT for an NME and it is NOT in the Program because there are 3 approved NDAs for the same active ingredient.

- The applicant has the right of reference to all 3 approved NDAs, making this new NDA a 505(b)(1) application.
- Not a breakthrough, orphan, or drug shortage product. The applicant's request for a priority review will be evaluated by the OND Division.
- NDA 22437 is referenced for the same 22.5 mg product, approved for prostate cancer. This new NDA is for a new indication, treatment of precocious puberty.

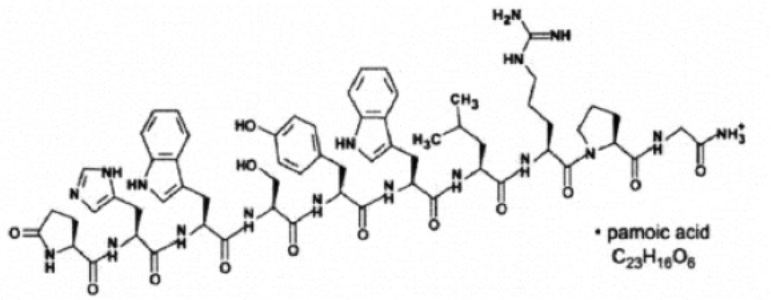
The drug substance is triptorelin pamoate. The drug product is triptorelin for injectable suspension. This NDA 208956 contains very little CMC information: the drug substance information is in DMF (b) (4), the drug product information is in DMF (b) (4), and the diluent SWFI is in DMF (b) (4).

Office of Pharmaceutical Quality

NDA FILING REVIEW

Drug Substance:

TRIPTODUR is a synthetic decapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LHRH).[31] The chemical name of triptorelin pamoate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide (pamoate salt). The molecular weight is 1699.9 and the structural formula is:[31]



DMF (b) (4) is referenced for all CMC information on the API. This DMF has previously been reviewed in support of other applications; the API reviewer will check for new amendments and review them if needed.

Drug Product:

TRIPTODUR 22.5 mg is provided as a sterile, lyophilized, biodegradable microgranule formulation in a single-dose vial, together with a syringe containing 2 mL Sterile Water for Injection for resuspension of the lyophilisate,. The triptorelin formulation is comprised of 22.5 mg triptorelin pamoate (base units), poly-*d,l*-lactide-co-glycolide, mannitol, carboxymethylcellulose sodium, and polysorbate 80. When 2 mL Sterile Water for Injection is added to the vial containing TRIPTODUR and mixed, a suspension is formed which is intended as an intramuscular injection.[32,33]

Each TRIPTODUR 22.5 mg kit (NDC 24338-150-20) contains:

- One single-dose vial (24338-150-01) with a Flip-Off seal containing sterile lyophilized (b) (4) (b) (4)
- One sterile, glass syringe with Luer Lock prefilled with *Water for Injection* (24338-150-02)
- Two sterile 21 gauge, 1½" needles (*thin-wall*) with safety cover
- One Package Insert

- DMF (b) (4) and NDA 22437 are referenced for all CMC information on the drug product. The holder of DMF (b) (4) (Debiopharm in Martigny, Switzerland) is the same drug product manufacturer approved in the referenced NDA 22437. In the 9/2/17 amendment, the applicant confirms that NDA 22437 and DMF (b) (4) have the same CMC information, including all recently approved supplements to NDA 22437. The primary reviews of the new NDA 208956 will verify this.
- DMF (b) (4) is referenced for all CMC information on the Sterile Water for Injection. NDA 22437 is referenced for the same product, but it appears that the co-packaged diluent has a different manufacturer. (b) (4). The SWFI suppliers in NDA 22437 are (b) (4).

