CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208956Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 21, 2017
To:	Jean-Marc Guettier, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Ramachandra, PharmD Regulatory Reviewer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRIPTODUR (triptorelin pamoate)
Dosage Form and Route:	extended-release injectable suspension, for intramuscular use
Application Type/Number:	NDA 208956
Applicant:	Arbor Pharmaceuticals, LLC

1 INTRODUCTION

On August 29, 2016, Arbor Pharmaceuticals, LLC submitted for the Agency's review a New Drug Application (NDA) for Triptorelin for (b) (4) Suspension for the treatment of children with central precocious puberty (CPP). On November 21, 2016, the Agency granted Arbor Pharmaceuticals, LLC the proprietary name TRIPTODUR for NDA 208956.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on April 4, 2017 and May 22, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRIPTODUR (triptorelin pamoate) extended-release injectable suspension, for intramuscular use.

2 MATERIAL REVIEWED

- Draft TRIPTODUR (triptorelin pamoate) extended-release injectable suspension, for intramuscular use MG received on June 1, 2017, and received by DMPP and OPDP on June 14, 2017.
- Draft TRIPTODUR (triptorelin pamoate) extended-release injectable suspension, for intramuscular use Prescribing Information (PI) received on August 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 14, 2017.
- Approved SUPPRELIN LA (histrelin acetate) subcutaneous implant comparator labeling dated May 19, 2017.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHARON W WILLIAMS
06/21/2017

MEENA RAMACHANDRA
06/21/2017

MARCIA B WILLIAMS
06/21/2017

LASHAWN M GRIFFITHS
06/21/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 19, 2017

To: Jennifer Johnson, Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208956
OPDP labeling comments for TRIPTODUR (triptorelin pamoate) extended-release injectable suspension, for intramuscular use

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On May 22, 2017, OPDP received a consult request from DMEP to perform a review of proposed Package Insert (PI) and Medication Guide (MG) for TRIPTODUR (triptorelin pamoate) extended-release injectable suspension, for intramuscular use (Triptodur).

OPDP conducted a review of the proposed PI provided by DMEP project manager Jennifer Johnson via e-mail on June 14, 2017 titled "Triptodur PI from sponsor 08 June 2017 annotated". OPDP's comments on the proposed labeling are provided below.

The Medication Guides will be reviewed in collaboration with DMPP and will be provided under a separate cover.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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/s/

MEENA RAMACHANDRA
06/19/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 12, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208956
Product Name and Strength:	Triptodur (triptorelin pamoate) for injectable suspension, 22.5mg
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC.
Submission Date:	May 31, 2017, June 1, 2017, and June 8, 2017
OSE RCM #:	2016-1983-1
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels, carton labeling, and Prescribing Information (PI) for Triptodur (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

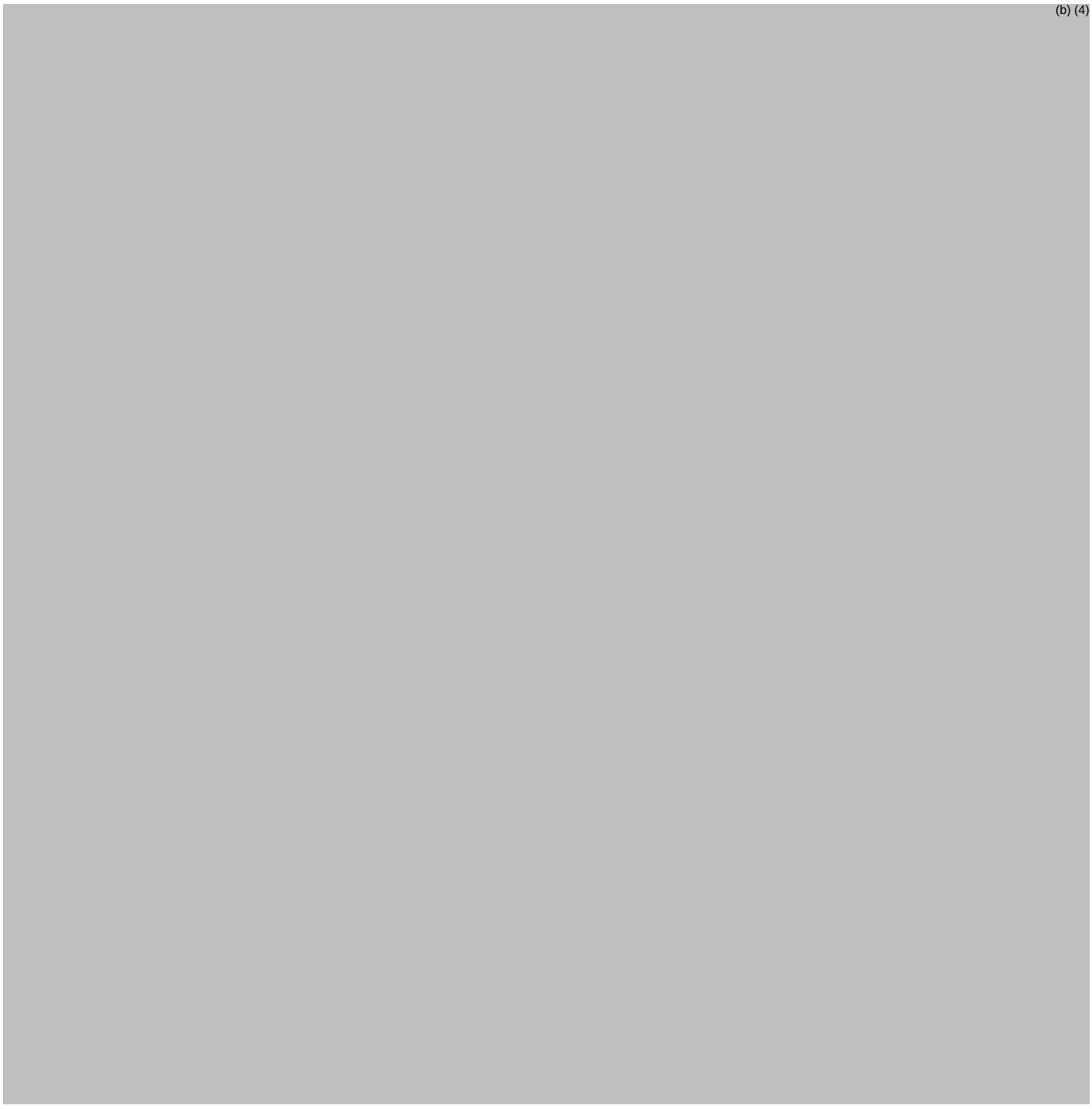
2 CONCLUSION

The revised container labels, carton labeling, and Prescribing Information (PI) for Triptodur is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Ogbonna, C. Label and Labeling Review for Triptodur (NDA 208956). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 26. RCM No.: 2016-1983.

APPENDIX A. LABEL AND LABELING SUBMITTED ON MAY 31, 2017, AND JUNE 1, 2017:

Container labels



Diluent Label:

Carton labeling

Carton Label:

Prescribing Information (PI):

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/s/

CASMIR I OGBONNA
06/12/2017

HINA S MEHTA
06/12/2017

INTERCENTER CONSULT MEMORANDUM

Device Constituent Part Design Review: CDER NDA 208956 - CDRH ICC1600637

Date: June 5, 2017

To: Jennifer Johnson, RPM
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II (ODEII)
Office of New Drug (OND)
Center for Drug Evaluation and Research (CDER)

From: Rong Guo
GHDB/DAGRID/ODE/CDRH

Through: CDR Alan Stevens, Branch Chief
GHDB/DAGRID/ODE/CDRH

Re: NDA 208956

Subject: Device Constituent Part Design Review: CDER NDA 208956 - CDRH ICC1600637; CDER review of triptorelin pamoate for (b) (4) suspension; CDRH review of device constituent part of the combination product (pre-filled syringe)

Applicant	ARBOR PHARMACEUTICALS LLC
Indication for Use	treatment of children with central precocious puberty (CPP)
Drug / Biologic Constituent	Drug/Device
Drug component	Triptodur (triptorelin pamoate for (b) (4) suspension)
Device Constituent	pre-filled syringe for sterile water for injection

Recommendation: CDRH recommends approval based on review of the device constituent of the combination product.

Digital Signature Concurrence Table	
Reviewer	Rong Guo -A (Affiliate) — Digitally signed by Rong Guo -A (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=2000718961, cn=Rong Guo -A (Affiliate) Date: 2017.06.07 08:48:57 -04'00'
Branch Chief	Alan M. Stevens -S — Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2017.06.07 09:15:08 -04'00'

Note: Reviewer comments are indicated by italics. Unless otherwise stated, all figures and tables presented below were taken from this submission NDA 208956.

Administrative

The CDRH/ODE reviewer performed a design review of submission materials intended to support the

safety and functionality of the device constituent parts of the subject combination product. This evaluation covered the intended design and design control information for the subject device constituent part.
Essential performance elements of the device under review by the consultant were considered to be:

Dose accuracy
Functionality of the syringe

This review did not cover the following content:

Review of drug product
Review of primary container closure-drug product interaction, sterility, or toxicology
Manufacturing of the drug product
Manufacturing of the device constituent part of the combination product

Documents Reviewed:

Cross-Referenced 510(k) # or DMF	Device	Letter of Authorization Included in NDA / BLA	
		YES	NO
DMF (b) (4)	(b) (4)	yes	
DMF		yes	
DMF		yes	
DMF		yes	
DMF		yes	
(b) (4)	(b) (4)	yes	

(b) (4)

(b) (4)

Purpose / Background

TRIPTODUR is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of children with central precocious puberty (CPP), which is defined as early onset of secondary sexual characteristics

(generally earlier than 8 years of age in girls and 9 years of age in boys) associated with pubertal pituitary gonadotropin activation. It may show a significantly advanced bone age that can result in diminished adult height.

Device Description and Performance Requirements

Indications for Use	treatment of children with central precocious puberty
Route of Administration	intramuscular injection

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 triptorelin pamoate microgranules (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 syringe plunger
- One Package Insert

The kit should be stored at 20-25°C (68-77°F) [see USP Controlled Room Temperature], and cannot be frozen.

Sterile Water for Injection is packaged in a (b) (4) glass syringe which is sealed with a (b) (4) stopper and (b) (4) cap (b) (4) and luer-lock adaptor.

Table 1: Primary Container Closure System for Sterile Water for Injection

Component	Supplier	Reference
(b) (4)		

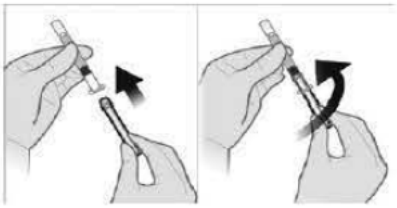
Device Characteristic	Description / Specification
Syringe Barrel Material Type	(b) (4) glass
Needle Specifications • Length(s) • Gauge(s) • Connection type	21 gauge, 1½" needles (thin-wall) with safety cover

○ ISO 594 ○ Prestaked	
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Healthcare Professionals (HCPs) only
Residual Medication Volume	n/a
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	mL
Storage conditions and expiry	20-25°C (68-77°F) not exceed 36 months
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.	IFU attached below
Safety Features • Needle safety	Safety cover

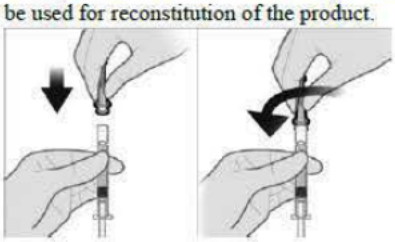
Instructions for use

Please read these instructions completely before you begin.

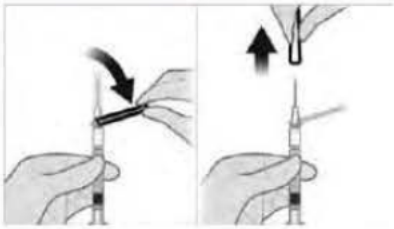
(b) (4)



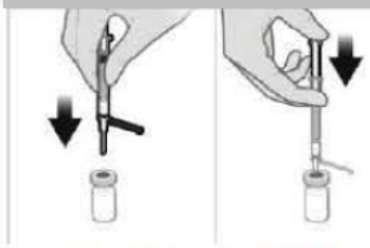
- Remove the cap from the syringe barrel.
- Firmly attach one of the sterile safety needles onto the Luer Lock syringe with a push and clockwise twist. This needle will only be used for reconstitution of the product.



  - Pull back on the safety cover toward the syringe and away from the needle.
  - [redacted] pull the clear needle shield [redacted] off.



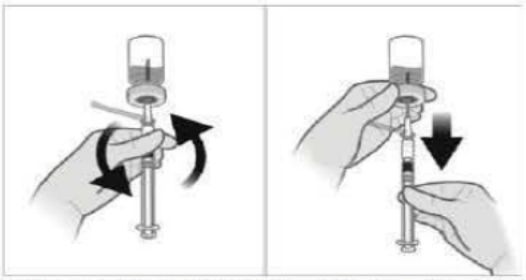
- [redacted] insert the needle [redacted] and inject the water into the vial [redacted] Do not release the plunger rod.



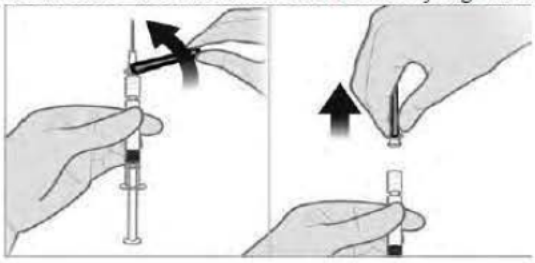
- [redacted] gently swirl the vial so that the diluent rinses the sides of the vial. [redacted] a milky suspension.

Important: Once mixed, proceed to the next steps and administer without delay.

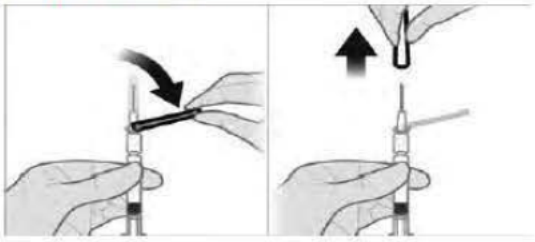
- Invert the vial and move back the syringe in order to position the end of the needle very near the level of the stopper, making sure the needle lumen is still completely in the vial.
- Pull back the plunger rod slowly to withdraw the reconstituted product into the syringe, withdrawing as much of the reconstituted product into the syringe as possible.



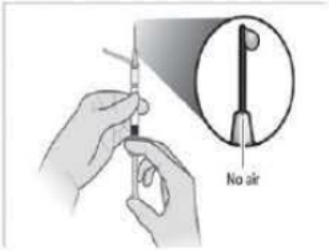
- Remove the first needle by first pushing the safety cover forward toward the needle until you hear and/or feel it lock. Grasp the needle hub to disconnect the needle from the syringe and discard it. **This (first) needle will no longer be used.**



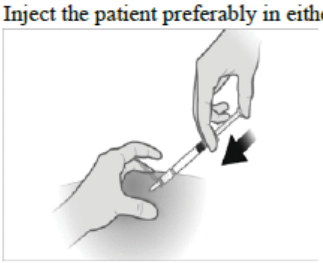
- Firmly attach the *second* sterile needle onto the Luer Lock and pull back the safety cover towards the syringe. This needle will be used for administration.



- Prime the needle to first remove air from the syringe, then administer the suspension immediately.



- Inject the patient preferably in either buttock or thigh using the entire contents of the syringe.



- **The injection of the suspension should be performed relatively rapidly and in a steady and uninterrupted manner in order to avoid any potential blockage of the needle.**

After administering the injection, immediately activate the safety cover:

- Center your thumb or forefinger on the textured finger pad area of the safety cover and push it forward over the needle until you hear or feel it lock.
- Use the one-handed technique and activate the mechanism away from yourself and others.
- Immediately discard the syringe assembly after a single use into a suitable sharps container.

Design Control Review

Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer		no	
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	yes		
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	yes		1.16
Validation Data	yes		
Traceability Documentation		no	

Design requirements

The Sponsor states that Arbor is a virtual company that outsources final product which has been previously approved/cleared through FDA (drug and device) and combines these items into a non-functional kit that is readied for commercial use. While Arbor maintains a design file citing the respective constituent parts (Table 1 shown below), the original suppliers maintain their own Design History Files. The justification is acceptable.

Table 1: Design Requirements

	Description	Specification	Current Design Revision Levels
1	One (1) (b) (4) syringe filled with (b) (4) SWFI	(b) (4)	N/A
2	One (1) Syringe plunger		N/A
3	One (b) (4) glass vial filled with triptorelin pamoate microgranule, 22.5 mg		N/A
4	Two (2) commercially available 21-gauge 1.5" needles		N/A
5	Individual Labels on each component		(b) (4)
6	(b) (4) package		
7	Outer package label		
8	Shipping Carton		N/A

Traceability Documentation
Traceability Documentation was not provided in the submission, however, after several IR communications, the reviewer was able to obtain all required information.

Design Verification and Validation Review

Standard / Guidance		Conforms		
		Yes	No	N/A
Syringes	ISO 11040-4 Prefilled Syringes – Glass Barrel for Injectables	yes		
	ISO 11040-5: Prefilled syringes - part 5: plunger stoppers for injectables.	yes		
	ISO 7886, Sterile Hypodermic Syringes for Single Use;	yes		
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use;	yes		
	ISO 9626, Stainless Steel Needle Tubing for Manufacture of Medical Devices;	yes		
Sharps Injury Prevention Feature	Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features	Yes		
	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	yes		
Connections	ISO 594-1: Conical Fittings with 6% (Lure) Taper for Syringes,	yes		

	Needles and Certain Other Medical Equipment - Part 1: General Specifications			
	ISO 594-2: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: Lock Fittings	yes		

Design Verification Review

Essential Performance Requirement	Specification	Verification Test Results	
		PASS	FAIL
Break Force	(b) (4)	pass	
Glide Force		pass	
Expelled Volume		pass	
(b) (4) Cap Removal			
Sharps Injury Protection – Simulated Use Testing		pass	
Biocompatibility of Sharps Injury Prevention Feature per ISO 10993		pass	
		pass	
		pass	
Stability and Simulated shipping/transportation Data adequately verifies device will meet essential performance requirements at expiry		pass	

Functionality of the syringe - initiating force and sustaining force

Break up force and gliding force are conducted at (b) (4) through Shelf Life to verify performance requirements of the proposed syringe per established criteria detailed in the lot release criteria shown below in section Design Transfer Activities – Release Specifications.

