

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213150Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: April 27, 2020

To: William A. Lubas, M.D., Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

Jennifer Johnson, Project Manager, (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for FENSOLVI (leuprolide acetate) for injectable suspension, for subcutaneous use

NDA: 213150

In response to DMEP's consult request dated April 17, 2020, OPDP has reviewed the proposed product labeling (PI), and Medication Guide (MG) for FENSOLVI (leuprolide acetate) for injectable suspension, for subcutaneous use (Fensolvi). This application is a 505(b)(2) relying on NDA 020263.

PI, MG: OPDP's comments on the proposed PI are based on the draft materials sent by DMEP via email on April 17, 2020. OPDP has no comments on the proposed labeling at this time.

Please note that comments on the MG will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
04/27/2020 03:54:52 PM

**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: April 22, 2020

To: Jennifer Johnson, Regulatory Project Manager
Division of General Endocrinology (DGE)

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: Maria Nguyen, MSHS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Charuni Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): FENSOLVI (leuprolide acetate)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: NDA 213150

Applicant: Tolmar International Limited

1 INTRODUCTION

On August 1, 2019, Tolmar International Limited submitted for the Agency's review New Drug Application (NDA) #213150 for FENSOLVI (leuprolide acetate). The proposed indication for FENSOLVI (leuprolide acetate) is for the treatment of central precocious puberty (CPP) in pediatric patients 2 years of age and older.

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 General Endocrinology (DGE) on April 17, 2020 and April 1, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for FENSOLVI (leuprolide acetate) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft FENSOLVI (leuprolide acetate) MG received on August 1, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on April 17, 2020.
- Draft FENSOLVI (leuprolide acetate) MG received on August 1, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on April 1, 2020.
- Draft FENSOLVI (leuprolide acetate) Prescribing Information (PI) received on August 1, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on April 17, 2020.
- Draft FENSOLVI (leuprolide acetate) Prescribing Information (PI) received on August 1, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on April 1, 2020.
- Approved LUPRON DEPOT-PED (leuprolide acetate for depot suspension) comparator labeling dated May 19, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, 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 document 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)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

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.

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/s/

MARIA T NGUYEN

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DMPP-OPDP review of leuprolide acetate (FENSOLVI) NDA 213150 MG

CHARUNI P SHAH

04/22/2020 03:24:11 PM

MARCIA B WILLIAMS

04/22/2020 03:28:39 PM

LASHAWN M GRIFFITHS

04/22/2020 04:22:41 PM

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:	April 6, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 213150
Product Name and Strength:	Fensolvi (leuprolide acetate) for injection, 45 mg
Applicant/Sponsor Name:	Tolmar Therapeutics
OSE RCM #:	2019-1425-1
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 27, 2020 for Fensolvi. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Fensolvi (Appendix A and Appendix B) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a We also sent an additional comment to the Sponsor based on revisions to the Syringe B container label and tray labeling that was submitted on January 24, 2020.^b

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Schlick J. URRA, CA, Label and Labeling Review for Fensolvi (NDA 213150). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 08. RCM No.: 2019-1432 and 2019-1425.

^b Johnson, J. Labeling Discussion Comments. Submitted to DARRTS on March 23, 2020.

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8054e99f&_afRedirect=4789907930596469

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/s/

JAMES H SCHLICK
04/06/2020 02:07:27 PM

MILLIE B SHAH
04/06/2020 02:38:28 PM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	12/17/2019		
To:	Jennifer Johnson		
Requesting Center/Office	CDER/OND	Clinical Review Division	N/A- CBER
From	Shanly Chen OPEQ/OHT3/DHT3C3		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C1		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C1		
Subject	NDA 213150 , Fensolvi (leuprolide acetate for injectable suspension), 45 mg ICC1900859		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☒ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies Mid-Cycle Recommendation Date: 12/20/2019 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☒ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 3/24/2019 ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Shanly M. Chen -S3 Digitally signed by Shanly M. Chen -S3 Date: 2020.03.25 14:14:18 -04'00'	Rumi Young -S	Rumi Young -S c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rumi Young -S, 0.9.2342.19200300.100.1.1=2002467913 2020.03.26 15:04:43 -04'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 213150
Sponsor	TOLMAR INC
Drug/Biologic	Fensolvi (leuprolide acetate for injectable suspension), 45 mg
Indications for Use	Treatment of central precocious puberty in pediatric patients
Device Constituent	Pre-Filled Syringe
Related Files	

Important Dates	
Filing	8/31/2019
74-Day Letter	
Midcycle Meeting/IRs due	12/20/2019
Final Lead Device Review Memo Due	3/24/2020
PDUFA Date	5/2/2020

2. EXECUTIVE SUMMARY AND [RECOMMENDATION](#)

CDRH recommends the combination product is:

- ☒ Approvable – the device constituent of the combination product is approvable for the proposed indication.
☐ Approvable with PMC or PMR, [See Section 2.3](#)
☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

2.1. [Comments](#) to the Review Team

- ☒ CDRH does not have any further comments to convey to the review team.
☐ CDRH has the following comments to convey to the review team:

2.2. [Complete Response](#) Deficiencies

- ☒ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☒

3. PURPOSE/BACKGROUND

3.1. Scope

TOLMAR INC is requesting approval of FENSOLVI (leuprolide acetate for injectable suspension), 45 mg. The device constituent of the combination product is a Pre-Filled Syringe.

The drug product, (leuprolide acetate for injectable suspension, 45 mg) under consideration for treatment of central precocious puberty (CPP) is the same product as the currently marketed drug product, ELIGARD 45 mg (6-month). The two products are identical in terms of active ingredients, dosage form, strength, composition, route of administration, manufacturing process, quality, safety and performance characteristics.

The two products differ only in terms of labeling and intended use. The labeling has been updated with instructions on proper administration for children 2 yrs and older. The previous indication was only for adults with prostate cancer, the new indication is for children 2 yrs and older for central precocious puberty (CPP). CPP is a condition that causes early sexual development in girls and boys, therefore Fensolvi is used to delay puberty until the appropriate age.

Tolmar submitted NDA 021731/S-39 and got FDA approval for removing the (b) (4) needle and adding (b) (4) on April 17, 2019. CDER contacted CDRH for an inter-center consult regarding this change. The review was done by Weihong Gu (CDRH/OHT3/DHT3C/THT3C1) on Feb 6, 2019 and will be leveraged in this review for device performance.

CDER/OGD has requested the following [consult](#) for review of the device constituent of the combination product:

Please review the proposed device (two-syringe mixing system with a sterile safety needle) for this drug product.

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

- ☒ Device performance
- ☐ Biocompatibility of the patient contacting components
- ☐ Sterility
- ☐ Stability – device performance on stability
- ☒ Essential Performance Requirements (EPR) Control strategy
- ☐ Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

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

3.2. [Prior Interactions](#)

3.2.1. [Related Files](#)

3.3. Indications for Use

Combination Product	Indications for Use
Fensolvi (leuprolide acetate for injectable suspension), 45 mg	Adding new indication: "Treatment of central precocious puberty in pediatric patients"
Pre-Filled Syringe	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
1	2.2 Summary and Intro
1	1.2 Reviewer's Guide
1	1.14.1.3 Draft Labeling Text
1	3.2.P.5.1 Specifications
1	3.2.P.5 Drug Product
(b) (4)	CDRH consult for NDA (b) (4)

4. DEVICE DESCRIPTION**4.1. Background**

ELIGARD® 45 mg (leuprolide acetate for injectable suspension), NDA 021731, was approved on December 14, 2004 as a gonadotropin releasing hormone (GnRH) agonist for use in the palliative treatment of advanced prostate cancer. It is injected into the body subcutaneously as a liquid, where it solidifies and delivers a dose of leuprolide acetate at a controlled rate for the specified therapeutic period of time. ELIGARD® 45 mg is a depot polymeric matrix formulation intended for subcutaneous dosing every six months. ELIGARD® 45 mg is provided in a single use kit of a two syringe-mixing system labeled for storage at Store at 2 - 8 °C (35.6 – 46.4 °F) for 24 months. Syringe A consist of the polymeric matrix, the ATRIGEL® Delivery System and Syringe B the lyophilized drug substance, leuprolide acetate. In addition to the six-month depot formulation of 45 mg leuprolide acetate, Tolmar Therapeutics, Inc. has commercialized one, three, and four month (ELIGARD® 7.5 mg, 22.5 mg, and 30 mg, respectively) formulations of leuprolide acetate. These are approved NDAs 021343, 021379, and 021488.