Office of Pharmaceutical Quality

NDA FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 **AND** 25.15(d) been provided?	x			categorical exclusion
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?	x			
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	x			
FACILITY INFORMATION					
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	x			
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	x			
DRUG SUBSTANCE INFORMATION					
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?				DMF (b) (4) triptorelin pamoate
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	x			DMF (b) (4) (sterile powder to be reconstituted for injectable suspension) and DMF (b) (4) (Sterile Water for Injection diluent)
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?		x		

Office of Pharmaceutical Quality

NDA FILING REVIEW

C. FILING CONSIDERATIONS					
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies*)			x	Referencing the approved NDA 22437
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.			x	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			x	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?			x	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?			x	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x		
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x			
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			x	
17.	For Biotech Products, is sufficient information provided in compoliance with 21 CFR 610.9 and 601.2(a)?			x	

APPLICATION ELEMENTS				
Initial Assessment		**Yes**	**No**	**Comments**
1.	Accelerated Review expected? (Priority or Breakthrough)		x	
2.	Narrow Therapeutic Index Drug		x	
3.	PET Drug, Drug Device Combination, Liposome product, Biosimilar product, Novel Dosage Form, Emerging Technology		x	
4.	Specialty Population (i.e., young children and/or elderly)	x		pediatric indication
5.	Sterile Drug Product (Aseptic, Terminal, Parametric Release)	x		
6.	Use of Models for Release (IVIVC, dissolution models for real time release)		x	

Office of Pharmaceutical Quality

NDA FILING REVIEW

APPLICATION ELEMENTS				
	Initial Assessment	**Yes**	**No**	**Comments**
7.	DMF(s) referenced for drug substance?	x		DMF (b) (4)
8.	Complex API (Polymeric molecules, Heterogeneous mixtures, Botanical, Antibody-Drug-Conjugate)		x	
9.	Real Time Release Testing, Continuous Manufacturing, PAT		x	
10.	EA Team: • NMEs • API with estrogenic, androgenic, or thyroid activity • API derived from plants or animals • Environmental Assessments		x	categorical exclusion request

Regulatory drug substance specification:

Table 1: Specifications for Triptorelin Pamoate

Test	Acceptance Criteria	Analytical Method
Appearance	Yellowish powder	Visual
Pamoic acid content	(b) (4)	HPLC
Identification		HPLC
Assay		HPLC
Water content		Coulometry (Karl Fischer)
Purity and related impurities		HPLC
Particle size		Laser diffraction
Bioburden		Microbial enumeration

Drug product composition:

Table 1: Quantitative Composition for Triptorelin Pamoate Microgranules 22.5 mg

Ingredient	Reference to Quality Standard	Function	Quantity Per Dose	Quantity Per Vial[1]
triptorelin (peptide base) [triptorelin pamoate]	(b) (4)	active substance	22.5 mg 31 mg (b) (4)	(b) (4)
poly-*d,l*-lactide co-glycolide (b) (4)		(b) (4)	(b) (4)	
(b) (4)				
mannitol	USP		74 mg	
carboxymethylcellulose sodium	NF		26 mg	
polysorbate 80	NF		1.7 mg	
water for injection	USP		N/A[6]	
(b) (4)	NF		N/A[7]	
	NF		N/A[8]	
		Total	(b) (4)	(b) (4)

Table 1: Quality Control Specifications

Test	Analytical Method	Release Criteria	Shelf Life Criteria
Tests on Lyophilized Cake			
Appearance	Visual inspection	(b) (4) slightly yellow lyophilized cake in glass vial	(b) (4) slightly yellow lyophilized cake in glass vial
Triptorelin & pamoate identity by TLC	USP<201>	(b) (4)	(b) (4)
Triptorelin identity	HPLC		
Triptorelin assay	HPLC USP<621>		
Triptorelin content uniformity	USP<905>		
Related substances	HPLC		
Water content	Coulometric		

(b) (4)

Office of Pharmaceutical Quality
NDA FILING REVIEW

Parameter	Analytical Method	Release Criteria	Shelf Life Criteria
In vitro dissolution	USP<711> Apparatus 2 USP<621>	(b) (4)	(b) (4)
Tests on Reconstituted Suspension			
Reconstitution time	Visual		
pH	USP<791>		
Particle size	USP<429>		
Integrity test[2]	(b) (4)		
Sterility	USP<71> Direct inoculation method		
Bacterial endotoxin			

(b) (4)

Su (Suong) Tran

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