An IR was conveyed to the Sponsor on May 2, 2017.

> *"You provided specifications of Break up force and Gliding force for Water for Injection, while did not provide Break up force and Gliding force for reconstituted final drug product. Please provide a justification that the specifications of Break up force and Gliding force for Water for Injection can be used for the reconstituted final drug product based on the drug uniformity and viscosity comparison with water, otherwise additional testing on the reconstituted final drug product may be necessary."*

The Sponsor responded on May 10, 2017, stating that the reconstituted drug product suspension does not have the same behavior and viscosity as Water for Injection. Tests were conducted on five (5) prefilled syringes containing the reconstituted suspension of final product equipped with 21G needles, and the results are shown below:

(b) (4)

***Reviewer comment**: The results showed that the average break up force is around (b) (4) and the average gliding force is around (b) (4) with the maximal gliding force as (b) (4). These data are compatible with the proposed specifications of Break up force and Gliding force (b) (4) for Water for Injection. The reviewer agrees that the specifications of Break up force and Gliding force for Water for Injection can be used for the reconstituted final drug product.*

Dose accuracy

(b) (4) evaluates Extractable Volume as a release test to ensure volume meets specification for SWFI. The accuracy of a delivered dose of lyophilized triptorelin pamoate (Lot 17-008919) after its reconstitution was also assessed with the syringe SWFI per the instructions in the Dosage and Administration section of the package insert and the result is shown here:

Table 2: Accuracy of Delivered Dose

Sample number:	Results	Acceptance criteria
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
Mean (mg)		
Acceptance Value (AV, %)		

The reviewer was not clear how the Sponsor performed the dose accuracy study. An IR requesting the protocol was sent to the Sponsor on May 2, 2017.

"Please provide a detailed protocol of the dose accuracy study of lyophilized triptorelin pamoate which you submitted in Response to FDA Request-Study Quality Information Feb 24 2017."

The Sponsor responded on May 10, 2017 and provided the detailed protocol of the dose accuracy study. The study was performed by Debiopharm Group for the Sponsor. Basically, the drug product is reconstituted with the syringes pre-filled with (b) (4) ml water for injection, and then the assay of the injected dose in mg by HPLC for each of the 10 vials tested and the uniformity of dosage units are calculated.

***Reviewer comment**: When reconstituted with the prefilled syringe, the dose delivered from the prefilled syringe is consistent and the mean assay value obtained is within (b) (4)% of the label claim, and the Acceptance Value for dose uniformity is lower than (b) (4)%, which complies with USP <905>. The dose accuracy study is acceptable.*

(b) (4) Cap Removal

The Sponsor did not provide (b) (4) cap removal information. An IR was sent to the Sponsor requesting this information on May 2, 2017.

"You provided quality control specifications for Sterile Water for Injection in 3.2.P.5. Control of Drug Product. Please contact the DMF holder and obtain the data for (b) (4) cap removal force and include (b) (4) cap removal force in the spec table, otherwise additional testing may be required."

(b) (4) responded on May 10, 2017, and provided two year stability data for pull-off-force for the (b) (4) The response is acceptable.

Sharps Injury Prevention

(b) (4) (b) (4) are co-packaged. The 510(k) submission, (b) (4) for (b) (4) is checked by the device reviewer. This device was cleared in 2001, before the FDA Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features was issued (2005). The sharps injury prevention feature of the needle contains a mechanism that covers the needlepoint after use. The reviewer accessed the 510(k) submission (b) (4) Simulated use study was included in the 510(k) submission and complies with Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features.

(b) (4) comply with the following standards when the 510(k) submission was cleared in 2001:
ISO 7864, Sterile Hypodermic Needles for Single-Use
ISO 594, Conical Fittings with 6% (LUER) Taper
ISO 6009, Hypodermic Needles for Single Use - Color Coding for Identification

Stability

Post-approval stability studies will be conducted by (b) (4), the DMF (b) (4) holder of Sterile Water for Injection. The Sponsor states that the expiration period will not exceed 36 months when stored at label storage recommendations of (b) (4) °C. The proposed storage of Sterile Water for Injection as part of the Triptorelin for (b) (4) Suspension kit is: Store at room temperature 20-25ºC (68-77ºF); (b) (4) The expiration date of the kit will be established based on the earliest expiry date of the components, either the triptorelin pamoate microgranules 22.5 mg or the Sterile Water for Injection.

DMF holder of Sterile Water for injection submitted the stability data on May 31, 2017.

Table 3. Stability Conditions and Time Points for Commercial Scale Batches of (b) (4) mL WFI PFS

Stability type	Conditions	Times
(b) (4)		

The results of the (b) (4) commercial scale validation batches (b) (4) at (b) (4) were conform to specifications across the lots and storage conditions. One representative data from (b) (4) are shown below:

Table 28. Stability Data for (b) (4)

(b) (4)

Reviewer comment: *The stability testing includes the essential performance requirements of the device: dose accuracy and functionality of the syringe. The Sponsor already provided dose accuracy of the final drug product at release. Based on there is no stability change for the drug product, dose accuracy of the*

diluent can be justified to substitute as dose accuracy of the final drug product. Dose accuracy is confirmed up to (b) (4) *The devices still meet the essential performance requirements after* (b) (4)*. The Sponsor is claiming a 36-month shelf life. The devices are constructed from well precedented materials. The shelf life for the combination product will be conservatively restricted by the shortest shelf life of the in-going components. The* (b) (4) *pre-filled syringe is packaged together with the drug product, in their original packaging, into the carton. The packaging and storage conditions (* (b) (4) *for the combination product will not adversely impact the devices, therefore additional testing of the device essential performance requirements after its intended shelf life and use life was not deemed necessary. The response is adequate.*

Connections
(b) (4) and (b) (4) syringe are used for this submission. The reviewer checked DMF (b) (4) for the syringe and 510(k) submission (b) (4) for the needle. They comply with ISO 594-1: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: General Specifications and ISO 594-2: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: Lock Fittings. No connection testing is required in this case.

Design Validation Review

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	yes		

The Sponsor did not provide Risk Evaluation and Mitigation Strategies (REMS). However, in section 1.16 Risk Management Plan, a risk analysis on the device constituent part was included.

Table 5: Summary of Identified Risks and Labeling Mitigation

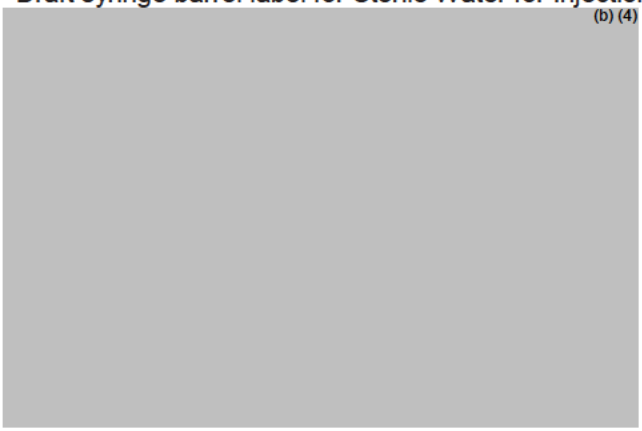
Step	Error and Harm	Identified Risk	Mitigation	Post Mitigation Severity/ Probability
Become familiar with the device and dosing information	User does not understand procedure for correctly reconstituting lyophilized triptorelin pamoate microgranules	Lyophilized triptorelin pamoate microgranules are not correctly reconstituted	Instructions to specify that the suspension is milky white prior to injection	Serious/ Improbable
	User does not understand the need to promptly administer the medication once prepared	Lyophilized triptorelin pamoate microgranules fall out of suspension - medication concentration below specification	Instructions will state once mixed, give without delay to avoid falling out of suspension	Serious/ Improbable
Prepare for injection	Transfer medication from vial into syringe: User does not understand procedure for correctly reconstituting lyophilized triptorelin pamoate microgranules	User holds the vial in a way that the diluent never actually mixes with the lyophilized drug and then aspirates the diluent back into the syringe	Instructions for use outline how to reconstitute medicine and insure that it was done properly	Serious/ Improbable
	Transfer medication from vial into syringe: User doesn't know how much	User doesn't transfer sufficient medication into syringe	Instructions for use specifically mention the placement of	Serious/ Improbable

	medication to transfer		needle in order to get 2 ml.	
	Transfer medication from vial into syringe: User doesn't know how much medication to transfer	Syringe lacks labeling to identify correct amount of medication to transfer	Once reconstituted with 2 cc of sterile water, the triptorelin vial holds the entire volume needed for injection. Instructions for Use specifically instruct the Healthcare Practitioner to withdraw as much of the reconstituted product as possible into the syringe.	Serious/ Improbable
	Transfer medication from vial into syringe:	User holds the needle above the fluid level in the vial and draw in some air, rather than medication	Instructions for use specifically mention the placement of needle near the stopper and include graphics	Negligible/ Improbable
Deliver an injection	User waits too long after reconstituting medication	Medication falls out of suspension and clogs needle	(b) (4)	Not Applicable

Reviewer comment: *The pre-filled syringe device risks have been managed to the point where it is appropriate for moving forward into commercial supply. The sponsor has identified no residual risks after mitigation steps from the device point of view.*

Labeling

Draft syringe barrel label for Sterile Water for Injection is shown below:



Draft carton label is shown below:

Design Transfer Activities – Release Specifications

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5.1:

Table 1: Quality Control Specifications

Test	Analytical Method	Release Criteria	Shelf Life Criteria
Appearance	In-house	Colorless, clear and free of visible particles	Colorless, clear and free of visible particles
Extractable volume	(b) (4)		(b) (4)
Particle contamination (b) (4)			
Particle contamination (b) (4)			
	USP monograph	Conforms	
Sterility	USP<71>	No growth	
Bacterial endotoxins	USP<85>	(b) (4)	
Break up force	Internal procedure	---	
Gliding force	Internal procedure	---	
Container integrity test	Internal procedure	---	Conforms

Information Requests

An IR was sent on February 27, 2017:

Regarding your submission, NDA 208956, you need to demonstrate safety and effectiveness of the combination product, including the device constituent parts. In order for the Agency to complete the assessment of the safety and effectiveness of your proposed drug product, please provide the following:

1. Information from dosing accuracy studies, biocompatibility studies, and leachable/extractable studies are needed to support this NDA. Please state as soon as possible where this information can be found. If this information is provided through a referenced DMF, please provide the exact location within the DMF as well as the date that the information was submitted to the DMF. A detailed description of the expected information is included in the following text.

2. Provide the following information for the devices included in the submission:

a. A description of the complete device, including individual device components, configurations, and packaging in its final form.

b. A document listing the design requirements specifications for the device constituents.

c. Risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states.

d. Verification and validation of the following specific system attributes. If this information is within a device master file, please provide the exact location.
i. Accuracy of delivered dose of reconstituted final drug product
ii. Biocompatibility of system components commensurate with the level and duration of patient contact (see question 3 for additional biocompatibility comments)
iii. Compatibility of the DP vial, luer-lock adaptor, and syringe (i.e. fitment of the adaptor to vial, and syringe to the adaptor without leakage)
e. The lot release specifications for the essential performance requirements of the device constituent part of the proposed combination product.
3. Please provide the location of the following information to address the biocompatibility of the device constituents of the combination product:
a. The leachables and extractables testing along with a toxicological risk assessment based on the intended patient population.
b. The biocompatibility testing commensurate with the level of patient contact according to ISO 10993, Biological Evaluation of Medical devices Part 1: Evaluation and Testing. The biocompatibility evaluation should take into account the repeated use of the device, which includes the re-use of the each syringe. The biocompatibility evaluation should also take into account the drug that is being delivered. Please provide the location of the test summaries, test method (including sample preparation and acceptance criteria), and the full test reports. The extractables and leachables testing may be used to address the systemic endpoints (e.g. acute and subchronic toxicity).

Another IR was conveyed to the Sponsor on May 2, 2017.

1. *You referenced 510(k) submission* (b) (4) *packaged in the combination product, while no authorization letter was provided. In order for the Agency to reference information regarding the needle, please provide a letter of cross-reference from* (b) (4)
2. *You provided specifications of Break up force and Gliding force for Water for Injection, while did not provide Break up force and Gliding force for reconstituted final drug product. Please provide a justification that the specifications of Break up force and Gliding force for Water for Injection can be used for the reconstituted final drug product based on the drug uniformity and viscosity comparison with water, otherwise additional testing on the reconstituted final drug product may be necessary.*
3. *You provided quality control specifications for Sterile Water for Injection in 3.2.P.5. Control of Drug Product. Please contact the DMF holder and obtain the data for* (b) (4) *cap removal force and include* (b) (4) *cap removal force in the spec table, otherwise additional testing may be required.*
4. *Please provide a detailed protocol of the dose accuracy study of lyophilized triptorelin pamoate which you submitted in Response to FDA Request-Study Quality Information Feb 24 2017.*

The Sponsor responded to the IRs and the responses are incorporated in the review memo. No more deficiencies are identified.

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

/s/

JENNIFER L JOHNSON
06/07/2017
CDRH consult review by Rong Guo (concurrence from team leader Alan Stevens)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Abdominal & Surgical Devices Branch

Date:	May 31, 2017
To:	Anika Lalmansingh, CDER/OPRO. WO75/4631 anika.lalmansingh@fda.hhs.gov
	Office of combination products at combination@fda.gov **RPM:** Anika Lalmansingh anika.lalmansingh@fda.hhs.gov
Through:	Acting Chief, Abdominal & Surgical Devices Branch, DMQ, OC, CDRH George K. Ngatha -S 2017.06.01 10:34:35 -04'00'
From:	Felicia Brayboy, CSO, Abdominal & Surgical Devices Branch, DMQ, OC, CDRH
Applicant:	Arbor Pharmaceuticals, LLC 6 Concourse Parkway, Suite 1800 Atlanta, Georgia 30328
Application # **Consult #**	ANDA 208956 ICC1600613
Product Name:	triptorelin pamoate for (b) (4) suspension

Combination Product Intended Use: Treatment of children with central precocious puberth (CPP).

Pre-Approval Inspection: No

Documentation Review: Under Review /Additional Information Required

Final Recommendation: **APPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of ANDA 208956.

PRODUCT DESCRIPTION

Triptorelin pamoate is the active pharmaceutical ingredient used for Triptorelin for (b) (4) Suspension 22.5 mg. The chemical name of the drug substance is L-pyroglutamyl-L-histidyl-Ltrytophyl-L-seryl-L-tyrosyl-Dtryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide, pamoate salt. The US adopted name is triptorelin pamoate, and the International Nonproprietary Name (INN) triptorelin embonate. The drug product triptorelin pamoate microgranules 22.5 mg will be provided in a kit with sterile water for injection used for reconstituting the lyophilizedmicrogranules. This product will be marketed by Arbor Pharmaceuticals LLC as an injectable suspension that is indicated for the treatment of children with central precocious puberty.

Container Closure System [Sterile Water for Injection, (b) (4) Injectable]

Sterile Water for Injection is packaged in a (b) mL (b) (4) glass syringe which is sealed with a (b) (4) stopper and (b) (4) cap (b) (4) and luer-lock adaptor.

Container Closure System [Triptorelin for (b) (4) Suspension 22.5 mg, Debiopharm Research & Manufacturing SA, Injectable Suspension]

Triptorelin pamoate microgranules 22.5 mg is packaged in (b) (4) glass vial with 20 mm (b) (4) stopper. The primary container-closure system is sealed with an aluminum overseal with a plastic Flip-off button.

Secondary Packaging:

(b) (4) secondary packaging (b) (4) will be used for the triptorelin pamoate microgranules 22.5 mg. The drug product vial is placed in a kit with a pre-filled syringe containing Sterile Water for Injection. In addition, two (2) commercially available 21-gauge 1.5” needles are provided in the kit as specified in Package Insert and kit labeling.

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

Facility	Responsibility
(b) (4)	(b) (4)

Inspectional History – An analysis of the firm's inspection history over the past (b) (4) showed that an inspection conducted on (b) (4) The inspection covered drug GMP requirements and was classified VAI.

This was a full GMP inspection of (b) (4)
This inspection was conducted to assess the cGMP state of the facility. Coverage was given to (b) (4)

The previous FDA inspection of this facility was conducted from (b) (4) The inspection covered four systems of (b) (4). The previous inspection was classified VAI, resulting in a two-item FDA observation form. During the (b) (4) the investigators verified the firm's corrections to the previous FDA 483 observation items and other verbal discussions and commitments. (b) (4)

(b) (4)

n

Inspection Recommendation:

An post approval inspection is required because:

(b) (4)

NOTE: If CDER is planning to conduct a pre-approval inspection at this site please include QSR coverage; otherwise a post approval inspection will suffice.

A comprehensive baseline (b) (4) inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Facility	Responsibility
Debiopharm Research & Manufacturing SA Rue du Levant 146 CH-1920 Martigny Switzerland Establishment Registration Number: 3002806850 DUNS Number: 481942860	Manufacturing of drug product Primary packaging Labeling of drug product Finished product release testing Finished product stability testing (b) (4)

Inspectional History – An analysis of the firm's inspection history over the past (b) (4) showed that an inspection conducted on (b) (4) The inspection covered drug GMP requirements and was classified NAI.

This comprehensive cGMP inspection and Pre-Approval Inspection (PAI) of a finished dosage small volume sterile injectable manufacturer was performed according to Compliance Program 7356.002 (Drug Manufacturing Inspections), 7356.002A (Sterile Drug Manufacturing Inspections) and 7346.832 (Pre-Approval Inspections). This inspection was conducted under PAC: 56002 Drug Manufacturing Inspections, 56002A Sterile Drug Manufacturing Inspections and 46832 Pre-Approval Inspections. This current inspection covered the following five systems: 1) Quality, 2) Laboratory, 3) Facilities and Equipment, 4) Production, 5) Materials. This current inspection verified that the firm continues to operate as a finished dosage small volume sterile injectable manufacturer. This Debiopharm Research & Manufacturing facility performs finished drug product manufacturing and filling operations under a (b) (4) The last inspection was conducted (b) (4) and at the conclusion of this inspection Form FDA 483 was issued for four deficiencies. The previous inspection was classified **VAI.** During the (b) (4) inspection it was verified that the firm had corrected the deficiencies noted on the previous FDA 483.

Inspection Recommendation:
An post approval inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed

NOTE: If CDER is planning to conduct a pre-approval inspection at this site please include QSR coverage; otherwise a post approval inspection will suffice.