Tolmar submitted NDA 021731/S-39 and got FDA approval for removing the (b) (4) needle and adding (b) (4) instead. The (b) (4) safety needle was already approved and not receiving any changes. CDER contacted CDRH for an inter-center consult regarding this change. The review was done by Weihong Gu (CDRH/OHT3/DHT3C/THT3C1) and will be leveraged in this review for device performance.

4.2. Device [Description](#)

ELIGARD® is packaged in two pre-filled syringes (Syringe A and Syringe B) along with a replacement plunger rod and a pre-packaged sterile needle for injection. Syringe A contains the ATRIGEL® delivery system and Syringe B contains the lyophilized drug substance (leuprolide acetate). Prior to administration, the syringes are removed from the packages, the plunger rod affixed into Syringe B, the syringe tip caps are detached, and the syringes are coupled. The drug product is prepared for administration by passing the contents back and forth from syringe to syringe until blended. The resulting drug product, referred to as the constituted product, is transferred into Syringe B, the syringes are decoupled and the sterile needle is affixed to Syringe B for subcutaneous administration.

Fensolvi (leuprolide acetate for injectable suspension), 45 mg
TOLMAR INC

The ELIGARD 45 mg was approved with the (b) (4) needle 18G x 5/8" and (b) (4) 18G x 5/8" needle for use in adults on April 17, 2019 as a gonadotropin releasing hormone (GnRH) agonist for use in the palliative treatment of advanced prostate cancer. Per Tolmar, the current device components is exactly the same as a previously cleared combo product Eligard 45mg (NDA 021731), which uses the (b) (4) needle 18G x 5/8" and (b) (4) 18G x 5/8" needles. With this current submission, Tolmar is seeking approval for treatment of central precocious puberty in pediatric patients 2 years and older for FENSOLVI 45 mg.

The drug product FENSOLVI 45 mg, (leuprolide acetate for injectable suspension, 45 mg) under consideration for treatment of central precocious puberty (CPP) is the same product as the currently marketed drug product, ELIGARD 45 mg (6-month). The two products are identical in terms of active ingredients, dosage form, strength, composition, route of administration, manufacturing process, quality, safety and performance characteristics. The two products differ only in terms of labeling and intended use. The drug product has a shelf life of 24 months at 2 - 8 °C (36 - 46 °F).

Using a 5/8 inch needle to give subcutaneous injection is a well established technique reference by the CDC Advisory Committee on Immunization Practices (<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm>). However, the CDC recommends using 23-25 gauge needles in reference to delivering vaccines. FENSOLVI 45 mg is using a 5/8 inch and 18 gauge needle, which is a larger bore needle. Presumably, FENSOLVI (b) (4) There is an ongoing pediatric study for the safety and effectiveness of FENSOLVI 45 mg, details can be found in Folder 1.9.6/Pediatric Study Plan and Folder 5.3.5.1.Synopsis.

The safety and effective of the larger gauge needle is being confirmed in the ongoing pediatric study, we'll will defer to CDER on the adequacy of the clinical study. We'll confirm with the sponsor that the needles used in the clinical study are (b) (4) 5/8 inch x 18G syringes.

4.3. Design Requirements

Basic Syringe Description/Requirements

Requirement	Reviewer Comment
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	For pediatric patients 2 years or older, but must be administered by a health care professional
Injection Site	Abdomen, upper buttocks, or another location with adequate amounts of subcutaneous tissue
Injection tissue and depth of injection	Subcutaneous
Type of Use (e.g. single use, disposable, reusable, other)	Single Use
Environments of use (e.g. home, clinic)	Clinic by healthcare professionals
Storage conditions and expiry	24 months at 2 - 8 °C (35.6 – 46.4 °F)
Needle connection (e.g. luer, slip tip, staked)	Luer lock
Syringe Volume	Polymer Side (b) (4) NMP) Drug Side (b) (4) NMP)
Device materials including lubricant	See below

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(b) (4)



The images below are taken from NDA (b) (4) and only provided for context. The removal of the (b) (4) needle and substituted with the (b) (4) needle has already been reviewed by CDRH and approved by

ICC1900859

Fensolvi (leuprolide acetate for injectable suspension), 45 mg
TOLMAR INC

CDER. We are leveraging the (b) (4) regarding device performance for this memo since nothing is changed regarding the device itself.

The new changes are to labeling and intended use per Tolmar. The labeling has been updated with instructions on proper administration for children 2 yrs and older. The previous indication was only for adults with prostate cancer, the new indication is for children 2 yrs and older for central precocious puberty (CPP).

The drug product FENSOLVI 45 mg, (leuprolide acetate for injectable suspension, 45 mg) under consideration for treatment of central precocious puberty (CPP) is the same product as the currently marketed drug product, ELIGARD 45 mg (6-month). The two products are identical in terms of active ingredients, dosage form, strength, composition, route of administration, manufacturing process, quality, safety and performance characteristics. The two products differ only in terms of labeling and intended use. Therefore the changes do not impact the already established EPRs (break loose, glide force, etc) and the sponsor can leverage data from the referenced product.

Table 3.2.P.2.4.1-1: Comparison of (b) (4) and (b) (4) Needles

Attribute	(b) (4) Safety Needle	(b) (4) Needle
Gauge	18G	18G
Insertion Depth (inches)	5/8"	5/8"
510(k) Cleared	Yes	Yes
ISO 594-2 Compliant Hub Material	(b) (4)	(b) (4)
Cannula Material	Stainless Steel	Stainless Steel
Sterilization Method	(b) (4)	(b) (4)
Cannula Type	(b) (4)	(b) (4)
Total Cannula Length (mm) ¹	33.26	21.78

Additional Syringe Description/Requirements

Requirement	Reviewer Comment
Hypodermic Needle: length, gauge, and configuration of the tip.	Length: 5/8" Gauge: 18G Configuration of the tip:
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility)	Not relevant, syringes are prefilled and users are expected to inject full quantity of drug substance.

criteria (for insulin syringes). Insulin Syringes: The scale on the barrel should be in units of insulin.	
Reuse Durability (for reusable piston syringes): number of times the device can be sterilized and still meet specifications (using sterilization method indicated in the labeling).	N/A, single use only
Safety Features (e.g. Needle safety component/device)	Needle safety shield on the (b) (4) to prevent needle stick injuries after injection
Automated Functions	N/A
Sterilization method	(b) (4)

*See [Design Verification Section](#) for verification of design requirements

4.4. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 12/20/2019	Date/Sequence Received: Click or tap to enter a date.
Information Request #1	Though you state in Folder 5.3.5.1 Protocol, that you are using syringe A and B for your study. It does not state the specific needles you are using. Confirm that the needles used in the pediatric clinical study for NDA 213150 are (b) (4) or (b) (4) 5/8 inch x 18G syringes by providing a statement to this effect.	
Sponsor Response	Seq 006 mod 1.11.1: Tolmar confirms the needle used in the pediatric clinical study for NDA 213150 was the (b) (4) (b) (4) safety needle 5/8 inch x 18G. The CofAs for the three (3) drug product lots used in the clinical study are provided in Module 5.3.5.1 Appendix 16.1.8.2 and indicate the needle gauge and length.	
Reviewer Comments	Response adequate since the needle used in the clinical study is the needle used in the final finished product (b) (4) (b) (4) safety needle with the same length and gauge (5/8 inch x 18G).	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

5. FILING REVIEW

CDRH performed Filing Review	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☒

5.1. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☐ Yes ☐ No ☒ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection Needed ☒ N/A
CDRH completed a review of the Quality Systems	☐ Yes ☐ No ☒ N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in [Appendix B](#)

5.2. Filing Recommendation

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☒ N/A	
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☒ N/A Site(s) needing inspection:	
Reviewer Comments: We weren't consulted in time for the filing review and the device is not a life sustaining device or emergency use. Therefore, per internal MAPP 5017.7 a facilities review will not be provided for this prefilled syringe file.	
Refuse to File Deficiencies: ☐ Yes ☐ No ☒ N/A 74-Day Letter Deficiencies: ☐ Yes ☐ No ☒ N/A	

No Additional Information Requests to add

6. DEVICE PERFORMANCE REVIEW**6.1. Design Verification/Validation***6.1.1. Device Specification Standards and Guidance Documents*

Syringe		Data Adequate		
		Yes	No	N/A
Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☒	☐	☐
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☐	☐	☒
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☒
Needle/Sharps		Data Adequate		
		Yes	No	N/A
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☒	☐	☐

Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☒	☐	☐
Sharps Injury Prevention Feature	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	☒	☐	☐
Luer Lock		Data Adequate		
		Yes	No	N/A
<u>Connection</u>	ISO 80369-7, Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications ** (replaces ISO 594-1 and 594-2 as of 2020) ISO 594-1, Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment - - Part 1: General requirements ISO 594-2, Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment - - Part 2: Lock fittings	☒	☐	☐
Other		Data Adequate		
		Yes	No	N/A
[Other]	[Other]	☐	☐	☒

The device performance evaluation is leverage from (b) (4) for (b) (4) and approved by CDER on April 17, 2019. There has been no change to the device itself and is identical to (b) (4). The changes are to labeling and intended use per Tolmar.

6.1.2. Device Performance Evaluation

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	(b) (4) of constituted product	Y	Y	Y	Y
Break loose Force	Equivalent between (b) (4) and (b) (4)	Y	Y	Y	Y
Glide Force	Equivalent between (b) (4) and (b) (4)	Y	Y	Y	Y
Cap Removal Force	Twist off, not revelant				
Other					

Reviewer Comment

The device performance evaluation is leverage from (b) (4) and approved by CDER on April 17, 2019. There has been no change to the device itself and is identical to NDA 021731. The changes are to labeling and intended use. Tolmar wishes to leverage performance data from NDA 021731 and has provided some specifications, verification method, validation and performance after aging.

IR #2: Though you provided the test method, validation, aging for ELIGARD 45mg in NDA 021731 and state it passed testing criteria. It appears you have not provided the break loose force data for the final finished product. Provide the average break loose force data up to the shelf life of your final finished product (syringe A, syringe B and the final syringe after mixing).

Sponsors response in seq 006 mod 1.11.1:

The purpose of the study provided for ELIGARD® 45 mg (in eCTD 0091, NDA 021731/S-039) was to demonstrate equivalency between (b) (4) and (b) (4)™ safety needles. Thus the break loose force measurements for syringe A and syringe B were beyond the scope of this study. Break loose forces were measured only after final mixing of contents of syringe A and syringe B, transfer of the reconstituted product to syringe B and extrusion through either the (b) (4) safety needle. The break loose force data at the end of shelf life (EOSL) for the final reconstituted product is given in Table 1 below.

	Break Loose Force (N)	Glide Force (N)
(b) (4)	3.752	15.95
Safety Average (b) (4)	0.3920	4.301
Safety SD		

(b) (4)	3.9044	13.95
Average		
(b) (4) SD	0.6746	1.499

I agree with the sponsor rationale that since the changes to the combo product was labeling and indications. They already have demonstrated break loose force and glide force after mixing are equivalent between (b) (4) needles. Furthermore, the average break loose force and glide force are well below generally acceptable injection forces. The change of (b) (4) was already approved on April 17, 2019. The review was done by Weihong Gu (CDRH/OHT3/DHT3C/THT3C1) on Feb 6, 2019.

IR#3: It appears you have not provided a test summary demonstrating that your final finished product still conforms to the essential performance requirements of dose accuracy, break loose force and glide force after shipping and transportation. Provide dose accuracy, break loose force and glide force testing of your final finished product (syringe A, syringe B and the final syringe after mixing) after simulated shipping/transportation.

Sponsor's response in seq 006 mod 1.11.1:

Tolmar has not conducted any simulated shipping/transportation studies that measure dose accuracy, break loose force and glide force. To ensure proper (b) (4) of environmental conditions, Tolmar uses (b) (4) of its approved product ELIGARD 45 mg. The same validated shipping methods will be utilized for FENSOLVI®. Hence, no additional shipping/transportation studies were conducted on the product.

It is Tolmar's understanding that, dose accuracy, break loose force and glide force are requirements of ISO 11040-8:2016 Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes. It clearly states that "Finished prefilled syringes which have undergone an additional preparation step by the user before injection (e.g., diluent syringes that have been emptied for reconstitution and in which the reconstituted drug solution has been aspirated after reconstitution) are excluded from the scope of ISO 11040-8:2016". It is Tolmar's understanding that these performance requirements are not applicable to syringe A, syringe B or the final product, but rather can be used as a reference or a guidance. Accordingly, as the contents of syringe A and the contents of syringe B cannot be injected independently, break loose force and glide force are not applicable to either syringe A or syringe B. The final finished product undergoes further preparation (i.e., reconstitution) and this requirement constitutes an additional preparation step by the end user prior to performing the injection; therefore it is excluded from the scope of ISO 11040-8. Further explanation as to why measurement of these forces for syringe A and syringe B are not applicable is given below.

Syringe B containing lyophilized leuprolide acetate has a male Luer that is designed to be used with the female hub of the safety needles (see Figure 1). In the event the end user were to attach the safety needle to syringe B without first mixing the contents of syringe B with the contents of syringe A, the user would be able to compress the lyophilized leuprolide acetate in syringe B (see Figure 2). However, the compressed lyophilized leuprolide acetate is unlikely to be injected as the compressed lyophilized leuprolide acetate powder is retained within the Luer of syringe B, and is unlikely to be extruded through the cannula of the safety needle (see Figure 3).

I agree with the sponsor's rationale that Tolmar has (b) (4) for ELIGARD 45 mg, this information can be leveraged for FENSOLVI and not further shipping/transportation validation is required. Since there has been no changes to the combo product,

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the previous CDRH memo (b) (4) clearing ELIGARD's shipping/transportation methods can be leveraged here and no further review of shipping method is needed.

6.1.3. Stability Review Summary

Shelf-life:	2 years
Storage conditions:	2 C-8 C
Time period and storage conditions provided for accelerated aging:	60 C for 135 days
Time period and storage conditions provided for real-time aging:	N/A

*Endpoint evaluation is provided in [section 6.1.2.](#)

Reviewer Comments

The device performance evaluation is leverage from (b) (4) and approved by CDER on April 17, 2019. There has been no change to the device itself and is identical to (b) (4). The changes are to labeling and intended use per Tolmar.

6.1.4. Biocompatibility Evaluation

- ☐ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]
- ☒ Biocompatibility was not evaluated **because**: it's a prefilled syringe. The needles are (b) (4) needles which are previously approved by CDER.

6.1.5. Sterility Evaluation

- ☐ Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)
- ☒ Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

Review Comments:

The sponsor did not provide the 510(k) number for the (b) (4) 18G x 5/8" syringe. I did a search of the FDA 510(k) database but there are many (b) (4) syringes and I'm unable to identify the specific syringe used by Tolmar. See Interactive Deficiency #4.

IR#4: Provide the 510(k) clearance numbers and letter of authorizations for your co-packaged needle (b) (4)

Sponsor's response in seq 006 mod 1.11.1:

The 510(k) number for the (b) (4) The filing (b) (4) (b) (4) for the (b) (4) contained only the 510K summary. The 510(k) number for the (b) (4) Safety Needle is (b) (4). The filing for it (eCTD 0086, (b) (4)) contained only the 510K statement. Tolmar has contacted manufacturers of both the needles (u) (u) and (u) (u) for Letters of authorization to their 510(k)s. (b) (4) (b) (4), Tolmar was unable to procure the LoAs within the Agency's response timelines of January 3rd, 2020. Tolmar is continuously in contact with the manufacturers and the LoAs will be submitted to the Agency promptly upon receipt.

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The sponsor did provide the letter of authorization for (b) (4) (seq 008 mod 1.4.1), they have identified the 510(k) number 2 for their selected needle 18G x 5/8". 2 has been cleared for the general population which includes adults and pediatrics which is appropriate for the indicated use of this combo product.

Using a 5/8 inch needle to give subcutaneous injection is a well established technique reference by the CDC Advisory Committee on Immunization Practices (<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm>). However, the CDC recommends using 23-25 gauge needles in reference to delivering vaccines. While the CDC recommendation is not directly applicable it can be used as a guide. FENSOLVI 45 mg is using a 5/8 inch and 18 gauge needle, which is a larger bore needle. Presumably, FENSOLVI (b) (4). There is an ongoing pediatric study for the safety and effectiveness of FENSOLVI 45 mg, details can be found in Folder 1.9.6/Pediatric Study Plan and Folder 5.3.5.1.Synopsis.

The safety and effective of the larger gauge needle is being confirmed in the ongoing pediatric study, we'll will defer to CDER on the adequacy of the clinical study. The sponsor has confirmed the needles used in the clinical study are the 5/8 inch x 18G needles.