A comprehensive baseline (b) (4) inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Facility	Responsibility
(b) (4)	

Inspectional History – An analysis of the firm's inspection history showed that the inspections below were conducted and classified NAI. The inspections covered medical device QS requirements.

Start Date	End Date	Basis	District Decision	483 YN
(b) (4)		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No

Inspection Recommendation:
An inspection is not required because:

- The last medical device inspection of the firm was acceptable.

Facility	Responsibility
(b) (4)	

Inspectional History – An analysis of the firm's inspection history showed that the inspections below were conducted and classified NAI. The inspections covered drug GMP requirements.

Start Date	End Date	Basis	District Decision	483 YN
(b) (4)		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Consumer Complaint	No Action Indicated (NAI)	No

Inspection Recommendation:
An inspection is not required because:

- The last 5 inspections have been NAI.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

(b) (4)

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(b) (4)

(b) (4)

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The application for triptorelin pamoate for (b) (4) suspension – ANDA 208956 is approvable from the perspective of the applicable Quality System Requirements.

1. The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

2. A post-approval inspection is recommended for:

   a. Facility 1 (b) (4)
   (b) (4)

   b. Facility 2
   Debiopharm Research & Manufacturing SA Rue du Levant 146
   CH-1920 Martigny Switzerland
   Establishment Registration Number: 3002806850

Felicia L.
Brayboy -S

Felicia Brayboy

Prepared: FBrayboy: May 31, 2017
Reviewed: GNgatha

CTS No.: ICC1600613
ANDA 208956

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

/s/

ANIKA A LALMANSINGH
06/01/2017
Uploading on behalf of Felicia Brayboy, CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and
Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: 5/22/2017 **Date consulted:** 4/20/2017

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Jane Liedtka, M.D., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Metabolism and Endocrinology Products (DMEP)

Drug: TRIPTODUR (triptorelin pamoate)

NDA : 208956

Applicant: Arbor Pharmaceuticals, LLC

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication(s): Treatment of central precocious puberty (CPP)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 208956
- DPMH Consult Request dated 4/20/2017, DARRTS Reference ID #4087281

Consult Question: "Please confirm that PLLR format is acceptable."

BACKGROUND

On August 29, 2016, Arbor Pharmaceuticals, LLC submitted NDA 208956 for TRIPTODUR (triptorelin pamoate) for (b) (4) Suspension, 22.5 mg for the treatment of children with central precocious puberty (CPP). The 505(b)(1) application relies on "right of reference" to currently approved TRELSTAR (triptorelin pamoate) (NDA 20715, NDA 21288, NDA 022437) which is indicated for the palliative treatment of prostate cancer. The applicant also performed a study to assess safety and efficacy in children with CPP. TRIPTODUR was designated an orphan drug on August 20, 2012 for the treatment of children with CPP. The most recent revised labeling was submitted on March 24, 2017 in response to a request for class labeling changes sent to the applicant on February 24, 2017.

TRIPTODUR (triptorelin pamoate) is a synthetic decapeptide agonist of gonadotropin releasing hormone (GnRH) with a molecular weight of 1699.9 Daltons. Comparative *in vitro* studies demonstrate that triptorelin is 20-fold more active than native GnRH in displacing ^{125}I-GnRH from pituitary receptor sites. It is administered as one 22.5 mg (b) (4) IM injection every six months. Triptorelin is distributed and eliminated according to a 3-compartment model with half-lives of six minutes, 45 minutes and three hours. It does not bind to plasma proteins. The reference product TRELSTAR is contraindicated in pregnancy, because it blocks the pulsatile secretion of LH and FSH, making miscarriage more likely, and is labeled Category X.

PLLR

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect.[1] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

DATA REVIEW

Pregnancy

Non-clinical

In pregnant rats administered triptorelin at doses of 2, 10, and 100 mcg/kg/day during the period of organogenesis, maternal toxicity (decrease in body weight) and embryo-fetal toxicities (pre-implantation loss, increased resorption, and reduced number of viable fetuses) was observed at 100 ug/kg, approximately 4 times the clinical dose based on body surface area. No embryonic and fetal developmental toxicities were observed in

[1] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

mice at doses up to 4 times the clinical dose. Teratogenic effects were not observed in viable fetuses in rats or mice.

Applicant's Review of the Literature

The applicant performed a search of the literature using PubMed and the following search terms, "triptorelin," and "pregnancy." The applicant notes, "though triptorelin is commonly used as part of *in vitro* assisted pregnancies, no clinical studies of its teratogenic effects have been conducted." Studies specifically identifying pregnancies exposed to triptorelin included a report of three women exposed to long-acting triptorelin acetate 3.75mg (used for the treatment of endometriosis) during the first trimester. Two of the pregnancies delivered healthy infants at term. These children were followed annually for five years and were determined to be developing normally. The third pregnancy, in a woman with diabetes and hypothyroidism, ended in a miscarriage at 14 weeks gestation.[2]

The applicant also identified a review of 346 pregnancies exposed to GnRH agonists. Of those 346 pregnancies, 46 were exposed to triptorelin, and of these 9/46 (19.5%) had spontaneous abortions.[3]

The applicant concluded that, "reported triptorelin exposures during pregnancy are too few to adequately assess possible detrimental effects during pregnancy or risks to the fetus."

DPMH Review of Literature:

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex[4] using the search terms, "triptorelin and pregnancy," "triptorelin and pregnant women," "triptorelin and pregnancy and birth defects," "triptorelin and fetal malformations," "triptorelin and stillbirth," and "triptorelin and miscarriage."

Micromedex[4] states, "Given the drug's clinical use in controlled ovarian stimulation, it is assumed the patient will be closely monitored for pregnancy status. Pregnancy must be excluded prior to initiation of triptorelin. Triptorelin is contraindicated for use during pregnancy due to possible fetal adverse effects."

Shepard's[5] describes the following reports,

> Congenital anomalies have been reported in three of 107 infants whose mothers conceived after being treated with triptorelin. One infant was born with cleft palate, another with polydactyly, and a third with trisomy

[2] Fatima P, et al. Outcome of pregnancies after inadvertent exposure to a GnRH agonist in early pregnancy. Mymensingh Med J. 2011. 20:303-307.
[3] Chardonnens D, et al. Triptorelin acetate administration early in pregnancy: case reports and review of the literature. Eur J Obstet Reprod Biol. 1998. 80:143-149.
[4] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 4/26/2017
[5] Shepard's Catalog of Teratogenic Agents 2017, accessed 4/26/2017.

13, which was unlikely to be related to maternal exposure since the mother's treatment began 15 days after conception.[6,7,8,9,10,11,12,13,14]

In a study that compared the development of children born after long-acting GnRH agonist treatment with that of children born after spontaneous pregnancies, it was found that growth and neurodevelopment were normal in all children with the exception of one child born after *in vitro* fertilization who had diffuse hypotonia, attention-deficit hyperactivity disorder, and hyperactivity.[15]

A search of Embase and PubMed produced a number of case reports of pregnancies exposed to triptorelin during the first trimester that are summarized in Table 1. These cases include the three cases of congenital anomalies noted by Shepard. In summary, of the eighty-two cases, there were the three congenital anomalies described by Shepard, ten spontaneous abortions (12%), one fetal death (the Trisomy 13 case), six cases of gestational diabetes (7%), five preterm deliveries (four of these were twins) and one small for gestational age infant.

[6] Golan A, et al, Fetal outcome following inadvertent administration of long-acting DTRP[6] GnRH microcapsules during pregnancy: a case report. Hum Reprod. 1990.5(1):123-124.
[7] Ron-El R, et al. Midluteal gonadotropin-releasing hormone analog administration in early pregnancy. Fertil Steril. 1990. 53(3):572-4.
[8] Herman A, et al. Impaired corpus luteum function and other undesired results of pregnancies associated with inadvertent administration of a long-acting agonist of gonadotropin-releasing hormone. Hum Reprod. 1992. 7(4):465-468
[9] Har-Tov J, et al. Pregnancy during long-term gonadotropin releasing hormone agonist therapy associated with clinical pseudomenopause. Fertil Steril. 1993. 59(2):446-447.
[10] Weissman A and Shoham Z. Favorable pregnancy outcome after administration of a long-acting gonadotropin-releasing agonist in the mid-luteal phase. Human Reproduction. 1993. 8(3):496-497.
[11] Abromovici H, et al. Pregnancies following treatment by GnRH-a (decapeptyl) and myomectomy in infertile women with uterine leiomyomata. Int J Fertil. 1994. 39(1):150-155.
[12] Elefant E, et al. Administration of a gonadotropin-releasing hormone agonist during pregnancy: follow-up of 28 pregnancies exposed to triptoreline. Fertil Steril. 1995. 63(5):1111-3.
[13] Chardonnens D, et al. Triptorelin acetate administration in early pregnancy: case reports and review of the literature. Eur J Obstet Gynecol Reprod Biol. 1998. 80:143-149.
[14] Mayer A, et al. Increased prevalence of gestational diabetes mellitus in *in vitro* fertilization pregnancies inadvertently conceived during treatment with long-acting triptorelin acetate. Fertil Steril. 2005. 84:789-792.
[15] Ron-El R, et al. Development of children born after ovarian superovulation induced by long-acting gonadotropin-releasing hormone agonist and menotropins, and by *in vitro* fertilization. J Pediatr. 1994. 125:734-737.

Table 1. Summary of Cases in the Literature*

Reference	Demographic data	Obstetrical history	Exposure	Medical Conditions/Medications	Pregnancy/Infant Outcome
Weissman A and Shoham Z[16]	24-year-old (Israel)	G0 P0 History of anovulation, hyperprolactinemia	First Trimester Pregnancy discovered on Day 22 3.2 mg long-acting triptorelin	Gestational diabetes	Induced delivery at 40 weeks; health male infant described as "normal" at 12 months follow-up
Taskin O, et al. [17]	5 women ages 24-36 years (Turkey)	All G0P0 with primary infertility due to stage 3 or 4 endometriosis	First trimester All treated with 3.75 mg depot Decapeptyl (triptorelin)	All had normal amniocentesis; no medical conditions are reported	All pregnancies delivered at 40 weeks (type of delivery not reported). All five infants reported as "normal and healthy"
Golan A, et al[18]	37 year-old (Israel)	Unknown; had secondary infertility following tubal surgery	3.2 mg DTRP[6] (triptorelin)	Preterm labor at 29 weeks treated with ritodrine and dexamethasone	Spontaneous vaginal delivery at 39 weeks; healthy male infant reported to be "normal" at 18 months follow-up
Chardonnens D, et al.[19]	4 women ages 26-33 (France)	3 women G0P0 (primary infertility) 1 woman G3 P0 with secondary	First Trimester Women with primary infertility treated with 0.1 mg/day Decapeptyl (triptorelin) Woman with secondary	Not reported	All three women with primary infertility had live infants (including a set of twins). Two had vaginal deliveries – one term, and one at 35 weeks (twins). A Cesarean delivery at 39 weeks was performed in the other case due to cephalo-pelvic disproportion. All infants were described as normal. Follow-up to age 6 describes all as having normal development.

[16] Weissman A and Shoham Z. Favorable pregnancy outcome after administration of a long-acting gonadotropin-releasing agonist in the mid-luteal phase. Human Reproduction. 1993. 8(3):496-497.
[17] Taskin O, et al. Normal pregnancy outcome after inadvertent exposure to long-acting gonadotropin-releasing hormone agonist in early pregnancy. Human Reproduction. 1999. 14(5):1368-1371.
[18] Golan A, et al. Fetal outcome following inadvertent administration of long-acting DTRP[6] GNRH microcapsules during pregnancy: a case report. Human Reproduction. 1990. 5(1):123-124.
[19] Chardonnens D, et al. Triptorelin acetate administration in early pregnancy: case reports and review of the literature. Eur J Obstet Gynecol Reprod Biol. 1998. 80:143-149.

Reference	Demographic data	Obstetrical history	Exposure	Medical Conditions/Medications	Pregnancy/Infant Outcome
		infertility	infertility treated with 3.75 mg Decapeptyl IM		The case of secondary infertility ended in miscarriage at 6 weeks.
Elefant E, et al.[20]	Twenty-eight cases reported Average age 35 (France)	15 cases nulliparous 11 cases previous healthy children	All first trimester exposures	Not reported	23 live births (7 Cesarean section, 16 vaginal deliveries) - all infants reported to be healthy 1 fetal death at 33 weeks during an emergency Cesarean delivery due to severe maternal renal vascular disease. Karyotyping showed Trisomy 13. 4 spontaneous abortions
Har-Toov J, et al.[21]	29 year-old (Israel)	G1P1 Stage 4 endometriosis	First trimester DTRP[6] 3.2mg IM monthly (pregnancy discovered at 8 weeks gestation after 6 months of therapy)	Not reported	Normal vaginal delivery at 39 weeks, male infant healthy and reported to be developing normally at 12-month follow-up.
Shulman A, et al.[22]	5 women ages 24-33 (Israel)	Case #1- G0P0 polycystic ovary disease Case #2 - G0P0 Case #3- previous history fetal demise at 32 weeks due to placental	All first trimester exposures Case #1- 3.2 mg long-acting DTRP[6] IM Case #2- Dose of DTRP[6] not reported Case #3 – 3 2 mg DTRP[6] IM	One case of ovarian hyperstimulation	Case #1- Spontaneous delivery at 36 weeks; male infant with hypospadias Case #2 –Vaginal delivery at 37 weeks of healthy female infant Case #3 – Cesarean delivery at 39 weeks of healthy male infant Case #4 – Vaginal ultrasound at gestational day 68 indicated 5 embryos. After 12 weeks gestation embryo reduction performed.

[20] Elefant E, et al. Administration of a gonadotropin-releasing hormone agonist during pregnancy: follow-up of 28 pregnancies exposed to triptoreline. Fertil Steril. 1995. 63(5):1111-3.
[21] Har-Tov J, et al. Pregnancy during long-term gonadotropin releasing hormone agonist therapy associated with clinical pseudomenopause. Fertil Steril. 1993. 59(2):446-447.
[22] Shulman A, et al. Inadvertent exposure of early pregnancy to gonadotropin releasing hormone analogue. J Assist Reprod Genet, 1993. 10(5):387-391.

Reference	Demographic data	Obstetrical history	Exposure	Medical Conditions/Medications	Pregnancy/Infant Outcome
		abruption Case # 4 – G0P0 polycystic ovary disease Case #5 – G0P0	Case #4 - 3.2 mg DTRP[6] IM Case #5 - 3.2 mg DTRP[6] IM		Delivered two female infants at 34 weeks (mode of delivery and fetal outcome details not described) Case # 5 – spontaneous abortion first 1-2 weeks
Mayer M, et al.[23]	Case series of 35 pregnancies – mean age= 35 (Israel)	15 women G0P0	All received Decapeptyl C.R. 3.75 mg IM	5 cases of gestational diabetes	34 pregnancy outcomes reported (one was lost to follow-up): 29 deliveries (27/29 full term), 4 spontaneous abortions, one extrauterine pregnancy One case of small for gestational age, One congenital malformation (polydactyly), Five pregnancies with gestational diabetes
Ron-El, et al.[24]	2 cases (Israel)	2 women G0P0 with endometriosis	Both received 3.2 mg long-acting DTRP[6] IM		One case ended in early spontaneous abortion; second case birth of female infant at 34 weeks gestation with cleft palate.

Source: Reviewer's Table

[23] Mayer A, et al. Increased prevalence of gestational diabetes mellitus in *in vitro* fertilization pregnancies inadvertently conceived during treatment with long-acting triptorelin acetate. Fertil Steril. 2005. 84:789-792.
[24] Ron-El R, et al. Midluteal gonadotropin-releasing hormone analog administration in early pregnancy. Fertil Steril. 1990. 53(3):572-4.

Lactation

Non-clinical

There are no data on triptorelin and lactation in animals**.**

Applicant's Review of the Literature

The applicant conducted a search on PubMed and LactMed using the terms "triptorelin and breast milk" and did not identify relevant studies.

DPMH Review of Literature:

DPMH conducted a search of *Medications in Mother's Milk,*[25] the Drugs and Lactation Database (LactMed),[26] Micromedex,[4] and of the published literature in PubMed and Embase using the search terms "triptorelin and lactation," and "triptorelin and breast-feeding."

Triptorelin is not referenced in LactMed.

In *Medications and Mother's Milk,*[25] Thomas Hale, a breastfeeding expert, describes triptorelin as – No Data – Probably compatible, and states that "due to its structure and molecular weight it is very unlikely to enter milk, or to be orally bioavailable in the infant."

Micromedex states, "Infant risk cannot be ruled out."

A search of Embase and PubMed did not yield any articles related to triptorelin and breastfeeding, milk production, or the effects of the medication on the breastfed infant.

Females and Males of Reproductive Potential

Non-clinical

After 60 days of subcutaneous treatment followed by a minimum of four estrus cycles prior to mating, triptorelin at doses of 2, 20, and 200 mcg/kg (approximately 0.2, 2, and 16 times the estimated human daily dose based on body surface area) or two monthly injections as slow release microspheres (~20 mcg/kg/day) had no effect on the fertility or general reproductive function of female rats. No studies were conducted to assess the effect of triptorelin on male fertility.

Applicant's Review of the Literature

The applicant conducted a search on PubMed and LactMed using the terms "triptorelin and "fertility." The applicant identified a number of studies evaluating the long-term

[25] Hale TW and Rowe HE. (2017) Medications and Mother's Milk. Springer Publishing Company, LLC. New York, NY.

[26] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

reproductive potential for women previously treated with triptorelin for central precocious puberty (see Appendix A). Overall, after withdrawal of triptorelin therapy, resumption of puberty occurs and ovarian function does not appear to be adversely affected.[27,28] Women previously treated with triptorelin were able to become pregnant and have normal infants after stopping treatment. Only one study[29] addressed fertility in men previously treated with triptorelin. In this study of nine young men, there was no alteration of the testes (by ultrasound examination) and no alteration in semen analysis. Fertility was not assessed.

The applicant noted that in a published review of the London New Drugs Group,[30] the treatment of endometriosis and uterine fibroids, non-hormonal contraception is recommended during the first month of treatment. Central precocious puberty was not discussed in the review. A recent Consensus Statement by the European Society of Pediatric Endocrinology and Lawson Wilkins Pediatric Endocrine Society regarding treatment of CPP with GnRH agonists did not address the need for pregnancy testing.

DPMH Review of Literature:
DPMH conducted a review of Embase, and PubMed using the terms, "triptorelin and fertility", "triptorelin and contraception", "triptorelin and oral contraceptives", and "triptorelin and infertility." No additional studies on fertility or contraception were found. No studies on drug-drug interactions with hormonal contraceptives were identified.