6.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments See above section for deficiencies		
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 12/20/2019	Date/Sequence Received: 12/20/2019
Information Request #2	Though you provided the test method, validation, aging for ELIGARD 45mg in NDA 021731 and state it passed testing criteria. It appears you have not provided the break loose force data for the final finished product. Provide the average break loose force data up to the shelf life of your final finished product (syringe A, syringe B and the final syringe after mixing).	
Sponsor Response	See above	
Reviewer Comments		
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: 12/20/2019	Date/Sequence Received: 12/20/2019
Information Request #3	It appears you have not provided a test summary demonstrating that your final finished product still conforms to the essential performance requirements of dose accuracy, break loose force and glide force after shipping and transportation. Provide dose accuracy, break loose force and glide force testing of your final finished product (syringe A, syringe B and the final syringe after mixing) after simulated shipping/transportation.	
Sponsor Response	See above	

Reviewer Comments	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: 12/20/2019	Date/Sequence Received: 12/20/2019
Information Request #4	Provide the 510(k) clearance numbers and letter of authorizations for your co-packaged needle (b) (4) and (b) (4)	
Sponsor Response	See above	
Reviewer Comments		
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Device Performance Review Section**

7. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use))*

Essential Performance Requirements	Control Strategy Description – The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or <u>release testing</u> activities:	Acceptable (Y/N/NA)
Dose Accuracy	(b) (4)	Y
Break loose Force	Container/closure components are controlled through incoming inspection and the supplier Certificate of Compliance (CofC) documents are compliant with applicable EN/ISO standards.	Y
Glide Force	See above	Y

Reviewer Comments

IR #5: In S001/3.2.P.5.1 you provided the specifications your finished final combination product. However, it does not include dose accuracy, break loose force and glide force essential performance requirements of syringe A, syringe B and/or final syringe after mixing. Update your specification table to include these EPRs for your final finished product (syringe A, syringe B and the final syringe after mixing). Furthermore, include the sampling plan for the release and stability testing the EPRs. Alternatively, provide an assessment of how the EPRs are controlled through incoming acceptance, in-process control, and/or release testing activities.

Sponsor's response in seq 006 mod 1.11.1:

The specifications provided in S001/3.2.P.5.1 are same as that for ELIGARD 45 mg. Tolmar has

made no changes to approved specifications. As stated in response to [Question 3](#), Tolmar believes that compliance to ISO 11040-8:2016 is not applicable to either the marketed ELIGARD products or to Fensolvi currently the under review in this NDA. However, Tolmar inspects all incoming container/closure components and the functionality of syringe A and syringe B is monitored (b) (4)

. Dose accuracy is also monitored through (b) (4)
. These activities are discussed in greater detail below. Product development procedures for combination products and medical devices are used to document product design requirements and changes made to the product design or process are managed through change controls.

All container/closure components for syringe A and syringe B, along with the secondary stopper, the white plunger rod and the safety needle are controlled (b) (4) *and the supplier Certificate of Compliance (CofC) documents which are compliant with applicable EN/ISO standards. The supplier, prior to release of the packaging components assures product performance to set specifications, by performing document review and quality testing as per EN/ISO standards. Further, upon receipt, syringe A and syringe B are tested for the following by Tolmar:*

Syringe A: visual, microbial testing, particulates, pressure test, and identification of the barrel, the plunger and lubricant.

Syringe B: visual, microbial testing, sterility, particulates, and identification of the barrel, and tip cap.

(b) (4)

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(b) (4)

I agree with the sponsor that control strategy is not applicable for EPRs (break loose and glide force) if the final finished product requires a mixing step by the user before injection into the patient. While dose accuracy may not be applicable to the combo product after mixing, it can be applied to the final finished product before mixing. The sponsor has provided their acceptance criteria to determine if syringe A and B meet dose accuracy requirements (b) (4) which was reviewed by (b) (4)

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

☒ Yes

☐ No

7.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☐ No ☒ N/A

Mid-Cycle Deficiencies:

☒ Yes ☐ No ☐ N/A

Final Deficiencies:

☐ Yes ☒ No ☐ N/A

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Reviewer Comments

See above section for deficiencies.

CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No

	Date Sent: 12/20/2019	Date/Sequence Received: 12/20/2019
Information Request #5	In S001/3.2.P.5.1 you provided the specifications your finished final combination product. However, it does not include dose accuracy, break loose force and glide force essential performance requirements of syringe A, syringe B and final syringe after mixing. Update your specification table to include these EPRs. Furthermore, include the sampling plan for the release and stability testing the EPRs. Alternatively, provide an assessment of how the EPRs of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities.	
Sponsor Response	See above	
Reviewer Comments		
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Filing/74-Day Information Requests

N/A

8.2. Mid-Cycle Information Requests

1. Though you state in Folder 5.3.5.1 Protocol, that you are using syringe A and B for your study. It does not state the specific needles you are using. Confirm that the needles used in the pediatric clinical study for NDA 213150 are (b) (4) or (b) (4) 5/8 inch x 18G syringes by providing a statement to this effect.
2. Though you provided the test method, validation, aging for ELIGARD 45mg in NDA 021731 and state it passed testing criteria. It appears you have not provided the break loose force data for the final finished product. Provide the average break loose force data up to the shelf life of your final finished product (syringe A, syringe B and the final syringe after mixing).
3. It appears you have not provided a test summary demonstrating that your final finished product still conforms to the essential performance requirements of dose accuracy, break loose force and glide force after shipping and transportation. Provide dose accuracy, break loose force and glide force testing of your final finished product (syringe A, syringe B and the final syringe after mixing) after simulated shipping/transportation.
4. Provide the 510(k) clearance numbers and letter of authorization for your co-packaged needles (b) (4) and (b) (4).
5. In S001/3.2.P.5.1 you provided the specifications your finished final combination product. However, it does not include dose accuracy, break loose force and glide force essential performance requirements of syringe A, syringe B and final syringe after mixing. Update your specification table to include these EPRs. Furthermore, include the sampling plan for the release and stability testing the EPRs. Alternatively, provide an assessment of how the EPRs of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities.

8.3. Interactive Information Requests

8.3.1. Interactive Information Requests sent on *Click or tap to enter a date.*

9. APPENDIX C (CONSULTANT MEMOS)

9.1. Insert Discipline Review Memo – Insert Consultant Name

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

/s/

JENNIFER L JOHNSON
03/26/2020 04:35:13 PM

Clinical Inspection Summary

Date	3/11/2020
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, 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	William Lubas, M.D., Ph.D., Clinical Reviewer Shannon Sullivan, MD, PhD, Clinical Team Leader Jennifer Johnson, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	213150
Applicant	Tolmar, Inc.
Drug	Leuprolide acetate for injectable suspension
NME	No
Therapeutic Classification	Gonadotropin releasing hormone agonist
Proposed Indication	Treatment of central precocious puberty (CPP) in pediatric patients 2 years of age and older
Consultation Request Date	9/26/2019
Summary Goal Date	3/24/2020
Action Goal Date	5/1/2020
PDUFA Date	5/2/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of two domestic clinical sites and one foreign clinical site.

The inspections of two of the sites found regulatory deficiencies as noted below, but the findings are not considered significant. In general, based on the inspections of the three clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

II. BACKGROUND

Tolmar, Inc. has submitted an original new drug application (NDA) for leuprolide acetate for injectable suspension for the treatment of central precocious puberty (CPP) in pediatric patients 2 years of age and older. Leuprolide acetate has been approved under the brand name LUPRON DEPOT-PED® as an injection formulation for treatment of children with CPP. This formulation can be administered as a once monthly intramuscular injection or once every 3 months. The study drug, leuprolide acetate for injectable suspension, 45 mg, is expected to provide extended-release characteristics of leuprolide acetate over a 6-month period. Leuprolide acetate for injectable suspension is the same product as Tolmar's currently marketed ELIGARD® (NDA 021731) for the palliative treatment of advanced prostate cancer. It differs only in terms of labeling and intended use.

A single pivotal study has been submitted, TOL2581A, entitled "An Open-label, Single-Arm, Multicenter Study on the Efficacy, Safety, and Pharmacokinetics of Leuprolide Acetate 45 mg for Injectable Suspension Controlled Release in Subjects with Central (Gonadotropin Dependent) Precocious Puberty".

The study involved 25 sites across six countries. One hundred and fourteen (114) subjects were screened, 64 subjects received study drug, and 60 subjects completed the study. The first subject was enrolled August 17, 2015 and the last subject visit was September 05, 2018. Database lock was October 2, 2018.

Study TOL2581A was a multi-center, open-label, single-arm 12-month, adaptive design study conducted in pediatric subjects diagnosed with CPP who had not yet received gonadotropin releasing hormone agonist (GnRHa) therapy. Subjects had to be females age 2 to 8 years (inclusive) or males age 2 to 9 years (inclusive) with a confirmed diagnosis of CPP within 12 months of Baseline Visit (Day 0) but had not received prior GnRH agonist treatment for CPP and pubertal-type luteinizing hormone (LH) response following an abbreviated GnRHa stimulation test before treatment initiation >5 IU/L.

The primary endpoint was percentage of subjects with serum LH concentrations < 4 IU/L at 30 minutes following an abbreviated GnRHa stimulation test at Visit 5, Week 24 (Month 6).

After a 28-day screening period, each subject received their first subcutaneous (SC) injection of the study drug at the start of the study and the second injection at Visit 5, Week 24 (Month 6). There were seven study visits for a total duration of approximately 48 weeks (12 months) for assessment of efficacy, safety and pharmacokinetics. The adaptive design of the study allowed for the potential of conducting the study in two parts, Part A and Part B. All subjects participated in Part A to evaluate the efficacy of leuprolide acetate for injectable suspension, 45 mg (study drug) in suppressing LH.

An interim analysis of LH suppression from the GnRHa stimulation test results was conducted after approximately 40% of the 40 subjects had data through Visit 5, Week 24 (Month 6). If post GnRHa stimulation LH concentrations were suppressed to < 4 IU/L in < 85% of the first 16

subjects, then Part B of the study would have been invoked. The progression to Part B extension, which included two additional study drug injections and overall study duration extension to 21 months, was to be based on evaluations by the Data and Safety Monitoring Board and the Sponsor. During the conduct of the study these criteria were not fulfilled; therefore, Part B was not invoked.

The central laboratory used in the conduct of this study was (b) (4) – (b) (4).
The bioanalytical laboratory used for PK sampling was (b) (4).
Hand and wrist x-rays were read on site and by a central reader, (b) (4).

As noted in the Clinical Study Report, for the abbreviated GnRHa stimulation test, aqueous leuprolide acetate was to be administered via SC injection at a planned dose of approximately 20 µg/kg body weight. Some of the study sites administered the abbreviated GnRHa stimulation test using a dose of 500 µg regardless of body weight (per investigator discretion based on local standard of care) instead of the planned dose of 20 µg/kg body weight, which was recognized as an acceptable standard practice. Although this change in dose for the abbreviated GnRHa stimulation test was still expected to provide adequate stimulation, it was not consistent with the protocol and, therefore, deemed a major protocol deviation.

III. RESULTS (by Site)

NOTE: Site inspections focused on 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. Mirta Graciela Gryngarten, M.D.
Hospital de Niños, Guido 1698-2nd Floor B
1016-CABA, General Lucio N. Mansilla 2771
(1425) Ciudad Autónoma de Buenos Aires
Argentina
Site: 101

Dates of inspection: December 9 – 13, 2019

There were 15 subjects screened and 13 subjects enrolled into the study; 13 subjects completed the study. There were 13 subject records reviewed.

A translator was available during the inspection.

Dr. Gryngarten is an employee of the Hospital de Niños, Ricardo Gutierrez, Centro De Investigaciones Endocrinológicas (CEDIE/Center of Endocrinological Investigations). The

hospital serves as the principal public referral hospital for pediatric endocrine cases in the city of Buenos Aires. Dr. Gryngarten has been an employee of CEDIE for 39 years. She also holds the position of staff physician, Division of Endocrinology, at the hospital. Her research has mainly been basic academic research. This was her first investigational drug trial.

The institutional review board of record was the ethics committee from the (b) (4). Subjects recruited into the study came through referrals for pediatric endocrinological and gynecological procedures or treatment. The site did not use any advertisement or patient outreach recruitment material.

All source documents were hand written and maintained in paper format. Source records were organized, legible, and attributable. The source case report forms (CRFs) used to document protocol required data were provided by (b) (4), a sponsor appointed local contract research organization (CRO). Captured data was later transcribed into (b) (4), a web-based (b) (4) platform provided by the sponsor. The sponsor provided to the site a thumb drive containing a complete record of subject eCRFs after study completion.

Per protocol, the wrist x-ray was required to be taken on the non-dominant hand. Source worksheets for six (6) subjects did not document which hand was non-dominant or which hand was used to take the required wrist x-ray. However, for the six subjects, the left hand was indicated as the non-dominant in the eCRFs. Dr. Gryngarten explained that they followed the hospital standard practice which includes providing the radiologist with written specific instructions to take the x-ray of the front left hand and wrist for each patient. These written instructions were not filed with the rest of the subject source records.

For the abbreviated GnRHa stimulation test, all subjects were administered 500 µg of leuprolide acetate instead of the protocol specified dose of 20 µg/kg. All subjects weighed more than 25 kg and 500 µg meets the standard of care recommendations for subjects with body weighed above 25 kg. This protocol deviation was documented and included with the data listings.

Source records were compared to the sponsor data line listings. There were two minor discrepancies that were due to human error in recording the results in the eCRF.

- (b) (6) source records identified the right hand as the non-dominant hand but indicated that the left hand was used for the x-ray. The left hand is documented as the non-dominant hand in the sponsor data listings.
- (b) (6) source records have Tanner stage 3 for breast and stage 1 for pubic hair. The sponsor data line listings and eCRF document that the subject's breast Tanner stage is 3 and pubic hair is stage 2.

There were also discrepancies between source subject bone age determination by the site and the bone age values in the sponsor data line listings. As noted earlier, hand and wrist x-rays were read on site and by the central reader, (b) (4). As directed by the sponsor, the sub-investigator used a digital camera to take a picture of the subject's

wrist x-ray films, uploaded them into a compact disc, and mailed the disc to the central image analysis laboratory, (b) (4). A copy of the digitized x-ray images was maintained in a thumb drive at the site. Dr. Gryngarten explained that the values included in the sponsor data listings were determined by the central laboratory using the x-ray images received from the study site and not subject bone age determination by the site. A summary of the differences is noted below:

Subject ID	Visit #	Bone Age	
		Data listings	Source records
(b) (6)	5	10	Not indicated
	8	10	10.5
	Screening/baseline	12.5	12
	5	13	12
	8	12	11
	Screening/Baseline	12	10
	5	12	10.5
	8	12	11
	Screening/Baseline	11	Not indicated
	8	12	11
	Screening/baseline	10	9.5
	5	10	10.5
	Screening/Baseline	12	11
	5	12	11
	8	12	11
	5	11	10
	8	11	10
	Screening/Baseline	11	10.5
	8	11	10
	5	12	11
	8	12	11
	Screening/Baseline	12	11
	5	12	11
	8	12	11
	Screening/Baseline	12	11
	5	12	11
	8	12	11.5

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

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.

2. Nelly Mauras, M.D.
Nemours Children's Specialty Care
Division of Endocrinology, Diabetes & Metabolism
807 Children's Way
Jacksonville, FL 32207
Site: 602

Dates of inspection: October 28 – 31, 2019

There were 15 subjects screened (all female) and 11 subjects enrolled into the study; 10 subjects completed the study; Subject (b) (6) discontinued early. There were 15 subject records reviewed.

The institutional review board of record was (b) (4)

Dr. Mauras is the Division Chief, Division of Pediatric Endocrinology Clinic and Director of the Center for Endocrinology, Diabetes and Metabolism at the Nemours Children's Health System, Nemours Children's Specialty Care. She is also a Professor of Pediatrics at the Mayo College of Medicine, Mayo Foundation. She has been conducting clinical research for approximately 30 years. Patients diagnosed with CPP were known to Dr. Mauras already or were referred to her from within the practice for consideration for study participation. No advertising was used for subject recruitment.

Source records were maintained in individual subject binders and were legible and well organized. Electronic medical records were printed and maintained in the subject binders. Source records were compared to the sponsor data line listings. Minor discrepancies were noted between the source data and the data listings regarding the values identified for bone age from the hand and wrist x-rays. There were slight differences in the values due to either rounding up of values to determine bone age or differences in the age assessment for the wrist versus the hand (wrist value slightly higher than hand value).

The most noted, related adverse event for subjects was a small nodule or bump at the injection site. This event was documented to be mild and resolved in the subjects. These nodules were not identified in the data listings for this study. All other adverse events that were captured by the site were reported to the sponsor. However, some of the post investigational product injection telephone calls were not completed. These calls were to evaluate nine specific adverse events (see below discussion).

The primary efficacy endpoint was verifiable. For the abbreviated GnRHa stimulation test, aqueous leuprolide acetate was administered via SC injection at the planned dose of approximately 20 µg/kg body weight per the protocol rather than a standard dose.