Use in Pediatric Patients
Section 8.4 should be updated with a brief sentence summarizing the pediatric study and reference section 14. DPMH recommends the following language for section 8.4.

The safety and effectiveness of TRIPTODUR have been established in pediatric patients 2 years of age and older based on a single-arm open-label study of 44 children 2 to 9 years of age with CPP [*see Clinical Studies (14)*]. The safety and effectiveness of TRIPTODUR have not been established in pediatric patients less than 2 years old.

DISCUSSION/CONCLUSIONS

There are no systematic studies of triptorelin exposure during pregnancy. Limited data in pregnant women (case reports and case series) do not indicate a pattern of congenital anomalies or adverse outcomes. The rates of spontaneous abortions and gestational

[27] Oostdijk W, et al. Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. Arch Dis Child. 1996. 75:292-297.
[28] Arrigo T, et al. Menstrual cycle pattern during the first gynaecological years in girls with precocious puberty following gonadotropin-releasing hormone analogue treatment. Eur J Pediatr. 2007. 166:73-74.
[29] Bertolloni S and Mul D. Treatment of central precocious puberty by GnRH analogues: long-term outcome in men. Asian J Androl. 2008. 10:525-34.
[30] London New Drugs Group. Triptorelin and GnRH Analogues Review. http://www.medicineresources.nhs.uk/upload/documents/News/2008%20-%20March/17/Triptorelin1107.pdf. February 2007 (updated November 2007), accessed 5/10/2017.

diabetes are within previously published prevalence rates for the United States population.[31,32] However, animal data on increased pre-implantation loss and reduced fetal viability, and the mechanism of action of triptorelin, indicate a potential for fetal risk; therefore the use of triptorelin during pregnancy should be avoided.

There are no data on the presence of triptorelin in animal or human breast milk, the effects on the breastfed infant, or the effects on milk production. However, the molecular weight (>800 Daltons) and low oral bioavailability of triptorelin should minimize passage into breastmilk and impact on a breastfed infant.

Limited data do not indicate a concern about fertility with triptorelin use in women. Data on men are limited to one study that did not show an adverse effect of past triptorelin therapy for CPP on sperm or testes development. The literature on CPP does not address pregnancy testing prior to GnRH agonist treatment. DPMH does not recommend Section 8.3 be included in labeling for TRIPTODUR.

RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2 and 8.4, in TRIPTODUR labeling for compliance with the PLLR (see below or see attached). DPMH refers to the final NDA action for final labeling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TRIPTODUR is contraindicated in women who are pregnant since expected hormonal changes that occur with TRIPTODUR treatment increase the risk for pregnancy loss. Limited available data with triptorelin use in pregnant women are insufficient to determine a drug-associated risk of adverse developmental outcomes. Based on mechanism of action in humans and findings of increased pregnancy loss in animal studies TRIPTODUR may cause fetal harm when administered to pregnant (b) (4) . Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. (b) (4) . In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% -20%, respectively.

Data

Animal Data

[31] DeSisto CL, et al. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS, 2007-2010. Prev Chronic Dis. 2014.:130415 DOI: http://dx.doi.org/10.5888/pcd11.130415

[32] American College of Obstetricians and Gynecologists Frequently Asked Questions: Miscarriage and Molar Pregnancy; 2011.

In pregnant rats administered triptorelin at doses of 2, 10, and 100 mcg/kg/day during the period of organogenesis, maternal toxicity (decrease in body weight) and embryo-fetal toxicities (pre-implantation loss, increased resorption, and reduced number of viable fetuses) was observed at 100 ug/kg, approximately 4 times the clinical dose based on body surface area. No embryonic and fetal developmental toxicities were observed in mice at doses up to 4 times the clinical dose. Teratogenic effects were not observed in viable fetuses in rats or mice.

8.2 Lactation

Risk Summary

There are no data on the presence of triptorelin in human milk, or the effects of the drug on the breastfed infant, or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRIPTODUR and any potential adverse effects on the breastfed child from TRIPTODUR or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of TRIPTODUR have been established in pediatric patients 2 years of age and older based on a single-arm open-label study of 44 children 2 to 9 years of age with CPP [*see Clinical Studies (14)*]. The safety and effectiveness of TRIPTODUR have not been established in pediatric patients less than 2 years old.

Appendix A. Applicant's Review of Published Studies Evaluating the Long-Term Reproductive Potential of Women with CPP Previously treated with Triptorelin

Publication, Year [Location]	Study Design [n sample size]	Patient Population and Study Methods	Triptorelin Treatment	Reproductive Outcomes and Conclusions
Heger et al, 2006 [Germany]	Clinical series from a single pediatric endocrinologist's practice. [n=46]	Woman, mean ± SD age 23.6 ± 3.3 years (range 19-31), who were former CPP patients treated with depot triptorelin. Mean age at the end of triptorelin treatment was 11.2 ± 1.3 years (range 8.8-14y). At 12.5 ± 3.7 years (range 6.8-20.2) after the last triptorelin treatment (573 patient years) the pediatric endocrinologist performed a structured telephone interview with each woman to determine whether prolonged triptorelin exposure had any negative long-term sequelae.	Depot triptorelin (IM 75 µg/kg every 4 weeks) for a mean of 5.6 ± 2.3 years (range 1.1-14y)	Among 43 of the women (3 mentally retarded women were excluded), 34 (79%) wished to have children. Among these 34 women 12 pregnancies had occurred. One woman had been pregnant three times, one twice and seven women once. None of them reported any health problems during the course of pregnancy. Two early miscarriages occurred within the first trimester of pregnancy. In another woman, one abortion was performed at the age of 17 years, but a subsequent pregnancy resulted in the birth of a healthy girl. None of the women who wanted to become pregnant had to utilize assisted methods for inducing pregnancies like ovulation induction and/or *in-vitro* fertilization. Five healthy boys and four healthy girls were delivered spontaneously after normal duration of pregnancies. Birth weight and length were within normal ranges and APGAR indices indicated normal postnatal adaptation. There were no birth defects, and at the time this paper was published, there was normal further development during infancy and early childhood. The author concluded that all of these observations appear to be within the normal range for healthy young women, that long-term treatment with depot GnRHa (in this study depot triptorelin) does not impair reproductive function.
Lazar et al, 2014 [Israel]	Matched historical cohort identified by reviewing medical files of CPP patients between the years 1975 and 2005 [n=214]	Reproductive outcome data were obtained by interview of these CPP women in the 2011-2012 timeframe. The study was conducted a median of 17.1 years (12.5-35.6 years) after the last follow-up visit in the investigators endocrinology clinic (Tel Aviv). Demographic data and gynecological history were obtained from 214 CPP women ages 25-56 years who had been previously treated with either (1) CyA tablets (cyproterone acetate, 70-100 mg/m2/d in 2-3 divided doses), (2) depot triptorelin, or (3) were untreated. These groups were compared to n=446 matched controls who had normal puberty.	Depot triptorelin every 4 weeks (1.5-3 µg/kg release per day; maximum dose 3.75 mg),	The proportion with spontaneous pregnancy was similar in treated CPP women and controls: triptorelin 90.4% vs 93.4%. The assisted fertilization rate was higher in untreated CPP women than treated CPP groups (p=0.006) and controls (p=0.03). Untreated CPP women were associated with fertility problems (OR=3.40, 95% CI 1.15-10.0, p=0.03). The course of pregnancy was uneventful in 90.2% of CPP women and 90.9% of controls. The authors concluded that pubertal suppression may have a protective effect since fertility problems were more prevalent only among untreated CPP women.

Appendix A. Applicant's Review of Published Studies Evaluating the Long-Term Reproductive Potential of Women with CPP Previously treated with Triptorelin

Publication, Year [Location]	Study Design [n sample size]	Patient Population and Study Methods	Triptorelin Treatment	Reproductive Outcomes and Conclusions
Magiakou et al, 2010 [Greece]	Clinical series from one center. [n=47]	Among n=47 girls with idiopathic CPP, 33 were treated with depot triptorelin for median of 2.75 years (range 1 to 5.16y) and n=14 received no treatment; long-term follow-up was reported. The median age at start of puberty for treated and untreated patients was 6.6-6.8 years, and the median age at the final long-term evaluation was 17.5 and 19 years, respectively. An interim history was obtained by interview to document characteristics of menstrual cycles (secondary amenorrhea, oligomenorrhea, regularity, dysmenorrhea) and a history of pregnancy and its outcome. A battery of reproductive hormone levels was also assessed, and ultrasonography was performed to evaluate for polycystic ovary syndrome and ovary volume.	n=33 were treated with depot triptorelin every 25-30 days (2.86 to 6.98 µg/kg/d) for median of 2.75 years (range 1 to 5.16y)	The only statistically significant differences between the groups were pubic hair staging, basal LH values, and basal LH to FSH ratios. The age at menarche was greater in the treated subjects (p=0.0001) as expected. Non-treated patients had a greater maximal ovarian volume (p=0.02), higher LH to FSH ratios (p=0.04) than triptorelin treated patients. Menstrual cycle characteristics, use of contraceptive drugs, and presence of acne did not differ between the groups. The investigators concluded that in this "long-term follow-up study, GnRH treatment with triptorelin in childhood and early adolescents does not adversely affect ovarian function at least in late adolescence and early adulthood.
Pasquino et al, 2008 [Italy]	Retrospective clinical series from a single center. [n=87]	Girls with idiopathic CPP were treated with triptorelin for 4.2 ± 1.6 years (range 3-7.9) and observed for 9.9 ± 2.0 years (range 4-10) after discontinuation of treatment. The girls discontinued treatment at a chronologic age of 12.6 ± 1.0 years (range 10.2-13.5). During treatment, FSA and LH levels, uterine length, and ovarian volumes at ultrasound were evaluated every 6 months. After discontinuation of treatment, the resumption of menarche, menstrual cycles, underachievement of pregnancy, and birth of a fetus were documented.	Depot triptorelin a a dose of 100-120 µg/kg every 21-25 days, IM. Cyproterone acetate was given orally 100 mg/d in two divided doses, for 21 days before and 21 days after the first triptorelin dose to prevent stimulatory effects during this flare- up period.	Plasma FSH and LH peaks after the LHRH test were suppressed during treatment significantly lower than pretreatment (peak LH 0.6 _0.7 vs. 24.2 ±28.3 IU/liter, peak FSH 1.6 ±1.0 vs. 13.2 ± 7.1 IU/liter, both $P < 0.005$); by 1 yr after therapy, peak LH arose back to 30.3 ± 16.0 and FSH to 11.5 ± 11.9 IU/liter ($P < 0.005$). Estradiol basal levels (26.9 ± 5.5 pg/ml) during treatment were significantly lower than pretreatment (8 ± 2.8 pg/ml; $P < 0.001$) and arose to 64.9 ± 13.6 pg/ml 1 yr after therapy withdrawal ($P < 0.001$). Ovarian volumes, reduced from 2.8 ± 1.3 to 1.9 ± 1.0 cm during treatment, increased to 5.4 ± 3.2 cm^3 ($P < 0.001$), and uterine length, unchanged during treatment (4.6 ± 0.8 cm), increased to 6.7 ± 0.9 cm ($P < 0.001$), both already after 1 yr without therapy. Menarche appeared at the age of 13.6 ±1.1 yr after withdrawal of GnRHa at 0.9 ±0.4 yr (range 0.3–2 yr). The history of menstrual pattern showed that 82 patients had regular menses; the remaining five showed oligomenorrhea due to intensive sport activity, which within 2–3 yr resolved after decrease of intensive exercise. Six girls (one of them twice) became pregnant and delivered normal offspring. The authors concluded that depot triptorelin used to treat girls with CPP is, "safe and reversible for the reproductive system."

Appendix A. Applicant's Review of Published Studies Evaluating the Long-Term Reproductive Potential of Women with CPP Previously treated with Triptorelin

Publication, Year [Location]	Study Design [n sample size]	Patient Population and Study Methods	Triptorelin Treatment	Reproductive Outcomes and Conclusions
Cassio et al, 2006 [Italy]	Randomized single center study with age matched controls [n=40 girls with CPP]	Girls with idiopathic early onset puberty (mean 7.7 years of age) seen between 1991 and 1992 were randomized to treatment with triptorelin (for a mean of 25 months and followed after treatment for a mean of 33 months) or to no treatment (followed for a mean of 41 months). In 2003, about 11-12 years later, these CPP girls were reevaluated: n=20 (mean ± SD age of 2.03±2.2 years) that had previously received triptorelin, and n=18 (20 ± 2.1 years of age) that had received no treatment. Gynecologic history with evaluation of menstrual pattern, oral contraceptive use, physical examination, blood samples (to assess LH, FSA, estradiol, progesterone, and delta-4-androstenedione), and pelvic ultrasound (to assess uterine and ovarian volumes, uterine echos and ovarian structure) were all evaluated. For comparison, 22 age- matched normal volunteers, mean age 21. ± 1.6 years, were similarly examined as a control.	Triptorelin 3.75 mg every 4 weeks as administered to the triptorelin group.	In the triptorelin group, the mean time at onset of menarche after discontinuation of triptorelin therapy was 16 ± 9 months (range 2-36 months). In the long-term follow-up evaluation, ovarian volume (as a measure of polycystic ovaries) was >10mL in 19% (3/17) of triptorelin subjects, 21% (3/14) of no treatment subjects, and 16% (2/16) of the matched controls. Characteristics of ovarian structures on ultrasound did not differ between the three groups. A greater percentage of normal results was found in the triptorelin subjects; a normal ovarian structure was observed in 82% (14/17) of triptorelin subjects, 71% (12/16) of no-treatment subjects, and 75% (12/16) of control normal subjects. Direct signs (corpus luteum) or indirect signs (endometrial echo, progesterone levels) of ovulation were observed in 13/14 normal subjects in the triptorelin, in 9/10 normal subjects in the no-treatment group, and in 10/12 normal controls, with normal functional signs of early or late follicular phase seen in the others. In all subjects with normal ovarian structure, the serum levels of gonadotropins, estradiol, and progesterone were within normal ranges for the phase of the menstrual cycle and were comparable in all groups. The percentage of subjects who reported being sexually active at the time of the examination was greater in patients with previous early puberty than in controls, but this difference was not significant (76% of cases in the triptorelin group, 72% in the no-treatment group, and 59% in the control group. The number of subjects who used oral contraception was comparable in all 3 groups. Two girls of the triptorelin group reported pregnancies (at age 17 and 17.5 years, respectively), both of which were terminated by elective abortion. "*The pregnancies that occurred in our patients confirm the normal reproductive outcome in subjects with previous CPP.*" "*Neither early puberty nor its treatment seem to significantly affect the normal adult function of the pituitary-gonadal axis.*"
Arrigo et al, 2007 [Italy]	Clinical series at one site. [n=101]	Girls with idiopathic CPP (n=101) treated with triptorelin for at least 2 years from their chronological age of 7.8 years (range 3.3-8.9) and for 24-96 months (median 43) until the age of	Depot triptorelin 60 µg/kg every 28 days	Median menarcheal (MA) age was 12.6 years (range 10.6–15.2), i.e. significantly higher ($p<0.0005$) with respect to that of their mothers (11.6; range 8–14). Menarcheal age was significantly associated with therapy duration ($r=0.42$, $p<0.001$). Time duration between therapy

Publication, Year [Location]	Study Design [n sample size]	Patient Population and Study Methods	Triptorelin Treatment	Reproductive Outcomes and Conclusions
		11.3 years (range 9.6-13.8). After triptorelin therapy was withdrawn, the subjects were re-examined semi-annually until menarche. After menarche patients were regularly re-evaluated at 1-year intervals for at least 5 years to obtain menstrual cycle information. Menstruation frequency was recorded in patients and their family's diaries. Mother's menarcheal age was confirmed by patients mothers. The aim of the study was to longitudinally investigate menarche timing and menstrual cycle patterns in the first 5 years.		withdrawal and menarche was 14.0 months (range 3–42). This time interval negatively correlated with treatment duration ($r = -0.34$, $p<0.01$). The history of menstrual cycle patterns showed both a progressive decrease of oligorrhea prevalence ($p<0.0001$) and a concomitant progressive increase of regular menstrual cycles and irregular menstrual cycles ($p<0.0001$) by increasing gynecological age. No cases of secondary amenorrhea were recorded during the entire follow-up and only a few cases of polymenorrhea were found during the first two gynecological years. Menstrual cycle abnormalities were observed only during the first gynecological years and their prevalence decreased with increasing gynecologic age, a pattern that is also frequently found in normal adolescents. "*These data confirm that GnRHa [triptorelin] therapy has no long-term detrimental effects on the menstrual cycle of girls with CPP even though prolonged over time...*" Time to menarche following triptorelin withdrawal inversely correlated with treatment duration. An unexpected finding was that the menarcheal age of our patients was higher than that of the respective mothers and unrelated to it. "*This confirms that GnRHa therapy is able to modify the natural course of puberty events in girls with CPP*."
Hager et al, 1999 [Germany]	Prospective multicenter single arm study [n=50]	Long-term outcome was evaluated in 50 young women with CPP treated with triptorelin over a mean ± SD of 4.4 ± 2.1 years (range 1.0-9.7). Treatment started at age 6.7 ± 2.0 years (range 2.1-9.0) and ended at a mean age of 11.0 ± 1.1 (range 8.8-13.9). Study assessments were performed 5.7 ± 2.8 years (range 1.2-11.0) after completion of treatment. The aim of the study included evaluation of the outcome after long-term triptorelin therapy in terms of reproductive function at young adult age. Puberty stages, plasma gonadotropins and estradiol, ovarian structure and volume and menstrual patterns were determined.	Depot triptorelin 75 µg/kg IM every 30 ± 2 days.	Menarche or re-menarche started at age 12.3 ±1.4 yr. Time duration between last injection of depot triptorelin and menarche was 1.1 ± 0.9 years (range, 0.1±5.8 yr). The history of menstrual patterns showed that 1 of 50 patients suffered from metrorrhagia, and 2 suffered from oligomenorrhea due to bulimia and anorexia. Nine patients reported irregular cycles, with bleeding intervals between 3 and 7 weeks, 5 of them were therefore treated with contraceptives. Two patients gave birth to healthy, mature, singleton children after normal pregnancies. Ultrasound investigations were performed on 34 patients. Ovarian volume was above 10 mL (a measure of polycystic ovary syndrome) in 20.5% (7 of 34) of patients; in 2 of them more than 10 microcysts were observed. One of these 2 patients was obese and had an elevated basal LH level of 28.2 IU/L, and mild 3β-hydroxysteroid dehydrogenase deficiency was diagnosed. There was no significant difference between