The review team asked the FDA inspector to determine why Subject (b) (6) was excluded from the final ITT analysis. According to the study report, the subject withdrew after 170 days following a single dose because of progressive disease that in the judgement of the investigator rendered the subject unacceptable for further treatment. The subject's records indicated the site investigator and the family found that the subject's growth (height) was suppressed since starting the investigational product. The investigator wished to treat the subject's height issue with additional medication or growth hormone. The sponsor denied the investigator's request to treat the subject and instructed the investigator to discontinue the subject's study participation to receive this treatment. The investigator and family

opted to discontinue the subject from the study so the subject could be treated with Oxandrolone. The sponsor stated that Oxandrolone would impact the primary and secondary endpoints of the study and no hormonal therapies of any kind were permitted. The date of discontinuation was (b) (4)

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for not conducting the study in accordance to the investigational plan. Specifically,

- a. The protocol was not followed regarding the collection of blood samples for serum luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol concentrations, and the pharmacokinetic (PK) leuprolide concentrations prior to and after the GnRHa stimulation testing for 2 of 11 subjects.
 - Subject (b) (6) had blood samples collected 62 minutes after the GnRH stimulation testing rather than 30 minutes as required by the protocol.
 - Subject (b) (6) had blood samples collected 54 minutes after the GnRH stimulation testing rather than 30 minutes as required by the protocol. In addition, Subject (b) (6) had no blood samples collected prior to the stimulation testing.

OSI Reviewer Comment: These deviations were picked up by the monitor and reported by the sponsor. The deviation reports state that the late sampling was due to many patients awaiting laboratory draws. Both subjects continued in the study and received investigational product.

In response to Form FDA 483, Dr. Mauras stated that she accepts that the site did not collect these laboratory samples according to the protocol. This was due to the use of the clinical laboratory/venipuncture blood drawing lab station with two siblings that were being done concomitantly. The missed blood sample for Subject (b) (6) was human error. This was noted during the study and the site transferred the study location to their clinical research center Wolfson Children's Hospital after agreement with the sponsor to assure accurate and timely sampling.

- b. The protocol was not followed regarding the conduct of post investigational product injection telephone contacts; the site did not evaluate changes in the acute and chronic hormonal responses associated with GnRH antagonist treatment for 5 of 11 subjects.
 - Subjects (b) (6) 4 and (b) (6) had no assessment conducted after the first injection.
 - Subjects (b) (6) had no assessment conducted after the second injection.

OSI Reviewer Comment: Telephone contact was attempted once, and a message was left. No additional attempts were documented. Although the protocol did not specifically state to attempt re-contact, it stated that contact was to be made. By not doing so, identified adverse events were not evaluated per the protocol. It is generally accepted as good clinical practice that at least three attempts should be made before it is determined that contact with a subject/subject's family is not possible. Of note, all had follow-up visits in which it was documented that no

adverse events were noted after drug administration.

- c. The protocol was not followed regarding the administration of the first injection to three subjects within 30 minutes or less after reconstitution.
- Subject (b) (6) injection was 35 minutes after reconstitution
 - Subject (b) (6) injection was 34 minutes after reconstitution
 - Subject (b) (6) injection was 33 minutes after reconstitution

OSI Reviewer Comment: The protocol Section 8.3.4, *Investigational Product Storage*, explains how to mix the two-syringe system. The section further states that once the contents of the two syringes are mixed, the final product must be administered in ≤ 30 minutes. Although out of window, the administration timing was not extremely off. The monitoring reports identified Subject (b) (6) but did not identify that Subjects (b) (6) and (b) (6) had the investigational product administered outside of the protocol required timeframe.

In response to Form FDA-483, Dr. (b) (4) stated that the protocol was not clear on how long the investigational product should be out of refrigeration prior to mixing. The protocol states the investigational product should be brought to room temperature at least 30 minutes prior to administration. The final product should be administered within 30 minutes or less after mixing. Site staff noted that if the product was not removed from the refrigerator early enough then it was not easily administered as it was too thick and was painful for the subject. In time, they would remove investigational product from refrigeration for a longer period of time prior to mixing, which allowed the administration to be done well within the 30 minutes or less timeframe. The study coordinator erroneously thought that 30 minutes must pass after reconstitution prior to administration. Dr. Mauras suggested that very specific instructions should be provided in the package insert for the investigational product. The site did not feel the protocol or pharmacy manual was specific enough regarding preparation.

- d. The protocol was not followed in that the urine pregnancy tests were not conducted at Visit 8, End of Treatment for Subjects (b) (6) and (b) (6).
- OSI Reviewer Comment:* These deviations were picked up by the monitor and reported by the sponsor. In response to Form FDA-483, Dr. Mauras stated the tests were not performed but the subjects could not become pregnant as the two subjects were 7 years old and had been on suppression therapy for one year. Subject records indicate Subject (b) (6) was 7 years old at the start of the study and 8 years old by the first injection. Subject (b) (6) was 8 years old by the first injection and 9 years old by the end of the study. The deviations were reported to the sponsor and IRB and neither child has been pregnant.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

3. Gad B. Kletter, M.D.
MultiCare Institute for Research and Innovation
314 Martin Luther King, Jr. Way, Suite 402
Tacoma, WA 98405
Site: 612

Dates of inspection: November 18 – 22, 2019

There were 9 subjects screened and 6 subjects enrolled into the study; 5 subjects completed the study. Subject (b) (6) was early terminated due to lack of efficacy. There were 9 subject records reviewed.

The institutional review board of record was New England Institutional Review Board.

Dr. Kletter is employed by MultiCare Health System as a physician and conducts clinical trials for various pediatric endocrinology conditions. He practices pediatric endocrinology at the Mary Bridge Endocrinology Clinic in Tacoma, Washington, located on the same campus as the MultiCare Institute for Research and Innovation. He recruited subjects for the study from his and his colleagues' active patient base at Mary Bridge Endocrinology Clinic.

Source records were organized, legible, contemporaneous, original, accurate, complete, and in good condition. They consisted of sponsor provided paper CRFs, printed records from the site's electronic medical records, written progress notes on paper, digital copies of x-rays, and laboratory reports. The records contained adequate information regarding the condition of the subjects at the time of entry into the clinical study, the subjects' exposure to the study drug, and observations and data on the condition of the subjects throughout participation in the study. After the close of the study, the sponsor's CRO provided the site with a USB containing the eCRF data from their site.

Source records were compared to the sponsor data line listings. There were minor discrepancies.

- The site source recorded Subject (b) (6)'s AE of migraine as starting in 9/2017 but according to the eCRF and FDA data listings, the migraine start date was 11/29/2017. Subject (b) (6) received ibuprofen for the migraines according to source documentation but ibuprofen is not documented as a concomitant medication in the eCRF or FDA data listings. The discrepancies were human error. The monitor had not observed these data discrepancies.
- For Subject (b) (6) the site documented the weight of the subject at the screening visit on 11/24/2015 as 25.7 kg, which is the same weight as that documented in the eCRF and data listings. However, the site documented Subject (b) (6) weight as 26.7 kg at the time of the GnRHa stimulation test used for screening, conducted on 11/6/2015, prior to the screening visit. The monitor had not observed this data discrepancy.

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

verifiable.

For Subject (b) (6) the site failed to conduct a bone age x-ray during the screening period and used an x-ray conducted on 8/9/2017 to determine eligibility when the subject was not consented and screened until 8/28/2017. Subject (b) (6) Visit 1 occurred on 9/6/2017, 28 days after the subject's 8/9/2017 bone x-ray. Furthermore, there is no documentation from the sponsor for pre-approval of this protocol deviation. *See discussion below.* Subject (b) (6) received one dose of study drug and was early terminated after Visit 3 due to lack of efficacy.

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

1. Not conducting the study in accordance to the investigational plan. Specifically,
 - a. For Subject (b) (6) the site failed to obtain the following tests during the 28-day screening period as required by the protocol: a bone age x-ray and a GnRHa stimulation test. Furthermore, there is no documentation from the sponsor for pre-approval of these protocol deviations.

*OSI Reviewer Comment: The protocol deviations were reported in the sponsor data line listings. The site consented and screened Subject (b) (6) on (b) (4). To determine eligibility, Dr. Kletter used a hand and wrist bone x-ray conducted on (b) (4) which he evaluated and read the bone age as **eight years and ten months** with the distal ulnar epiphysis appearing younger, according to his progress note at screening. The radiologist read Subject (b) (4) (b) (4) bone x-ray as bone age **7 years and 10 months**, according to the central x-ray report. Subject (b) (6) was **seven years and zero months old** on (b) (4).*

The review team asked the FDA inspector to determine why Subject (b) (6) was excluded from the final intent-to-treat analysis. Per the Clinical Study Report, Subject (b) (6) was excluded from the final intent-to-treat analysis for not meeting the inclusion criterion of "bone age more than one year greater than chronological age" at the time of screening. It appears this was based on the reading of the (b) (4) central x-ray reading.