Publication, Year [Location]	Study Design [n sample size]	Patient Population and Study Methods	Triptorelin Treatment	Reproductive Outcomes and Conclusions
				the mean ovarian volume of patients with normal menstrual patterns and that of those who reported irregularities (7.0 ± 4.5 vs. 8.5 ± 7.7 mL; P = NS). Ovarian volumes were larger than those in normal girls and were comparable in size to the upper normal range in women. The prevalence of enlarged ovaries was 20.5% in our patient group. However, only 6% of our patients had more than 10 ovarian microcysts. The study showed that hormonal suppression achieved with triptorelin is fully reversible. Menses started spontaneously in all patients after the end of treatment. There was no increase in the incidence of polycystic ovary syndrome. (one patient only) compared to that in healthy women.
Oostdijk, 1996 [The Netherlands]	Clinical series [n=21 girls; 5 boys were also evaluated but not for reproductive capacity]	Girls (n=31) and boys (n=5) with CPP were treated only with triptorelin (n=28), and 8 were treated with buselrelin or cyproterone acetate before starting triptorelin. In girls the chronologic age at start of treatment was a mean (SD of 7.7 (0.8) years. Duration of treatment was a mean (SD) of 3.4 (1.0) years and was followed up for 4.0 (1.2) years after treatment was stopped. Data were not reported separately for triptorelin.	Triptorelin 3.75mg IM was given every 4 weeks.	Menarche occurred at 1.1 years (median) (range: 0.4 to 2.6 years) after discontinuation of treatment and at a chronological age of 12.3 (1.1) years, mean (SD). At the final visit, 5/31 girls were using oral contraceptives. The menstrual cycles were regular in 26 out of the 31 girls. Pelvic ultrasonography was performed in 22 girls. Four of them were using contraceptives and in all four girls normal ovaries were observed. In the remaining 18 girls, the volume of the uterus was 33.9 (15.6) cm^3, which represents the upper limit of the normal adult volume. The volumes of the ovaries were within the normal range, at 7.9 (3.9) cm^3 compared to the reference value of 7.4 (4.8) cm. In four girls, one of the ovaries was larger than normal. In two of these, 2-3 cysts with a diameter 0.6 cm were visualized, coinciding with the norm for this stage of puberty. In the remaining two girls, 8-10 cysts of ≤0.6 cm diameter were observed. The menstrual cycles were regular in these four girls. In the ovaries of the remaining 14 girls, a maximum of two to six cysts with a diameter ≤ 0.9 cm were observed. In two of the 14 girls, cysts were documented with a diameter of 2.0 cm. However, this was observed 12 to 14 days after the first day of the menstruation, that is, at the point of ovulation. Rapid resumption of puberty was observed, menarche occurring 1.1 years (range 0.4 to 2.6 years) after withdrawal of treatment, at a mean age of

Appendix A. Applicant's Review of Published Studies Evaluating the Long-Term Reproductive Potential of Women with CPP Previously treated with Triptorelin

Publication, Year [Location]	Study Design [n sample size]	Patient Population and Study Methods	Triptorelin Treatment	Reproductive Outcomes and Conclusions
				12.3 (1.1) years. Ultrasound evaluation showed normal ovaries 4.0 (1.2) years after discontinuation of treatment. The authors concluded that after withdrawal of therapy, resumption of puberty occurs rather rapidly, without evidence of polycystic ovaries.

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/s/

CATHERINE A ROCA
05/22/2017

JANE E LIEDTKA
05/22/2017

LYNNE P YAO
05/26/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	04/26/2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208956
Product Name and Strength:	Triptodur (triptorelin pamoate) for injectable suspension, 22.5mg
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC.
Submission Date:	August 29, 2016 and March 24, 2017
OSE RCM #:	2016-1983
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Arbor Pharmaceuticals, LLC submitted a New Drug Application (NDA 208956) for Triptodur (triptorelin pamoate) for injectable suspension, 22.5 mg on August 29, 2016. Triptodur is indicated for "treatment of children with Central Precocious Puberty" (CPP).

The Division of Metabolism and Endocrinology Products (DMEP) requested that DMEPA review the applicant's container labels, carton labeling, and Prescribing Information (PI) for areas that may lead to medication errors.

1.1 REGULATORY HISTORY

Triptorelin pamoate is approved under the Proprietary Name, Trelstar, as 3.75 mg every 4 weeks, 11.25 mg every 12 weeks, and 22.5 mg every 24 weeks for palliative treatment of advanced prostate cancer. Trelstar has been approved since 2000 marketed by Actavis. Arbor Pharmaceuticals is seeking the approval of Triptodur (triptorelin pamoate) for injectable suspension only in the 22.5 mg strength every 24 weeks for the treatment of children with Central Precocious Puberty (CPP).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Arbor Pharmaceuticals, LLC submitted an NDA 208956 for Triptodur (triptorelin pamoate) for injectable suspension, 22.5 mg for the treatment of children with central precocious puberty (CPP). DMEPA evaluated the proposed Prescribing Information (PI), container label, and carton labeling for areas of vulnerability in regards to medication error.

We identified areas of concern in the PI in addition to the Triptodur container vial label, the Sterile Water diluent for Injection container vial label, container kit label, and carton kit labeling that should be revised to improve the clarity of the information presented.

We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the PI and 4.2 for the carton and container label to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Dosage and Administration
    - The supplied diluent is not included in the section. Revise to "Triptodur 22.5 mg reconstituted with accompanying Diluent (Sterile Water) 2 mL, and administered as a single intramuscular injection every 24 weeks."

B. RESCRIBING INFORMATION

1. Section 2: Dosing and Administration, Subsection 2.2: Reconstitution Instructions for Triptodur.
    - This section is overly detailed for the intended Healthcare Professional (HCP) audience. It includes a lot of basic instructions and illustrations that may not be needed for the HCP. Consider removing the first five bullets and the illustration of the vial and replace with "Use appropriate aseptic technique for preparation and administration."
    - The first bullet should read: "Screw the plunger rod into the barrel end of the sterile water diluent syringe."
    - Combine steps for removing safety cover and shield on needle to read: "Pull back on the safety cover towards the syringe and away from the needle. Then pull the clear needle shield off."
    - Replace the bullet [redacted (b) (4)]…." with "Inject the Sterile Water diluent into the vial. Do not release the plunger rod. Gently swirl the vial ensuring the diluent rinses the sides of the vial. The reconstituted solution is a milky suspension."

2. Section 3: Dosage Forms and Strengths
    - The supplied diluent is not included in the section. Revise to "Triptodur for injectable suspension, 22.5 mg supplied with Diluent (Sterile Water) 2 mL for reconstitution of the accompanying Triptodur.

4.2 RECOMMENDATIONS FOR ARBOR PHARMACEUTICALS, LLC.

We recommend the following be implemented prior to approval of this NDA 208956:

A. CONTAINER KIT LABEL

1. The lot and expiration numbers are missing. Ensure the expiration date conforms with the format outlined in 21 CFR 201.10(i) and Draft Guidance for Industry[a], where the expiration date must be written as either 3-letter text for month with 4-digit numerals for year MMMYYY (e.g. FEB2020), or 3-letter text for month, with 2-digit numerals for day, and 4-digit numerals for the year MMMDDYYYY (e.g. FEB012020).
2. Revise the statement [redacted] (b) (4) on the container kit label contents section to "One Pre-filled Syringe of Diluent for Triptodur, 2 mL". This will highlight that the medication comes with a diluent and must be used for reconstitution before use.
3. Add "Do not freeze" with the storage information as currently presented this key information is missing.

B. CONTAINER VIAL LABEL:

1. Revise the route of administration from [redacted] (b) (4) to "For Intramuscular Injection". Dangerous abbreviations, symbols, and dose designations are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products.
2. The barcode is in a horizontal position. Barcodes placed in a horizontal position may not scan due to curvature of the vial. We recommend reorientation of the barcode to a vertical position to improve scannability. Ensure the barcode is surrounded by enough white space to allow scanners to read the barcode properly in accordance with 21CFR201.25(c)(1)(i).
3. Revise [redacted] (b) (4) to "For Reconstitution, Use Accompanying Diluent" as currently presented the statement is unclear and may cause confusion.

C. CARTON KIT LABELING:

1. Revise the content statement [redacted] (b) (4) to "One Pre-filled Syringe of Diluent for Triptodur, 2 mL". This will highlight the need to reconstitute before use.
2. Consider adding the cautionary statement "Reconstitute With Accompanying Diluent Before Use" to ensure this important information is not missed.

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[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication errors. Draft Guidance [Internet].FDA. April 2013 [cited 2017 April 19]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

D. DILUENT STERILE WATER FOR INJECTION LABEL:

1. Revise the statement [redacted] (b) (4) as presented below to prevent confusion and ensure that that the diluent is not administered alone:

   Diluent
   For Triptodur for Injection

2. Revise the statement [redacted] (b) (4) to "For drug diluent use only – reconstitute as directed" to ensure this important information is not misinterpreted.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Triptodur that Arbor Pharmaceuticals, LLC submitted on August 29, 2016 and the listed drug (LD) Trelstar (triptorelin pamoate for injectable suspension), 22.5 mg

Table 2. Relevant Product Information for Triptodur and the Listed Drug

Initial Approval Date	N/A	2000
Active Ingredient	Triptorelin pamoate	Triptorelin pamoate
Indication	Treatment of children with central precocious puberty (CPP)	Palliative treatment of advanced prostate cancer (b) (4) [redacted]
Route of Administration	Intramuscular (IM) injection	Intramuscular (IM) injection
Dosage Form	For injectable suspension	For injectable suspension
Strength	22.5mg	22.5mg
Dose and Frequency	22.5mg every 24 weeks	22.5mg every 24 weeks
How Supplied	Each kit contains one single-dose vial, one pre-filled syringe containing 2mL of sterile water for injection, two thin-walled 21 gauge, 1½ needles	As a single dose vial with a flip-off seal containing sterile lyophilized Triptorelin Pamoate microgranules, or in the Trelstar MIXJECT single-dose delivery system. The MIXJECT delivery system consists of a vial with a flip-off seal containing sterile lyophilized Triptorelin Pamoate microgranules, a MIXJECT vial adapter, and a pre-filled syringe containing sterile water for injection, USP, 2 mL.
Storage	20 to 25°C (68 to 77° F)	20 to 25°C (68 to 77° F)
Container Closure	**Sterile Water for Injection** Sterile Water for Injection is	Components of the Vial: • (b) (4) glass vial, 20 mm, (b) (4)

System	packaged in a (b) (4) glass syringe which is sealed with a (b) (4) stopper and (b) (4) (b) (4) cap (b) (4) (b) (4) and luer-lock adaptor. **Triptorelin for (b) (4) Suspension 22.5 mg** Triptorelin pamoate microgranules 22.5 mg is packaged in a (b) (4) glass vial with 20 mm (b) (4) (b) (4) (b) (4) (b) (4) stopper. The primary container closure system is sealed with an aluminum overseal with a plastic Flip-off (b) (4)	(b) (4) • (b) (4) stopper, 20 mm. • Aluminum overseal, 20 mm, with flip-off plastic cover For commercial use the drug product will be packaged in one of two secondary packaging configurations: • A single drug product vial (b) (4). • A single drug product vial packaged with the MIXJECT (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 21, 2017, we searched the L:drive and AIMS using the terms, Triptodur to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous Proprietary Name Review (PNR).[b]

[b] Vee, S. Proprietary Name Review for Triptodur NDA 208956. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 10. RCM No.: RCM No. 2016-9931101.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Triptodur (triptorelin pamoate for (b) (4) suspension) for injection, 22.5mg labels and labeling submitted by Arbor Pharmaceuticals, LLC on August 29, 2016.

- Container label
- Carton labeling
- Prescribing Information
  \\cdsesub1\evsprod\nda208956\0009\m1\us\prescribing-information-03-2017.pdf

G.2 Label and Labeling Images

Proposed Triptodur (triptorelin pamoate for (b) (4) suspension) for injection, 22.5mg

Container Kit Label

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Container Vial Label

Container Vial for Sterile Water for Injection 2 mL Label

Carton Labeling

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

/s/

CASMIR I OGBONNA
04/26/2017

HINA S MEHTA
04/26/2017

Clinical Inspection Summary

Date	4/19/2017
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shannon Sullivan, M.D., Clinical Reviewer Marina Zemskova, M.D., Medical Team Leader Jennifer Johnson, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 208956
Applicant	Arbor Pharmaceuticals, LLC
Drug	Triptorelin pamoate (b) (4) for (b) (4) suspension, 22.5 mg
NME (Yes/No)	No
Therapeutic Classification	Gonadotropin-releasing hormone (GnRH) agonist
Proposed Indication(s)	Treatment of children with central precocious puberty
Consultation Request Date	11/18/2016
Summary Goal Date	5/25/2017
Action Goal Date	6/29/2017
PDUFA Date	6/29/2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of one domestic and one foreign clinical site. The inspection of one clinical investigator revealed regulatory violations.

The classification for Dr. Yang is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application. The full Establishment Inspection Report (EIR) was submitted for review.

The classification for Dr. Cassorla is No Action Indicated (NAI). Data from these sites are considered reliable based on the available information. The full Establishment Inspection Report (EIR) was submitted for review.

In general, based on the inspections of the two clinical sites, the inspectional findings support validity of data as reported by the Sponsor under this NDA.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity.

II. BACKGROUND

Arbor Pharmaceuticals, LLC is seeking approval under NDA 208956 of a 6-month formulation of triptorelin pamoate in the United States for the "treatment of central precocious puberty" of idiopathic origin. The original sponsor of the study was Debiopharm International SA.

Inspections were requested for the following clinical study:

- **Debio 8206-CPP-301** An open-label, non-comparative, multicenter study on the efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin-dependent) precocious puberty

The first subject was screened August 9, 2012 and the last subject completed the study July 14, 2014. There were 44 subjects who were enrolled and all completed the study.

The trial was performed at 18 centers (16 in the US, one in Mexico and one in Chile).

Children enrolled were to be aged 2-8 years inclusive (i.e. < 9 years) for girls and 2- 9 years inclusive (i.e. < 10 years) with onset of development of sex characteristics before age 8 in girls and age 9 in boys 18 months or less before treatment.

The primary efficacy endpoint measure was the percentage of participants with LH suppression to prepubertal levels (serum LH ≤5 IU/L 30 minutes after GnRH agonist [leuprolide acetate 20 μg/kg SC] stimulation) at Month 6 (Day 169).

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 208956 in accordance with Compliance Program 7348.811. General instructions were also provided with this assignment.

There were 13 sites that enrolled subjects. Site 81 was chosen as it is the highest enroller. Site 25 was chosen as it had not been audited during the study by the sponsor and is a high US enroller. The Office of Scientific Investigations (OSI) Risk-Based Site Selection Tool (RBSST) was not submitted by the sponsor.

III. RESULTS (by Site):

Name of CI/ Address Site#	# of Subjects Randomized	Inspection Date	Classification
Dr. Joshua Yang Arnold Palmer Pediatric Endocrinology Practice Arnold Palmer Hospital For Children 89 West Copeland Street 2nd Floor Orlando, Florida 32806-1134 Site 25	5 subjects	3/13 – 3/17/2017	Voluntary Action Indicated (VAI)
Dr. Fernando Cassorla IDIMI – Instituto de Investigaciones Materno Infantil Santa Rosa 1234 Santiago de Chile 836016 Chile Site 81	15 subjects	1/23 – 1/27/2017	No Action Indicated (NAI)

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. Joshua Yang/ Site 25

There were seven subjects screened and five subjects enrolled into the study; five subjects completed the study. There were seven subject records reviewed.

Subjects were initially screened/enrolled/treated at Arnold Palmer Hospital for Children, Division of Pediatric Endocrinology, 32 West Gore St., 3rd Floor, Orlando, FL 32806. Subjects continued with the clinical trial and completed the trial at Arnold Palmer Hospital Endocrine & Diabetes Center, 89 West Copeland St., 2nd Floor, Orlando, FL 32806.

The IRB used for this clinical trial was Orlando Health Arnold Palmer Medical Center (APMC) IRB.

From (b) (4) (during the timeframe of the audited trial) clinical research in Orlando Health was being conducted by a site management organization (SMO) (b) (4) . Dr. Yang's study was staffed by both Orlando Health employees and (b) (4) employees. In (b) (4) the contract with the SMO was terminated. Most of the employees/study staff who participated during the audited trial were employees of (b) (4) and are no longer working at Orlando Health.

The source records and regulatory binders were maintained in good order and well organized. Whiteout was used on several source documents; specifically, in the pharmacy reconciliation binder by a person was an employee from (b) (4) and who no longer works at the site.

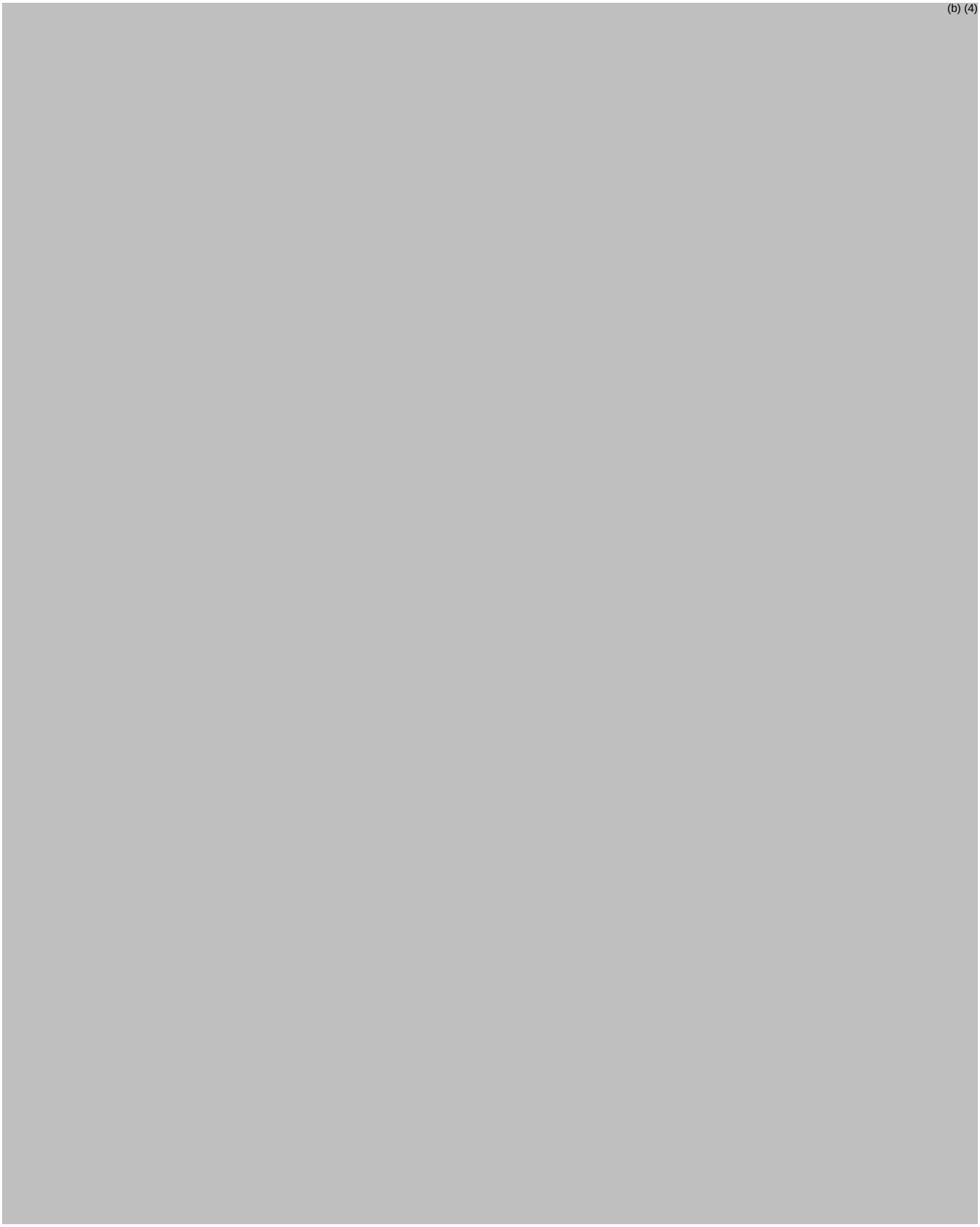
Three out of five subjects had baseline laboratory tests missing in the source; one out of five subjects had labs for Visit 10/Month 12 missing in the source; and one out of five subjects had missing labs for unscheduled visit/Day 183 missing in the source. These inclusion and safety laboratory test results were sent directly to the sponsor from the central laboratory and then the sponsor would e-mail the results to the site to be included in the subjects' source. The site stated that this information was inputted into the eCRF directly by the sponsor. The site requested the missing labs from the sponsor. The only lab still missing upon closing of the inspection was for subject 250504, unscheduled visit/Day 183.

There was no under-reporting of adverse events seen. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

(b) (4)

(b) (4)



(b) (4).

2. Fernando Cassorla/ Site 81

There were 28 subjects screened and 15 subjects enrolled into the study; 15 subjects completed the study. There were 15 subject records reviewed.

The Government of Chile Ministry of Health, Servicio de Salud Metropolitano Central, Scientific Ethics Committee approved the protocol and informed consent forms.

A review of source documents for all subjects along with electronic case report forms found them to be consistent with the data line listings provided by the sponsor. The record review found no significant inspectional observations and no evidence of underreporting of adverse events. The subject records were well organized.

Of note, Subject 8101 and Subject 8103 received a 3rd injection of the test IMP (Triptorelin) on Day 337 instead of the commercial formulation available in Chile. Both injections were administered after the subjects completed all study procedures.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.
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CC:

Central Doc. Rm./ NDA 208956
DMEP/Division Director/ Jean-Marc Guettier
DMEP /Deputy Director/Jim P. Smith
DMEP/Team Lead/Marina Zemskova
DMEP/Clinical Reviewer/ Shannon Sullivan
DMEP /Regulatory Project Manager/Jennifer Johnson
OSI/DCCE/Division Director/Ni Aye Khin
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OSI/DCCE/GCPAB/Team Leader/Janice Pohlman
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Joseph Peacock/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

CYNTHIA F KLEPPINGER
04/19/2017

JANICE K POHLMAN
04/19/2017

KASSA AYALEW
04/19/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	April 3, 2017
Reviewer/Team Leader:	Christian Cao, MPAS, PA-C, Safety Evaluator Team Leader Division of Pharmacovigilance I (DPV-I)
Division Director:	Cindy Kortepeter, PharmD, Division Director DPV-I
Product Name:	Triptodur (triptorelin pamoate for injectable suspension)
Subject:	Review of Applicant's Postmarketing Safety Analysis and FAERS Analysis
Application Type/Number:	NDA 208956, IND 111504
Applicant/Sponsor:	Arbor Pharmaceuticals, LLC
OSE RCM #:	2017-477
TSI #:	None

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The purpose of this Pharmacovigilance (PV) Review is for the Division of Pharmacovigilance-I (DPV-I) to provide to the Division of Metabolism and Endocrinology Products (DMEP) an analysis of the following:

1) Arbor Pharmaceuticals' (hereafter referred to as the Applicant) review of the postmarketing data for triptorelin used to treat central precocious puberty (CPP) from the (b) (4) and Debiopharm databases, and
2) FDA Adverse Event Reporting System (FAERS) data for triptorelin used in children for CPP, short stature, or gender dysphoria.

Information from this review will help DMEP determine whether there are any potential safety issues that may need further review or inclusion in the label for Triptodur (triptorelin pamoate for injectable suspension, NDA 208956).

In review of the Applicant's analysis and FAERS data, DPV-I identified eye disorders, intracranial hypertension, and bone marrow/blood disorders as potential safety issues with the use of triptorelin in pediatric patients with CPP. These potential safety issues are not proposed for inclusion in the Triptodur label by the Applicant. Because there are compelling cases of these adverse events, the adverse events are clinically significant, and a vulnerable patient population (i.e., children) is affected, DPV-I recommends additional investigations for eye disorders, intracranial hypertension, and bone marrow/blood disorders with the use of triptorelin to determine whether these potential safety issues should be included in the Triptodur label. DPV-I specifically recommends that DMEP submit an information request to the Applicant for the following:

- An analysis of the risk for eye disorders, intracranial hypertension, and bone marrow/blood disorders with the use of triptorelin in all pediatric patients from data sources including but not limited to their safety data and the medical literature.
- Submit a line listing and CIOMS (or MedWatch) reports of all pediatric cases of eye disorders, intracranial hypertension, and bone marrow/blood disorders.

In addition, DPV-I suggests DMEP consider consulting the Division of Transplant and Ophthalmology Products, particularly Dr. Wiley Chambers, to review cases of eye and vision disorders with the use of triptorelin in children with CPP.

1 INTRODUCTION

The purpose of this Pharmacovigilance (PV) Review is for the Division of Pharmacovigilance-I (DPV-I) to provide to the Division of Metabolism and Endocrinology Products (DMEP) an analysis of the following:

1) Arbor Pharmaceuticals' (hereafter referred to as the Applicant) review of the postmarketing data for triptorelin used to treat central precocious puberty (CPP) from the (b) (4) and Debiopharm databases, and
2) FDA Adverse Event Reporting System (FAERS) data for triptorelin used in children for CPP, short stature, or gender dysphoria.

Information from this review will help DMEP determine whether there are any potential safety issues that may need further review or inclusion in the label for Triptodur (triptorelin pamoate for injectable suspension, NDA 208956).

1.1 BACKGROUND

Triptorelin and Gonadotropin Releasing Hormone Agonist

Triptorelin is a gonadotropin releasing hormone (GnRH) agonist. Triptorelin was initially developed as a soluble acetate salt for immediate release (triptorelin acetate), then subsequently as an insoluble pamoate salt formulated as microgranules designed to deliver the active moiety over 28 days (1-month formulation), over 84 days (3-month formulation), and over 168 days (6-month formulation).

Gonadotropin-releasing hormone is secreted by neurons in the hypothalamus. It travels through the hypothalamic-pituitary venous portal plexus to the anterior pituitary, where it binds to G protein-coupled receptors on the plasma membranes of gonadotrophs. Pulsatile GnRH secretion is required to stimulate the gonadotrophs to produce and release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The GnRH agonists are occasionally used for stimulation of gonadotropin production in the treatment of conditions such as male and female infertility.

Sustained non-pulsatile administration of GnRH or GnRH agonists inhibits the release of FSH and LH by the pituitary in both women and men, resulting in hypogonadotropic hypogonadism (i.e., hypoandrogenism and hypoestrogenism). GnRH agonists are used to induce gonadal suppression in men with prostate cancer, women with endometriosis, or children with CPP.

1.2 REGULATORY HISTORY

The Applicant licensed Triptorelin for (b) (4) Suspension 22.5 mg for CPP from Debiopharm and is seeking its marketing approval in the United States under NDA 208956 Triptodur (triptorelin pamoate for injectable suspension). Triptodur is a 6-month formulation of triptorelin pamoate. NDA 208956 was received on August 29, 2016 and is currently under review by DMEP with a PDUFA due date of June 29, 2017.

Formulations of triptorelin are manufactured by Debiopharm and its licensee (b) (4), and are marketed under license from Debiopharm in various countries throughout the world for

indications including advanced prostate cancer, endometriosis, uterine fibromyoma, female infertility as part of an in vitro fertilization program, reversible reduction of testosterone to castration level in order to decrease sexual drive in adult men with severe sexual deviation, and precocious puberty. The first marketing authorization for the treatment of central precocious puberty (CPP) was granted for a 1-month sustained release formulation of triptorelin acetate in France in 1986. In the USA, triptorelin 1-month, 3-month, and 6-month formulations have been approved for treatment of men with advanced prostate cancer under NDAs 20715, 21288, and 22437 (Actavis Pharma), respectively.

1.3 PRODUCT LABELING

The Applicant provided a proposed label for Triptodur and is available at the link below. Safety information from the proposed label is listed in Table 1.

EDR Location: \\cdsesub1\evsprod\nda208956\0009\m1\us\prescribing-information-03-2017-annotated.pdf

Table 1. Safety information listed in proposed Triptodur label by section.

Contraindications	**4.1 Hypersensitivity** TRIPTODUR is contraindicated in individuals with a known hypersensitivity to triptorelin or any other component of the product, or other GnRH agonists or GnRH *[see Adverse Reactions (6.2)]*.
Warnings and Precautions	(b) (4) **5.2 Initial Rise of Gonadotropins and Sex Steroid Levels** During the early phase of therapy, gonadrotropins and sex steroids rise above baseline because of the (b) (4) stimulatory effect of the drug [see Clinical Pharmacology (12.2)]. Therefore, a transient increase in clinical signs and symptoms of puberty, including vaginal bleeding, may be observed during the first weeks of therapy. **5.3 Psychiatric Events** Psychiatric events have been reported in patients taking GnRH agonists. Postmarketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with TRIPTODUR. **5.4 Convulsions** Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including triptorelin. These included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies, or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above *[see Adverse Reactions (6)]*.

Table 1. Safety information listed in proposed Triptodur label by section.	
Adverse Reactions	**6.1 Clinical Trials Experience** (b) (4) [redacted] **6.2 Postmarketing Experience** The following adverse reactions were reported from postmarketing experience of triptorelin in patients with central precocious puberty (CPP): *Hypersensitivity:* anaphylactic shock, anaphylactoid reaction, angioedema, urticaria; *Cardiovascular:* hypertension; *Psychiatric:* Emotional lability, such as crying, irritability, impatience, anger, and aggression, has been observed with GnRH agonists. Depression, including rare reports of suicidal ideation and attempt, has been reported for GnRH agonists in children treated for CPP. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression. *Nervous System:* convulsions.

2 METHODS AND MATERIALS

2.1 APPLICANT'S REVIEW OF POSTMARKETING DATA FOR TRIPTORELIN

DPV-I reviewed the following materials submitted to NDA 208956 pertinent to postmarketing data for triptorelin.

- **Clinical Overview, section 2.5.5.6 Postmarketing Experience**
  EDR location: \\cdsesub1\evsprod\nda208956\0000\m2\25-clin-over\clinical-overview.pdf

- **Summary of Clinical Safety, section 2.7.4.6 Postmarketing Data and section 2.7.4.7 Appendix**
  EDR location: \\cdsesub1\evsprod\nda208956\0000\m2\27-clin-sum\summary-clin-safety.pdf

2.2 FAERS Case Selection Criteria

Inclusion criteria:

- Pediatric patient by age less than 18 years or if patient was described as a child.
- Triptorelin was used for CPP, short stature, or gender dysphoria.

Exclusion criteria:

- Duplicate report
- Report lacked details for analysis
- Adult patient at time of triptorelin use

2.3 FAERS Search Strategy

DPV-I searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	March 29, 2017
Time period of search	1969† - March 28, 2017
Search type	FBIS Product-Manufacturer Summary Report
Product Terms	Product - Active Ingredient: Triptorelin; Triptorelin Acetate; Triptorelin Pamoate
Age to (years)	17.99; not reported
Reported Reason For Use	Precocious puberty; Product used for unknown indication; Drug use for unknown indication; Central precocious puberty; Off label use; Gender identity disorder; Body height below normal; Puberty precocious; not reported
* See Appendix A for a description of the FAERS database. † Initiation of FAERS database	

2.4 Data Mining Search Strategy

The Empirica Signal database was searched with the strategy described in Table 3. OSE uses Empirica Signal software to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. If a drug-event combination has a score (EB05) of ≥ 2, this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

Table 3. Data Mining Search Strategy*	
Data Refresh Date	March 3, 2017
Product Terms	Triptorelin†
Empirica Signal Run Name	Generic By Age (S)
EB05	≥ 1.0
* See Appendix A for description of Data Mining of FAERS using Empirica Signal. † Triptorelin acetate and triptorelin pamoate are not available terms	

3 RESULTS

3.1 APPLICANT'S REVIEW OF POSTMARKETING DATA FOR TRIPTORELIN

The Applicant provided information regarding estimated exposure, description of the safety databases, and an analysis of the postmarketing data for triptorelin in the **Clinical Overview, section 2.5.5.6 Postmarketing Experience** and **Summary of Clinical Safety, section 2.7.4.6 Postmarketing Data** of NDA 208956. The following is a summary of pertinent information together from both sections.

Using sales data, the Applicant estimated that the cumulative worldwide patient exposure for all triptorelin formulations and all indications is greater than 3 million treatment-years through August 2015. An estimate of triptorelin exposure for patients with CPP, however, was not provided by the Applicant.

Two safety databases for triptorelin maintained by Debiopharm and (b) (4) were searched by the Applicant. The first was the (b) (4) database, which was initiated in 1986 and contains the global pharmacovigilance data for all triptorelin formulations. The second database, maintained by Debiopharm, contains cases just for the Debiopharm triptorelin pamoate formulations and was initiated in 1997. The Debiopharm and (b) (4) databases contain overlapping information.

The Applicant provided an overview of the overall triptorelin postmarketing experience and a separate summary of postmarketing surveillance data for triptolein for treatment of CPP. Since initiation of triptorelin marketing in 1986 through March 3, 2016, there have been 5448 cases received by Debiopharm and its licensees to the (b) (4) database. Of these 5448 reports, 1427 were serious, 3964 were non-serious, 18 were unclassified (not classified as serious or non-serious, mainly exposure during pregnancies without associated adverse events) and 39 were of unknown/unstated seriousness or non-seriousness.

There were 395 cases of patients who used triptorelin for CPP, which included 91 serious, 295 non-serious, and 9 not designated as serious or non-serious. These 395 cases reported 711 events (some cases reported multiple events), of which the most commonly reported events were injection site pain (4.1%, 29/711), inappropriate schedule of drug administration (3.8%, 27/711), headache (3.4%, 24/711), hypersensitivity (2.4%, 17/711), and urticaria (2.4%, 17/711). Of the 711 reported adverse events, 203 were designated as serious and notable serious adverse events were hypersensitivity (6.4%, 13/203); angioedema (7/203, 3.4%); urticaria (7/203, 3.4%); and hypertension (2.46%, 5/203). The applicant proposed inclusion of these four notable and serious adverse events in the Triptodur label in section 6.2 Postmarketing Experience section.

The Debiopharm database contains 697 adverse event reports for all Debiopharm triptorelin pamoate formulations. Of these, 9 were reports of patients who had used triptorelin for CPP; however, the Applicant stated that 5 reports concerned children treated off-label (inappropriate age, or unapproved indication). Thus, there appears to be only 4 reports of patients who had used triptorelin for CPP. The adverse event in these 4 reports were injection site itching, swelling at injection site, lack of hormonal suppression, and brain infarction secondary to carotid artery dissection. Only the report of brain infarction was coded as serious.

The Applicant, additionally, provided brief summaries of analyses of the serious adverse events (SAEs) classified as Identified Risks and Potential Risks for patients who used triptorelin regardless of indication, age, or gender as well as for when triptorelin was used to treat CPP. For the purpose of this review, only the information regarding CPP will be discussed further and are summarized below.

Identified Risks:

- Hypersensitivity and related reactions:
    - Thirteen serious hypersensitivity (preferred term) reactions were reported.
    - When reported, ages ranged from 8 to 11 years.
    - Serious hypersensitivity related reactions reported in more than one patient included angioedema (7), urticaria (7), rash generalised (2), anaphylactic reaction (2), erythema (2), face oedema (2), pruritus (2), rash (2).
    - All events were assessed as related to triptorelin.

Potential Risks:

- Bone mass changes:
    - Six cases with SAEs were reported – 4 in children and 2 in adults.
        - Reported SAEs in children were osteoporosis (1); osteochondritis (1); osteoarthropathy (1); and upper limb fracture (1).
        - Reported SAEs in adults were chrondropathy, joint destruction, and osteoarthritis (1); and fracture and osteoporosis (1). The latency period after the last dose in these adults was not reported.
- Slipped capital femoral epiphysis:
    - One SAE of slipped capital femoral epiphysis (outcome: not recovered) in an 11-year-old female patient treated for CPP with triptorelin.
    - There are literature reports of slipped capital femoral epiphysis in five girls with CPP treated with triptorelin formulations[1,2] and in four girls and one boy with CPP treated with other GnRH agonists.[3,4,5]
- Metabolic changes:
    - Two SAEs of new-onset type 1 diabetes mellitus were reported in patients treated with triptorelin for CPP.
        - Represents 1% (2/203) of all CPP SAEs reported, and 0.3% (2/711) of all CPP events (serious and non-serious) reported.