Subject (b) (6) received two doses of study drug and completed the study on (b) (4). The FDA inspector asked specifically why the subject was excluded from the intent-to-treat analysis. According to an (b) (4) email from the CRO to the site during the inspection, Subject (b) (6) was not included in the analysis because of the major protocol deviation regarding bone age at screening, which is also documented in the protocol deviation log.

Dr. Kletter used a GnRHa stimulation test from (b) (4) prior to informed consent and more than 28 days prior to the subject's study Visit 1. Furthermore, Subject (b) (6) GnRHa stimulation test from (b) (4) was not conducted as per the protocol in that estradiol and FSH were not repeated 30 minutes after leuprolide stimulation.

Dr. Kletter explained he did not want to put the child through additional tests if they were not necessary as the child is autistic. He claimed he obtained the sponsor's verbal pre-approval for these protocol deviations via phone calls. He did not have written documentation of the sponsor's pre-approval at the site during the inspection.

However, in response to the Form FDA-483, Dr. Kletter had received a letter dated November 11, 2015 from Jack McLane, PhD, Vice-President of Clinical Development at Tolmar approving the use of local results for determination of subject entry criteria. This letter was received by the site via email on November 12, 2015. This letter was located following the FDA inspection and submitted with the response. However, the letter states testing must be less than 28 days prior to the subject's study Visit 1. The GnRHa stimulation test from 11/6/2015 was performed more than 28 days.

- b. For Subject (b) (6) the site failed to obtain a 30-minute post-stimulation LH for the GnRHa stimulation test used to determine study eligibility as required by the protocol and sponsor.

OSI Reviewer Comment: The site consented and screened Subject (b) (6) on 7/29/2016. Dr. Kletter used a GnRHa stimulation test from 7/15/2016, prior to informed consent, to determine eligibility for Subject (b) (6). The site drew blood for LH two hours and three hours after leuprolide stimulation but not 30 minutes after leuprolide stimulation for this 7/15/2016 test on Subject (b) (6).

Furthermore, Subject (b) (6)'s GnRHa stimulation test from 7/15/2016 was not conducted as per the protocol in that a baseline FSH was not obtained, and FSH and estradiol were not repeated 30 minutes after leuprolide stimulation.

An email thread, dated 12/31/2015 - 1/3/2016, from the monitor to Dr. Kletter's study coordinator documented approval to use a local GnRHa stimulation test for determining Subject (b) (6)'s eligibility with no need to repeat the GnRHa stimulation test during the screening period as long as it is within 28 days of study Visit 1 (baseline visit) and as long as a sample was obtained 30 minutes post stimulation, which it was not.

Per Dr. Kletter's response to the Form FDA-483, he acknowledged the error. He used the clinic standards for the testing and not those of the protocol (Baseline labs: LH, FSH, estradiol [female]; 60 minutes- LH, FSH; 120 minutes- LH, FSH; 180 minutes- LH, FSH, estradiol [female]).

Subject (b) (6) received two doses of study drug and completed the study on 7/19/2017.

- c. The site failed to conduct the GnRHa stimulation test per the protocol requirements, in that the site dosed subjects with 500 mcg or 1000 mcg of

leuprolide, as per usual clinical practice, rather than per the protocol required 20 mcg/kg of leuprolide. Subjects (b) (6) and (b) (6) received two doses of study drug and completed the study. In summary:

Subject	Visit	Body weight (kg)	Leuprolide acetate 20 mcg/kg calculated dose (mcg)	Leuprolide acetate actual dose given for stimulation test (mcg)
(b) (6)	Pre-study on 11/6/2015 (used for eligibility, and not repeated during screening period)	26.7	534	500
	Visit 5 on 6/1/2016	29.9	598	500
	Visit 6 on 8/25/2016	29.5	590	500
	Visit 8 on 11/21/2016	30.4	608	500
	Pre-study on 7/15/16 (used for eligibility, and not repeated during screening period)	41	820	500
	Visit 3 on 11/9/2016	43.3	866	500
	Visit 5 on 12/20/2017	51.5	1030	1000
	Visit 6 on 3/21/2018	55	1100	1000
	Visit 8 on 6/28/2018	58.9	1178	1000

OSI Reviewer Comment: In response to the Form FDA-483, Dr. Kletter acknowledged the error. He explained his routine clinical order for a GnRH α stimulation test uses the standard 500 mcg dose of leuprolide. Dr. Kletter explained he used the maximum 1000 mcg dose of leuprolide as per the seminal study in which no more than 1000 mcg was used. These deviations were picked up by the monitor and reported by the sponsor. Corrective procedures were developed at the site that were deemed acceptable.

- d. The site failed to conduct the protocol required urine pregnancy test on Subject (b) (6), an eight-year-old female, prior to dosing her at the study Visit 5.

OSI Reviewer Comment: Dr. Kletter said he did not order the test as the subject is autistic and always supervised by adults. He did not request or receive sponsor approval for this protocol deviation. The monitor identified this protocol deviation and requested the site obtain a urine pregnancy test at Visit 6. The site conducted the test on 8/25/2016 and it was negative.

2. Investigational drug disposition records are not adequate with respect to quantity. Specifically, the site failed to document the quantity of study drug kits actually received and any unused study drug upon completion of the study. According to the study drug invoices, the site was sent 18 study drug kits. The site documented the disposition of only 16 study drug kits.

OSI Reviewer Comment: In his response to the Form FDA-483, Dr Kletter explained that two kits from Lot#7688C1 were pulled on May 18, 2016 and placed into quarantine on May 19, 2016. Destruction occurred on December 1, 2016. He is confident that all drug cartons are accounted for, but he acknowledged that he did not document the destruction of these two kits.

Dr. Kletter submitted a response to the Form FDA-483 and it was determined to be acceptable.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses.

{See appended electronic signature page}

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

/s/

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03/11/2020 05:14:05 PM

MIN LU
03/11/2020 08:26:21 PM

KASSA AYALEW
03/12/2020 08:48:58 AM

USE-RELATED RISK ANALYSIS; COMPARATIVE ANALYSES; AND LABEL/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:	January 8, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 213150
Product Type:	Combination Product
Drug Constituent Name and Strength	Fensolvi (leuprolide acetate) for injection 45 mg
Device Constituent:	Pre-filled Syringe
Rx or OTC:	Rx
Applicant Name:	Tolmar Therapeutics
Submission Date:	July 2, 2019
OSE RCM #:	2019-1425 and 2019-1432
DMEPA Safety Evaluator (Human Factors):	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

1. REASON FOR REVIEW

The review evaluates the use-related risk analysis (URRA) and comparative analyses submitted under NDA 213150 for Fensolvi (leuprolide acetate) for injection to determine whether the applicant needs to submit the results of a human factors validation study as part of the marketing application. This is a combination product with proposed pre-filled syringe device constituent parts that is intended to treat pediatric patients 2 years of age and older with central precocious puberty (CPP). This NDA is a 505(b)(2) application and the reference products (RPs) are Eligard (NDA 021731) and Lupron Depot-Ped (NDA 020263). As part of the overall review, we also evaluated the labels and labeling.

1.1. PRODUCT DESCRIPTION

Leuprolide acetate for injectable suspension is administered subcutaneously by healthcare professionals and is supplied in two (2) prefilled syringes with a sterile safety needle. One syringe (Syringe A) contains the diluent/delivery system and the other syringe (Syringe B) the lyophilized powder of the drug substance, leuprolide acetate. Prior to administration, Syringe A and B are joined and the contents are mixed together to yield the reconstituted drug product. When thoroughly mixed, the drug product is transferred into Syringe B, the syringes are decoupled, and the sterile safety needle is affixed to Syringe B for injection. The drug product is the same product as the currently marketed drug product, Eligard 45 mg (6-month), except for the active ingredient.

1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

In January 2019, DMEPA participated in a written response only pre-NDA meeting for IND 123631. We requested the applicant's plan on the mitigation strategies they plan to implement given the Eligard device platform has had usability and device malfunction problems in the market. Tolmar provided their response on January 14, 2019 and we provided feedback to that response on January 23, 2019.¹

After submitting their NDA application, we reviewed the applicant's comparative analyses with Eligard, and we issued an information request on September 2, 2019, requesting that the applicant provide a comprehensive use-related risk analysis that includes a

¹ Johnson, J. IND Information Request or Advice. Written Responses for IND 123631. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2019 JAN 23. Available in DARRTS: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804d5ca9&afrRedirect=305959660417726>

comprehensive and systematic evaluation of all steps involved in using the product. The applicant responded on September 16, 2019.²

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Use-related risk analysis (and/or comparative analyses)	C
Information Requests Issued During the Review	D
CDRH Human Factors Consult Review	E N/A
Label and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the use-related risk analysis (and/or comparative analyses).