- Cardiovascular disease:
  - Fifteen SAEs were reported in patients treated with triptorelin for CPP.
    - Includes hypertension (5), hot flush (3), intracranial pressure increased (2), pallor (2), benign intracranial hypertension (1), systolic hypertension (1), tachycardia (1), cardiac hypertrophy (1), myocarditis (1), and flushing (1).
  - Additionally, a fetus whose mother was exposed to triptorelin during in vitro fertilization experienced fetal distress with arrhythmia in the context of vasa previa and polyhydramnios; complications of pregnancy were the probable cause of the cardiac event in this case.
- Mood changes, including depression and suicide attempts:
  - Three SAEs were reported in patients treated with triptorelin for CPP.
  - Includes affective disorder and mood altered (2), and disturbance in sexual arousal in a 23-year-old male patient treated with triptorelin during childhood (1).
  - In all 3 cases, causality was assessed as related.
- Disease flare:
  - Two SAEs were reported in patients treated with triptorelin for CPP.
  - Includes breast enlargement (1), and vaginal discharge (1)
  - Both events were assessed as related.
- Convulsions:
  - One SAE was reported in a 7-year-old child, who experienced partial epileptic seizures 245 days after the first dose of triptorelin. The event was assessed as related.

Risks proposed for inclusion in Triptodur label:
The Applicant proposed to include anaphylactic shock, anaphylactoid reaction, angioedema, urticaria, and hypertension in section 6.2 Postmarketing Experience of labeling because these reactions occurred in patients using triptorelin to treat CPP, occurred with notable frequency, or are clinically significant.

The Applicant provided a list of serious postmarketing adverse event reports in patients who used triptorelin for CPP from 1986 through March 3, 2016 (n=91) in Table 15 of the **Summary of Clinical Safety, section 2.7.4.7 Appendix**. DPV-I reviewed the list of cases and identified 15 cases listing notable adverse events, which are grouped as eye disorders, intracranial hypertension, and bone marrow/blood disorders (see Table 4 below). The Applicant did not propose to include these adverse events in the Triptodur label. See Appendix B for a list of cases containing these adverse events as provided by the Applicant.

Table 4. Notable Cases by Preferred Terms and Event Type from serious postmarketing adverse event reports from 1986 through March 3, 2016 provided by the Applicant (n=15)

Event Type	Preferred Terms*
Bone marrow disorder/ blood disorder (n=3)	Thrombocytopenia (2); Bone Marrow Failure (1); Pancytopenia (1); Leukopenia (1); Neutropenia (1)
Intracranial hypertension (n=3)[†]	Intracranial Pressure Increased (2); Benign Intracranial Hypertension (1)

Table 4. Notable Cases by Preferred Terms and Event Type from serious postmarketing adverse event reports from 1986 through March 3, 2016 provided by the Applicant (n=15)	
Event Type	**Preferred Terms***
Eye disorder (n=10) †	Papilloedema (2); Accommodation Disorder (1); Diplopia (1); Amblyopia (1); Diplopia (1); Vision Blurred (1); Visual Impairment (1); Hemianopia (1); Visual Impairment (1); Retinal Detachment (1); Blindness Unilateral (1); Visual Field Defect (1); Colour Blindness (1)
* a report may list one or more PT † one reported listed PT Intracranial Pressure Increased and PT Papilloedema	

3.2 FAERS Case Selection

The FAERS search retrieved 97 reports. There were three duplicate reports. Of the remaining 94 reports, **51** reports were of pediatric patients who had used triptorelin for CPP, short stature, or gender dysphoria. Notable findings from these 51 FAERS reports are summarized below in Table 5.

Table 5. Descriptive characteristics of pediatric FAERS cases for triptorelin, received by FDA through March 28, 2017. (n=51)		
Case Characteristic		**Number of Reports**
Triptorelin salt	Triptorelin pamoate	44
	Triptorelin acetate	4
	Triptorelin	3
Type of Report	Expedited	50
	Periodic	1
	Direct	0
Year	2001-2005	23
	2006-2010	10
	2011-2015	13
	2016-2017	5
Country	USA	2
	Europe†	40
	Latin America‡	4
	Middle East§	5
Serious* (n=49)	Death	0
	Hospitalization	23
	Life-threatening	3
	Disability	8
	Other-serious	23
Reason for use	Precocious puberty	44
	Short Stature	2
	Gender identity dysphoria	2
	Not reported	3

Table 5. Descriptive characteristics of pediatric FAERS cases for triptorelin, received by FDA through March 28, 2017. (n=51)		
Case Characteristic		**Number of Reports**
Age in Years (n=45)	Mean	8.7
	Median	9
	Range	1-13
Sex	Female	44
	Male	4
	Not reported	3
Top 10 Reported MedDRA Preferred Terms (PTs)	Off label use	5
	Angioedema	4
	Epiphysiolysis	4
	Urticaria	4
	Arthralgia	3
	Drug hypersensitivity	3
	Headache	3
	Hypertension	3
	Pyrexia	3
	Vomiting	3
Notable PTs by System Organ Class (SOC) ¶	Blood and lymphatic system disorders (SOC)	
	Bone marrow failure	1
	Leukopenia	1
	Neutropenia	1
	Pancytopenia	1
	Thrombocytopenia	2
	Eye Disorder (SOC)	
	Accommodation disorder	1
	Amblyopia	1
	Diplopia	2
	Heterophoria	1
	Vision blurred	1
	Nervous system disorders (SOC)	
	Benign intracranial Hypertension	2
	Visual field defect	1

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A report may be coded with one or more serious outcomes.
† Belgium (2) ; Switzerland (2); Germany (1); Spain (2); France (17); Great Britain (1); Italy (3); Macedonia (2); Netherlands (7); Poland (1); Sweden (2)
‡ Argentina (1); Chile (3)
§ Iran (1); Israel (3); Jordan (1)
¶ A report may list one or more PTs

Almost all of the FAERS reports listed a serious outcome (49/51). There were no fatal reports; however, there were three reports that listed the outcome life-threatening. The first report (Case# 3913951, Italy, 2003) was of an 8.5-year-old girl who experienced angioedema with urticaria and dyspnea 3-4 hours after an intramuscular injection of Decapeptyl 3.75 mg for treatment of precocious puberty. A prick test was highly positive for Decapeptyl. The second report (Case# 3909928, France, 2003) is of a 10-year-old girl with CPP who started to experience severe left thigh pain 6 months after initiating Trelstar (b) (4) (triptorelin pamoate) and was diagnosed with

osteogenic sarcoma of the left femur 9 months later (15 months after Trelstar [redacted] (b) (4) The last case (Case# 11813406, Great Britain, 2015) was of a 7-year-old girl who experienced dyspnea on the same day of initiating treatment with Trelstar (triptorelin) 1.875 mg for treatment of precocious puberty.

Two FAERS reports were listed as from the USA. The first report (Case# 8511548) was of a 9-year-old girl who experienced syncope while receiving the 5th dose of Trelstar 3.75 mg for an unknown indication. Though USA was the listed country of event, this may have been a foreign case because the triptorelin product was also referred to as Neo Decapeptyl, which is not the approved product in the USA (Trelstar is the FDA-approved product) and Brazil was the listed country of the reporter. The second report (Case# 12558319) was of a 7-year-old girl who received two incomplete doses of Trelstar 3.75 mg for precocious puberty because the nurse was unable to completely depress the plunger while administering the drug. No other adverse event was reported in this case.

The most commonly reported MedDRA Preferred Terms (PTs) for the FAERS cases are generally non-specific (off label use, headache, pyrexia, vomiting) or have been identified for inclusion in the proposed label for Triptodur (angioedema, urticaria, drug hypersensitivity, and hypertension). Epiphysiolysis is a commonly reported PT and was evaluated by the Applicant (see section 3.1 above under Slipped capital femoral epiphysis) as well as by DPV-I for the FDA-approved GnRH agonists.[6] Neither the Applicant nor DPV-I determined that epiphysiolysis is an identified risk for triptorelin or the FDA-approved GnRH agonists, respectively.

In review of the PTs by System Organ Class (SOC) for all 51 FAERS reports, DPV-I identified clusters of PTs of adverse events not proposed for inclusion in the Triptodur label. There are three reports of blood disorders (pancytopenia, bone marrow failure, leukopenia, neutropenia, and thrombocytopenia); five reports of eye disorders; and two reports of benign intracranial hypertension. See Table 6 for summaries of these cases.

Table 6. Summary of FAERS cases reporting adverse events not proposed for inclusion in the Triptodur label.

Case# Year	Preferred Term	Summary of Case
Blood and lymphatic system disorders (SOC)		
5768924 2005	Pancytopenia; Bone marrow failure	A 9.5-year-old girl from France experienced pancytopenia 13 months after starting Decapeptyl 11.25 mg for precocious puberty. Blood tests demonstrated thrombocytopenia of 14 000/mm3, leukopenia of 1500/mm3 and anemia of 2.000.000/mm3. The patient received transfusions of platelets and white blood cells and Decapeptyl was discontinued. The treating endocrinologist considered the bone marrow depression was possibly related to Decapeptyl because it was the only long term treatment the patient was receiving.
6451674 2007	Leukopenia; Neutropenia	A pharmacist from France reported that a 27 month-old girl was found to have leukopenia with neutropenia during a routine lab exam 7 months after receiving triptorelin pamoate (Decapeptyl 3 mg) to treat precocious puberty. In December 2006, her white blood cell count was 5500 / uL and in September 2007, it had dropped to 1000 / uL.

Table 6. Summary of FAERS cases reporting adverse events not proposed for inclusion in the Triptodur label.		
Case# Year	**Preferred Term**	**Summary of Case**
5791248 2005	Thrombocytopenia	A pediatric endocrinologist from France reported that a 7-year-old girl experienced severe thrombocytopenia (platelets 11,000 platelets/mm3) with ecchymoses and petechiae while on Decapeptyl LP 3 mg for 3 months to treat precocious puberty (triptorelin) requiring human immunoglobulin (Tegeline, 1 g) treatment. An infectious workup was negative and there were no recent vaccinations. The patient was not taking any drugs concomitantly.
Eye Disorder (SOC)		
3782550 2001	Hemianopia heteronymous	A 12-year-old girl from Italy experienced bitemporal hemianopsia 12 months after starting Decapeptyl 3.75 mg/28 days for precocious puberty discovered during visual field examination for hypermetropy.
3785245 2002	Visual Field Defect; Colour Blindness	A 9.5-year-old girl from France experienced bilateral concentric constriction of field of vision 12 months after starting triptorelin 3 mg PR for precocious puberty. The patient subsequently experienced severe aggravation of visual acuity loss, colour vision disturbances, and a very narrow visual field 5 additional months later.
3856679 2002	Heterophoria; Amblyopia	An 8-year-old girl from France was treated with Decapeptyl in Dec 2001 for precocious puberty and experienced a recurrence of amblyopia (previously treated prior to Decapeptyl therapy) 4 months later.
4105074 2004	Visual Field Defect; Diplopia; Accommodation Disorder	A 9-year-old girl from France treated with triptorelin 3 mg for 2.5 years for precocious puberty experienced accommodation disorders, diplopia and triplopia.
6559511 2008	Vision Blurred; Diplopia	A pediatrician reported that an 8.5 -year-old girl experienced diplopia and cephalgia 5 days after the third injection of Decapeptyl LP 3mg (triptorelin pamoate) for treatment of precocious puberty requiring hospitalization. Triptorelin therapy was maintained and the patient has not yet recovered from the diplopia at the time of report.
Nervous system disorders (SOC)		
11722415 2015	Benign intracranial hypertension	A literature article from Spain reported that a child (age and gender not reported) experienced benign intracranial hypertension while taking triptorelin and recombinant human growth hormone for an unknown indication.
11888324 2016	Benign intracranial hypertension	A literature article reported that an 11.8 year-old girl experienced arterial hypertension and benign intracranial hypertension while being treated with triptorelin for gender dysphoria. Triptorelin was stopped and both adverse events recovered. Triptorelin was re-administered after 3 months under close supervision and hypertension re-occurred. The patient received treatment for hypertension with nifedipine and labetalol, while increased intracranial pressure did not reoccur.

3.3 DATA MINING

Using the parameters in Table 3, Empirica Signals identified four drug-event pairs with an EB05 $\geq$ 1.0 reported with triptorelin use in children, see Table 7 below. None the EB05 scores for these drug-event pairs were $\geq$ 2.0. There were no drug-event pairs for the age groups 12-16 or 17-20 years with an EB05 $\geq$ 1.0.

Table 7. Data mining results using Empirica Signal for any adverse event with an EB05 ≥ 1.0 reported with triptorelin use in children, sorted by EB05

	Age Group	Drug	MedDRA PT	N	EB05	EBGM	EB95
1	06-11 Years*	Triptorelin	Arthralgia	4	1.496	3.637	8.375
2		Triptorelin	Angioedema	3	1.348	4.231	18.718
3		Triptorelin	Drug hypersensitivity	3	1.191	3.362	9.326
4		Triptorelin	Bone sarcoma	2	1.013	6.115	64.196

A score (EB05) of ≥ 2 indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database.
* There were no drug-event pairs for the age groups 12-16 or 17-20 years with an EB05 ≥ 1.0.

4 DISCUSSION

In review of the safety data from the clinical program for triptorelin and its postmarketing experience, the Applicant identified several safety issues and proposed to list these in the Triptodur label. These adverse reactions include hypersensitivity reactions (including anaphylaxis, angioedema, and urticaria), psychiatric events (i.e., emotional lability and depression), convulsions, injection site reactions, and hypertension. In addition to these adverse reactions, the Applicant also identified four potential risks with triptorelin use; however, they did not propose to list them in the label for Triptodur. These risks include: bone mass, slipped capital femoral epiphysis, metabolic changes, and cardiovascular disease (not including hypertension).

In review of the Applicant's analysis and FAERS data, DPV-I identified potential safety issues that are not proposed by the Applicant for inclusion in the Triptodur label. DPV-I identified adverse events grouped as eye disorders, intracranial hypertension, and bone marrow/blood disorders from the Applicant's listing of serious postmarketing adverse event reports (see Table 4 above) and similarly also from review of cases from FAERS. Overall, there are few reports for any of these potential safety issues; however, DPV-I considers some of the cases compelling and that these adverse events are clinically significant. For example, a child in FAERS Case# 5768924 experienced profound pancytopenia requiring transfusions and in FAERS Case# 3785245, a child experienced bilateral concentric visual field constriction that was aggravated later with visual acuity loss, colour vision disturbances, and a very narrow visual field. Because there are compelling cases of these adverse events, the adverse events are clinically significant, and a vulnerable patient population (i.e., children) is affected, additional investigation for these potential safety issues is warranted and their inclusion in the Triptodur label should be considered.

Musculoskeletal adverse events with the use of GnRH agonists were recently identified by DVP-I.[7] The Applicant did not identify any musculoskeletal adverse events as a potential risk with the use of triptorelin; however, DPV-I noted a few reports of musculoskeletal adverse events in review of the Applicant's list of serious postmarketing adverse event reports in patients who used triptorelin for CPP. Several of these reports were of adult patients; however, it is not known if these cases were of adults who had taken triptorelin as children for CPP because the narratives were not provided by the Applicant. The FAERS search also identified few reports of musculoskeletal adverse events with triptorelin: arthralgia (n=3), muscular weakness (n=1) and myalgia (n=1). Overall, there is insufficient information at this time to determine if any musculoskeletal adverse event is a risk specifically in patients with CPP using triptorelin.

5 CONCLUSION

DPV-I identified eye disorders, intracranial hypertension, and bone marrow/blood disorders as potential safety issues with the use of triptorelin in pediatric patients with CPP.

6 RECOMMENDATIONS

Because there are compelling cases, the adverse events are clinically significant, and a vulnerable patient population (i.e., children) is affected, DPV-I recommends additional investigations for eye disorders, intracranial hypertension, and bone marrow/blood disorders with the use of triptorelin to determine whether these potential safety issues should be included in the Triptodur label. DPV-I specifically recommends that DMEP submit an information request to the Applicant for the following:

- An analysis of the risk for eye disorders, intracranial hypertension, and bone marrow/blood disorders with the use of triptorelin in all pediatric patients from data sources including but not limited to their safety data and the medical literature.
- Submit a line listing and CIOMS (or MedWatch) reports of all pediatric cases of eye disorders, intracranial hypertension, and bone marrow/blood disorders.

In addition, DPV-I suggests DMEP consider consulting the Division of Transplant and Ophthalmology Products, particularly Dr. Wiley Chambers, to review cases of eye and vision disorders with the use of triptorelin in children with CPP.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatics structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.2 APPENDIX B. NOTABLE SERIOUS POSTMARKETING ADVERSE EVENT REPORTS PROVIDED BY THE APPLICANT NOT PROPOSED FOR INCLUSION IN THE TRIPTODUR LABEL (FROM 1986 THROUGH MARCH 3, 2016)

	MCN Source Country	Age (Yr) Sex	Preferred Term Decode (Rank 1 only)	Outcome Reporter (Rank 1 only)	Product Description	Salt	Causality Reporter (Rank event 1 only)	All Events And Co-Manifestations [Preferred Term]
1	10E20040085 Spontaneous France	9 F	Accommodation disorder	Not yet recovered	Decapeptyl LP 3 mg	Triptorelin pamoate	NR	Accommodation Disorder (rank 1) [Accommodation Disorder] Diplopia (rank 2) [Diplopia]
2	10E20020413 Spontaneous France	8.5 F	Amblyopia	Not yet recovered	Decapeptyl LP 3 mg	Triptorelin pamoate	Not assessable	Amblyopia (rank 1) [Amblyopia] (Recurrence (rank 2) [Condition Aggravated], Decompensated Esophoria (rank 3) [Heterophoria])
3	2015-7148 Literature Spain	5 F	Benign intracranial hypertension	UNK	Triptorelin	Triptorelin salt unknown	Related	Suspected Benign Intracranial Hypertension (rank 1) [Benign Intracranial Hypertension] Petechiae On Upper Chest And Armpit (rank 2) [Petechiae] Persistent Low-Grade Fever (rank 3) [Pyrexia]
4	10E20050275 Spontaneous France	9.5 F	Bone marrow failure	Not yet recovered	Decapeptyl SR 11.25 mg	Triptorelin pamoate	Possible	Bone Marrow Hypoplasia (rank 1) [Bone Marrow Failure] Pancytopenia (rank 2) [Pancytopenia]
5	10E20080080 Spontaneous France	9 F	Diplopia	Recovered without sequelae	Decapeptyl LP 3 mg	Triptorelin pamoate	Related	Diplopia (rank 1) [Diplopia] Blurred Vision (rank 2) [Vision Blurred] Cephalgia (rank 3) [Headache]
6	2011-2153 Spontaneous France	9 F	Fatigue	UNK	Decapeptyl LP 3 mg	Triptorelin pamoate	Related	Fatigue (rank 1) [Fatigue] Nausea (rank 2) [Nausea] Vertigo (rank 3) [Vertigo] Mood Disorder (rank 4) [Affective Disorder] Chest Discomfort (rank 5) [Chest Discomfort] Abdominal Pain (rank 6) [Abdominal Pain] Headache (rank 7) [Headache] Visual Disturbances (rank 8) [Visual Impairment] Vomiting (rank 9) [Vomiting] Hot Flushes (rank 10) [Hot Flush] Myalgia (rank 11) [Myalgia]
7	21220010691 Spontaneous Italy	12 F	Hemianopia	Not yet recovered	Decapeptyl SR 3.75 mg	Triptorelin acetate	Not Related	Bitemporal Hemianopsia (rank 1) [Hemianopia]
8	2013-0090 Spontaneous United Kingdom	9 F	Intracranial pressure increased	Recovered without sequelae	Decapeptyl SR 11.25 mg	Triptorelin acetate	Not Related	Raised Intracranial Pressure (rank 1) [Intracranial Pressure Increased] (Papilledema (rank 7) [Papilloedema], Nausea (rank 8) [Nausea], Vomiting (rank 9) [Vomiting]);Mild Systolic Hypertension (rank 2) [Systolic Hypertension] Headaches (rank 3) [Headache] Vaginal Discharge (rank 4) [Vaginal Discharge] Change In Behaviour And Mood (rank 5) [Mood Altered] Abdominal Pain (rank 6) [Abdominal Pain] Incorrect Treatment Interval (rank 10) [Inappropriate Schedule Of Drug Administration]

	MCN Source Country	Age (Yr) Sex	Preferred Term Decode (Rank 1 only)	Outcome Reporter (Rank 1 only)	Product Description	Salt	Causality Reporter (Rank event 1 only)	All Events And Co-Manifestations [Preferred Term]
9	10E20071489 Spontaneous France	2.25 F	Leukopenia	Not yet recovered	Decapeptyl LP 3 mg	Triptorelin pamoate	Possible	Leukopenia (rank 1) [Leukopenia] Neutropenia (rank 2) [Neutropenia])
10	2013-1451 Health authority Ireland	9 F	Migraine with aura	Recovered without sequelae	Decapeptyl 3-month, 11.25 mg	Triptorelin pamoate	NR	Migraneous-Type Aura Secondary To Triptorelin Injection (rank 1) [Migraine With Aura] Visual Impairment (rank 2) [Visual Impairment] Headache (rank 3) [Headache]
11	2013-5516 Health authority Spain	5 F	Papilloedema	Recovered without sequelae	Decapeptyl 3.75 mg	Triptorelin acetate	NR	Papilledema (rank 1) [Papilloedema] Petechial Rash (rank 2) [Petechiae] Intracranial Hypertension (rank 3) [Intracranial Pressure Increased] Fever (rank 4) [Pyrexia] Headache (rank 5) [Headache] Stiffness Nape (rank 6) [Musculoskeletal Stiffness]
12	2016-00133 Spontaneous France	9 F	Retinal detachment	Recovered/ resolved with sequelae	Decapeptyl	Triptorelin salt unknown	Reasonable possibility	Unilateral Blindness Related To Retinal Detachment (rank 1) [Retinal Detachment] Unilateral Blindness (rank 2) [Blindness Unilateral]
13	10E20050414 Health authority France	7 F	Thrombocytopenia	Recovered without sequelae	Decapeptyl LP 3 mg	Triptorelin pamoate	Possible	Thrombocytopenia (rank 1) [Thrombocytopenia] (Ecchymoses (rank 2) [Ecchymosis], Petechiae (rank 3) [Petechiae])
14	2012-0876 Literature Macedonia	7 F	Thrombocytopenia	Recovered without sequelae	Triptorelin	Triptorelin acetate	Related	Thrombocytopenia (rank 1) [Thrombocytopenia]
15	10E20010799 Solicited France	8.5 F	Visual field defect	Not yet recovered	Decapeptyl LP 3 mg	Triptorelin pamoate	Possible	Bilateral Concentric Constriction Of Field Of Vision (rank 1) [Visual Field Defect] (Colour Vision Disturbance (rank 2) [Colour Blindness])
Notable PTs highlighted in yellow and listed in Table 4.								

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

	FAERS Case#	Version	Manufacturer Control Number
1	3646938	1	9900032DE
2	3646998	1	9800179DE
3	3776158	2	2002096585NL
4	3782550	2	2001075729IT
5	3785245	1	2002101289FR
6	3856679	1	2002128705FR
7	3909928	1	2003146224FR
8	3913951	1	2003147615IT
9	3954568	1	2003160269FR
10	4016269	1	2003178143FR
11	4025033	1	2003181309FR
12	4029134	2	2003182242DE
13	4105074	1	2004199916FR
14	4159947	1	2004217869ES
15	4197941	1	2004227249NL
16	4198019	1	2004227250NL
17	4198030	1	2004227160NL
18	4198034	1	2004227247NL
19	5661664	2	2004240096FR
20	5768924	1	2005-00883
21	5791248	2	2005-01387
22	5917372	1	2005-03913
23	5941892	2	2005-04591
24	6080213	2	2006-02604
25	6221613	2	2007-00052
26	6305447	2	2007-01765
27	6339520	1	2007-02685
28	6451674	1	2007-04620
29	6559511	4	2008-00622
30	6631050	1	2008-02267
31	6663345	1	FR-WATSON-2008-02267
32	6701425	1	IR-WATSON-2008-04047
33	7608816	1	MK-WATSON-2010-12442
34	8405664	1	MK-WATSON-2012-02168
35	8511548	1	BR-WATSON-2012-05564
36	9221112	1	SE-WATSON-2013-06325
37	9796649	1	AR-WATSON-2013-23977
38	10260121	1	IT-WATSON-2014-14120
39	10517454	1	CH-ABBVIE-14P-151-1294889-00
40	10566251	1	SE-WATSON-2014-23689
41	10665152	1	IL-WATSON-2014-27299
42	10786324	1	CL-WATSON-2015-02190
43	11158082	1	2015FE01744
44	11531803	3	BE-FERRINGPH-2015FE03148

	FAERS Case#	Version	Manufacturer Control Number
45	11722415	1	ES-WATSON-2015-19366
46	11813406	1	GB-WATSON-2015-26225
47	11888324	1	NL-WATSON-2015-28293
48	11888328	1	NL-WATSON-2015-28300
49	12245875	1	CL-ALLERGAN-1652835US
50	12440631	1	CL-ALLERGAN-1658899US
51	12558319	1	US-ALLERGAN-1649205

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/s/

CHRISTIAN T CAO
04/06/2017

CINDY M KORTEPETER
04/06/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Abdominal & Surgical Devices Branch

Date:	December 15, 2016
To:	Anika Lalmansingh, CDER/OPRO. WO75/4631 anika.lalmansingh@fda.hhs.gov
	Office of combination products at combination@fda.gov **RPM:** Anika Lalmansingh anika.lalmansingh@fda.hhs.gov
Through:	Ronald Swann, Chief, Abdominal & Surgical Devices Branch, DMQ, OC, CDRH Ronald L. Swann -S 2016.12.16 17:23:23 -05'00'
From:	Felicia Brayboy, CSO, Abdominal & Surgical Devices Branch, DMQ, OC, CDRH
Applicant:	Arbor Pharmaceuticals, LLC 6 Concourse Parkway, Suite 1800 Atlanta, Georgia 30328
Application # **Consult #**	ANDA 208956 ICC1600613
Product Name:	triptorelin pamoate for (b) (4) suspension

Combination Product Intended Use: Treatment of children with central precocious puberth (CPP).

Pre-Approval Inspection: No

Documentation Review: Under Review /Additional Information Required

Final Recommendation: **DELAY**(or) **APPROVAL** (or) **DISAPPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of ANDA 208956.

PRODUCT DESCRIPTION

Triptorelin pamoate is the active pharmaceutical ingredient used for Triptorelin for [redacted] Suspension 22.5 mg. The chemical name of the drug substance is L-pyroglutamyl-L-histidyl-Ltrytophyl-L-seryl-L-tyrosyl-Dtryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide, pamoate salt. The US adopted name is triptorelin pamoate, and the International Nonproprietary Name (INN) triptorelin embonate. The drug product triptorelin pamoate microgranules 22.5 mg will be provided in a kit with sterile water for injection used for reconstituting the lyophilizedmicrogranules. This product will be marketed by Arbor Pharmaceuticals LLC as an injectable suspension that is indicated for the treatment of children with central precocious puberty.

Container Closure System [Sterile Water for Injection, [redacted] Injectable]

Sterile Water for Injection is packaged in a [redacted] glass syringe which is sealed with a [redacted] stopper and [redacted] cap [redacted] and luer-lock adaptor.

Container Closure System [Triptorelin for [redacted] Suspension 22.5 mg, Debiopharm Research & Manufacturing SA, Injectable Suspension]

Triptorelin pamoate microgranules 22.5 mg is packaged in a [redacted] glass vial with 20 mm closure fitted with a 20 mm [redacted] stopper. The primary container-closure system is sealed with an aluminum overseal with a plastic Flip-off button.

Secondary Packaging:

[redacted] secondary packaging [redacted] will be used for the triptorelin pamoate microgranules 22.5 mg. The drug product vial is placed in a kit with a pre-filled syringe containing Sterile Water for Injection. In addition, two (2) commercially available 21-gauge 1.5” needles are provided in the kit as specified in Package Insert and kit labeling.

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

Facility	Responsibility
(b) (4)	(b) (4)

Inspectional History – An analysis of the firm's inspection history over the past (b) (4) showed that an inspection conducted on (b) (4) The inspection covered drug GMP requirements and was classified VAI.

This was a full GMP inspection of (b) (4)
This inspection was conducted to assess the cGMP state of the facility. Coverage was given to (b) (4)

The previous FDA inspection of this facility was conducted from (b) (4) The inspection covered four systems of (b) (4) The previous inspection was classified VAI, resulting in a two-item FDA observation form. During the (b) (4), the investigators verified the firm's corrections to the previous FDA 483 observation items and other verbal discussions and commitments. (b) (4)s (b) (4)

Inspection Recommendation:

An post approval inspection is required because: (b) (4)

NOTE: If CDER is planning to conduct a pre-approval inspection at this site please include QSR coverage; otherwise a post approval inspection will suffice.

A comprehensive baseline (b) (4) inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Facility	Responsibility
Debiopharm Research & Manufacturing SA Rue du Levant 146 CH-1920 Martigny Switzerland Establishment Registration Number: 3002806850 DUNS Number: 481942860	Manufacturing of drug product Primary packaging Labeling of drug product Finished product release testing Finished product stability testing (b) (4)

Inspectional History – An analysis of the firm's inspection history over the past (b) (4) showed that an inspection conducted on (b) (4). The inspection covered drug GMP requirements and was classified NAI.

This comprehensive cGMP inspection and Pre-Approval Inspection (PAI) of a finished dosage small volume sterile injectable manufacturer was performed according to Compliance Program 7356.002 (Drug Manufacturing Inspections), 7356.002A (Sterile Drug Manufacturing Inspections) and 7346.832 (Pre-Approval Inspections). This inspection was conducted under PAC: 56002 Drug Manufacturing Inspections, 56002A Sterile Drug Manufacturing Inspections and 46832 Pre-Approval Inspections. This current inspection covered the following five systems: 1) Quality, 2) Laboratory, 3) Facilities and Equipment, 4) Production, 5) Materials. This current inspection verified that the firm continues to operate as a finished dosage small volume sterile injectable manufacturer. This Debiopharm Research & Manufacturing facility performs finished drug product manufacturing and filling operations under a (b) (4) (b) (4) (b) (4) The last inspection was conducted (b) (4) and at the conclusion of this inspection Form FDA 483 was issued for four deficiencies. The previous inspection was classified **VAI.** During the (b) (4) inspection it was verified that the firm had corrected the deficiencies noted on the previous FDA 483.

Inspection Recommendation:

An post approval inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed

NOTE: If CDER is planning to conduct a pre-approval inspection at this site please include QSR coverage; otherwise a post approval inspection will suffice.

A comprehensive baseline (b) (4) inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Facility	Responsibility
(b) (4)	(b) (4)

Inspectional History – An analysis of the firm's inspection history showed that the inspections below were conducted and classified NAI. The inspections covered medical device QS requirements.

Start Date	End Date	Basis	District Decision	483 YN
(b) (4)		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No

Inspection Recommendation:
An inspection is not required because:

- The last medical device inspection of the firm was acceptable.

Facility	Responsibility
(b) (4)	(b) (4)

Inspectional History – An analysis of the firm's inspection history showed that the inspections below were conducted and classified NAI. The inspections covered drug GMP requirements.

Start Date	End Date	Basis	District Decision	483 YN
(b) (4)		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Surveillance	No Action Indicated (NAI)	No
		Consumer Complaint	No Action Indicated (NAI)	No

Inspection Recommendation:
An inspection is not required because:

- The last 5 inspections have been NAI.

DOCUMENTATION REVIEW – Additional information needed

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

(b) (4)

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

Prepared: FBrayboy: December 15, 2016
Reviewed: RSwann: 12/16/2016

CTS No.: ICC1600613
ANDA 208956

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

/s/

ANIKA A LALMANSINGH
01/09/2017
Uploading on behalf of Felicia Brayboy, CSO.

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208956

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Triptodur (triptorelin for (b) (4) suspension), 22.5 mg

Applicant: Arbor Pharmaceuticals, LLC

Receipt Date: August 29, 2016

Goal Date: June 29, 2016

1. Regulatory History and Applicant's Main Proposals

The applicant, Arbor Pharmaceuticals, LLC, is developing Triptodur (triptorelin pamoate for (b) (4) suspension) for the treatment of children with central precocious puberty. To support approval of this NDA, the applicant submitted results from Study Debio 8206-CPP-301 entitled, "An open-label, non-comparative, multicenter study on the efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin dependent) precocious puberty (CPP)."

Other products, also gonadotropin releasing hormone (GnRH) agonists, currently approved for treatment of CPP include the following: Lupron Depot-Ped (leuprolide acetate for depot suspension), Supprelin LA (histrelin acetate) subcutaneous implant and Synarel (nafarelin acetate) nasal spray.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

NOTE TO RPM: SEE THE *LABELING DEVELOPMENT TEAM (LDT) INTRANET SITE* FOR ADDITIONAL PI LABELING RESOURCES.

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

NO 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *Applicant will be requested to update the revision date once labeling negotiations begin later in the review cycle.*

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment: *There are Contraindications listed in the FPI.*

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JENNIFER L JOHNSON
11/10/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208956 BLA# N/A	NDA Supplement #: S- N/A BLA Supplement #: S- N/A	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Triptodur Established/Proper Name: triptorelin pamoate for (b) (4) suspension Dosage Form: injection Strengths: 22.5 mg		
Applicant: Arbor Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A		
Date of Application: August 29, 2016 Date of Receipt: August 29, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: June 29, 2017	Action Goal Date (if different):	
Filing Date: October 28, 2016	Date of Filing Meeting: October 24, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of children with central precocious puberty		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 111504	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		Orphan designation granted on August 20, 2012.
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 7 years ***Note:*** *An applicant can receive exclusivity without requesting it;*	☒	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		Orphan designation #12-3760 granted on August 20, 2012

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	A non-REMS risk management plan was included in the NDA submission.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☒ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR)	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

format?[4]				
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☐	☒	☐	Labeling consult will be sent after the filing meeting.
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	CDRH consult for review of device (syringe) for sterile water diluent was sent on 9/15/16.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** December 3, 2015	☒	☐		Meeting minutes issued on December 30, 2015.
Any Special Protocol Assessments (SPAs)? **Date(s):** Clinical SPA Agreement letter issued on October 21, 2011	☒			

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 24, 2016

BACKGROUND: The applicant, Arbor Pharmaceuticals, LLC, is developing Triptodur (triptorelin pamoate for (b) (4) suspension) for the treatment of children with central precocious puberty. (This product is also marketed as Trelstar 6-Month by Actavis Laboratories UT, and approved under NDA 022437 in the Division of Oncology Products 1 for the palliative treatment of advanced prostate cancer.) To support approval of this NDA, the applicant submitted results from Study Debio 8206-CPP-301 entitled, "An open-label, non-comparative, multicenter study on the efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin dependent) precocious puberty (CPP)."

Communication about development of this product took place under IND 111504, originally submitted on May 11, 2011 (with former sponsor Debiopharm International SA). A SPA-Agreement letter was issued on October 21, 2011. Orphan drug designation was granted for this product and indication on August 20, 2012. A Pre-NDA meeting was held on December 3, 2015, and minutes issued on December 30, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Johnson	Y
	CPMS/TL:	Pam Lucarelli	Y
Cross-Discipline Team Leader (CDTL)	Marina Zemskova		Y
Division Director/Deputy	Jean-Marc Guettier		Y
Office Director/Deputy	N/A		
Clinical	Reviewer:	Shannon Sullivan	Y
	TL:	Marina Zemskova	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Jianmeng Chen	Y
	TL:	Jaya Vaidyanathan	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	Jiwei He	Y
	TL:	Mark Rothmann	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Federica Basso	Y
	TL:	Ron Wange	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Su Tran	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	Xavier Ysern	N
• Drug Product	Reviewer:	Christopher Galliford	N
• Process	Reviewer:	Yong Hu	N
• Microbiology	Reviewer:	Denise Miller	N
• Facility	Reviewer:	Michael Klapa	N
• Biopharmaceutics	Reviewer:	Suneet Shukla	N
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	N/A	
	TL:	N/A	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	TBD	
	TL:	TBD	
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sarah Vee	
	TL:		

OSE/DRISK (REMS)	Reviewer:	Till Olickal	Y
	TL:	Cynthia Lacivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
CDRH/DAGID (device)	Reviewer:	Onwuatuegwu Echezona	N
	TL:	Robert Meyer Alan Stevens	N N
Other attendees	Deveonne Hamilton-Stokes (OSE RPM)		Y
	Christian Cao (OSE/DPV I)		Y
	Jennifer R. Pippins (DMEP DDS)		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues:	☒ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

If no, explain:	
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Request for percentage of children with LH suppression to prepubertal levels within subgroups by gender, race and ethnicity will be included in the 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted?	 ☒ YES ☐ NO ☐ YES ☐ NO

Comments:	
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Jean-Marc Guettier, M.D. (DMEP Division Director) **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): N/A **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74

☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

JENNIFER L JOHNSON
11/10/2016