3.1 USE-RELATED RISK ANALYSIS (URRA)

The applicant completed a URRA as part of this NDA and did not identify any new or unique risks in the use of the proposed pre-filled syringe (PFS). The applicant proposes to mitigate the risk of known use errors associated with the critical tasks related to pre-filled syringes and subcutaneous administration through the overall product design, labeling, and instructions for healthcare providers in the prescribing information.

We reviewed the applicant's URRA for the proposed Fensolvi PFS and found the assessment acceptable from a medication error perspective as there are no new or unique risks introduced with their proposed product.

² <\\cdsesub1\evsprod\nda213150\0002\m1\us\111-information-amendment\quality-information-amendment-9-16-19-0002.pdf>

3.2 COMPARATIVE ANALYSES

Tolmar Therapeutics submitted a side by side physical and task comparison analyses, between Fensolvi and Eligard, which has the same PFS design as the proposed Fensolvi PFS. We reviewed this information and identified a difference in the intended recipient of the injection. However, there is no difference in administration tasks between older males and children as young as two years of age. Therefore, this is not a new or unique risk and we find their conclusion acceptable.

3.3 LABELS AND LABELING

We reviewed the container labels, tray and carton labeling, and prescribing information to determine if they are acceptable from a medication error perspective. We identified areas in the labeling that can be improved to increase the readability and understanding of important information. Recommendations for the Division can be found In Section 4.1 and recommendations for the Applicant can be found in Section 4.2.

4. CONCLUSION AND RECOMMENDATIONS

Our review of the applicant's comparative analyses to Eligard and URRA determined the applicant has considered and adequately assessed the risks associated with the Fensolvi PFS and that the differences do not impact or create new critical tasks of use. We agree with the applicant's conclusion that results of an HF validation study do not need to be submitted to support the NDA. Additionally, DMEPA concludes that the labeling can be improved to promote the safe use of the product. We provide recommendations for the Division in Section 4.1 and recommendations for the Applicant can be found in Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

- We note the package type term is presented as "single-use" throughout the PI, which is inconsistent with Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.³ We defer to Office of Pharmaceutical Quality to determine the correct package type term for this product and convey this to the Applicant.

³ Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. October 2018. Available from <https://www.fda.gov/downloads/Drugs/Guidances/UCM468228.pdf>

4.2 RECOMMENDATIONS FOR TOLMAR THERAPEUTICS

Carton Labeling

1. Revise the presentation of the proprietary name from all lowercase (e.g. fensolvi) to title case (e.g. Fensolvi) to increase readability and align with the presentation of the brand name on the syringe label and tray labeling.
2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.⁴ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

⁴ The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Fensolvi received on July 2nd and September 16th, 2019 from Tolmar Therapeutics, and the reference products Eligard and Lupron Depot Ped.

Table 3. Relevant Product Information for Proprietary name and the Listed Drug		
Product Name	Fensolvi	Eligard⁵ and Lupron Depot Ped⁶
Initial Approval Date	N/A	Eligard - January 23, 2002 Lupron Depot-Ped – April 16, 1993
Therapeutic Drug Class or New Drug Class	Gonadotropin releasing hormone agonist	Same
Active Ingredient	Leuprolide Acetate	Same
Indication	Treat pediatric patients 2 years of age and older with central precocious puberty (CPP).	Eligard – Palliative treatment of advanced prostate cancer Lupron Depot-Ped - Treatment of children with central precocious puberty (CPP).
Route of Administration	Subcutaneous	Eligard – subcutaneous Lupron Depot-Ped - intramuscular
Dosage Form	For injectable suspension	Same
Strength	45 mg	Eligard – 7.5 mg, 22.5 mg, 30 mg, 45 mg Lupron Depot-Ped – 7.5 mg, 11.25 mg, 15 mg for every

⁵ Eligard [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 OCT 29. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b78d1919-9dee-44fa-90f9-e0a26d32481d&audience=professional>.

⁶ Lupron Depot-Ped [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 OCT 29. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e99f47d2-da10-3127-ecb3-e5d942ae6e81>

		month injection AND 11.25 mg and 30 mg for every 3-month injection
Dose and Frequency	45 mg once every 6 months	Eligard – 7.5 mg every month; 22.5 mg every 3 months; 30 mg every 4 months; 45 mg every 6 months Lupron Depot-Ped – 7.5 mg to 15 mg every month OR 11.25 mg to 30 mg every 3 months
How Supplied	Supplied in a 45 mg single-dose kit consisting of a two-syringe-mixing system with a sterile safety needle.	Eligard - a single-dose kit consisting of a two syringe-mixing system with a sterile safety needle Lupron Depot-Ped - 1-month Kit with prefilled dual-chamber syringe OR 3-month Kit with prefilled dual-chamber syringe
Storage	Refrigerated	Eligard- Refrigerated Lupron Depot-Ped – Room temperature
Container Closure/Device Constituent	Supplied in two prefilled syringes (Syringe A and Syringe B) with a sterile safety Needle (5/8 inch). Prior to administration, Syringe A and B are joined and the contents are mixed together to yield the reconstituted drug product.	Eligard – Same Lupron Depot-Ped - one prefilled dual-chamber syringe containing 1½ inch needle with LuproLoc® safety device
Intended Users	Health care providers only	Eligard – Health care provider only Lupron Depot-Ped – Under the supervision of a physician
Intended Use Environment	Medical office, clinic, or hospital setting	Same

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On October 29, 2019, we searched the L:drive and AIMS using the terms, IND 123631; Tolmar, Eligard, and Leuprolide to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous interaction with the applicant, one previous review, and two memoranda relevant to this application.

Previous Interaction:

Johnson, J. IND Information Request or Advice. Written Responses for IND 123631. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2019 JAN 23. Available in DARRTS:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804d5ca9&_afRedirect=305959660417726

Previous DMEPA Review:

Gao, Tingting. Label and Labeling Review for Eligard NDA 021731. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 28. RCM No.: 2019-184.

Previous DMEPA Memoranda:

Gao, Tingting. Label and Labeling Review Memorandum for Eligard NDA 021731. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 18. RCM No.: 2019-184-1.

Gao, Tingting. Label and Labeling Review Memorandum for Eligard NDA 021731. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 22. RCM No.: 2019-184-2.

APPENDIX C. COMPARATIVE ANALYSES

The comparative analyses can be accessed in EDR via:

<\\cdsesub1\evsprod\nda213150\0001\m1\us\12-cover-letters\reviewers-guide.pdf>

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW REQUESTING A USE-RELATED RISK ANALYSIS

We sent an information request on September 3, 2019 requesting the Applicant provide a comprehensive use-related risk analysis that includes a comprehensive and systematic evaluation of all steps involved in using the product, the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. The applicant responded on September 16, 2019.

The information request response can be accessed in EDR via:

<\\cdsesub1\evsprod\nda213150\0002\m1\us\111-information-amendment\quality-information-amendment-9-16-19-0002.pdf>

APPENDIX E: CDRH HUMAN FACTORS CONSULT REVIEW – N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed and Images

Using the principles of human factors and Failure Mode and Effects Analysis,⁷ along with postmarket medication error data, we reviewed the following Fensolvi labels and labeling submitted by Tolmar Therapeutics.

- Container label received on July 2, 2019
 - Syringe A - <\\cdsesub1\evsprod\nda213150\0001\m1\us\114-labeling\draft\carton-and-container\04006142-45mg-syr-a-safety.pdf>
 - Syringe B - <\\cdsesub1\evsprod\nda213150\0001\m1\us\114-labeling\draft\carton-and-container\04006143-45mg-syr-b-safety.pdf>
- Tray Lidding and Carton labeling received on July 2, 2019
 - Tray Lidding Syringe A - <\\cdsesub1\evsprod\nda213150\0001\m1\us\114-labeling\draft\carton-and-container\04006144-45mg-syr-a-tray-safety.pdf>
 - Tray Lidding Syringe B - <\\cdsesub1\evsprod\nda213150\0001\m1\us\114-labeling\draft\carton-and-container\04006143-45mg-syr-b-safety.pdf>
 - Carton Labeling - <\\cdsesub1\evsprod\nda213150\0001\m1\us\114-labeling\draft\carton-and-container\03000911-45mg-carton-safety.pdf>
- Prescribing Information (Image not shown) received on July 2, 2019
 - <\\cdsesub1\evsprod\nda213150\0001\m1\us\114-labeling\draft\annotated\04006141-annotated-draft-labeling-text-rx-0619.pdf>

⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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01/08/2020 08:19:54 PM

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01/08/2020 11:57:19 PM