CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213150Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Office of Pharmaceutical Quality

Integrated Quality Assessment for New Drug Application (NDA)

N213150

FENSOLVI® (leuprolide acetate)

for injectable suspension, for subcutaneous use (45 mg)

CONTENTS

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213150

Assessment Review Cycle #1

Drug Product Name	FENSOLVI® (Leuprolide Acetate) for Injectable suspension
Dosage Form	Injection (depot injection)
Strength	45 mg
Route of Administration	Subcutaneous Injection
Rx/OTC Dispensed	Rx
Applicant	Tolmar, Inc. 10 Earlsfort Terrace Dublin Dublin2 Ireland D02 T380
US agent, if applicable	Michelle R. Ryder, Vice President, Regulatory Affairs 701 Centre Ave Fort Collins, Colorado 80526
Regulatory	Leuprolide Acetate is an approved drug. This NDA was submitted as a 505b2 for a new indication (central precocious puberty in children) of Tolmar's currently marketed drug Eligard (N021731 for 45mg dose strength/6 months release time period), which is a Reference Listed Drug approved for advanced prostate cancer in adults. Eligard is Leuprolide acetate for injectable suspension, 45 mg. Tolmar conducted a single, pivotal 48-week clinical trial (TOL2581A) with Eligard in support of the application. Cross references were made to Tolmar's Eligard NDA 021731, (b) (4) DMF (b) (4) (leuprolide acetate drug substance), (b) (4) DMF (b) (4) (leuprolide acetate drug substance) and (b) (4) Safety hypodermic needle).

Submissions		
Submission(s) Assessed	**Receipt Date**	**Contents**
0001	07-Feb-2019	New NDA
0006	03-Jan-2020	Response to CDRH IR for needles, break loose force and testing.
0009	11-Feb-2020	Response to Micro IR. Updated DP specifications for endotoxins

CMC Information Requests			
Information Request	**Issue Date**	**Disciplines**	**Details**
001	17-Jan-2020	Micro	Endotoxin limits

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Anne Marie Russell, Ph.D	Danae Christodoulou, Ph.D.
Drug Product		
Facilities (OPMA)	Steven Hertz	Frank Wackes
Inspection (ORA)		
Microbiology	Barnard Marasa	Neal Sweeney
Biopharmaceutics	NA	
CDRH Consult	Shanly Chen	Rumi Young
Regulatory Business Process Manager	Leeza Rahimi	
Application Technical Lead	Anne Marie Russell, Ph.D.	
Laboratory (OTR)	none	
Environmental	Anne Marie Russell, Ph.D.	Danae Christodoulou, Ph.D.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Pending acceptable labeling, CMC recommends for approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Proposed Indication	Fensolvi is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of pediatric patients 2 years of age and older with central precocious puberty.
Duration of Treatment	Fensolvi 45 mg is administered subcutaneously every 6 months.
Maximum Daily Dose	
Alternative Methods of Administration	None for this product

B. Quality Assessment Overview;

This product is identical to Tolmar's Eligard (leuprolide acetate) for injectable suspension, for subcutaneous use (45 mg) – differing only in the indication and labeling. All CMC information was cross referenced to Eligard N021731. As advised, the CMC section of the Fensolvi application (M3) contained only specifications for the drug substance and drug product.

Drug Substance: Adequate

The drug substance, leuprolide acetate, is manufactured by (b) (4), under DMFs (b) (4) and (b) (4), respectively.

Drug Product: Adequate

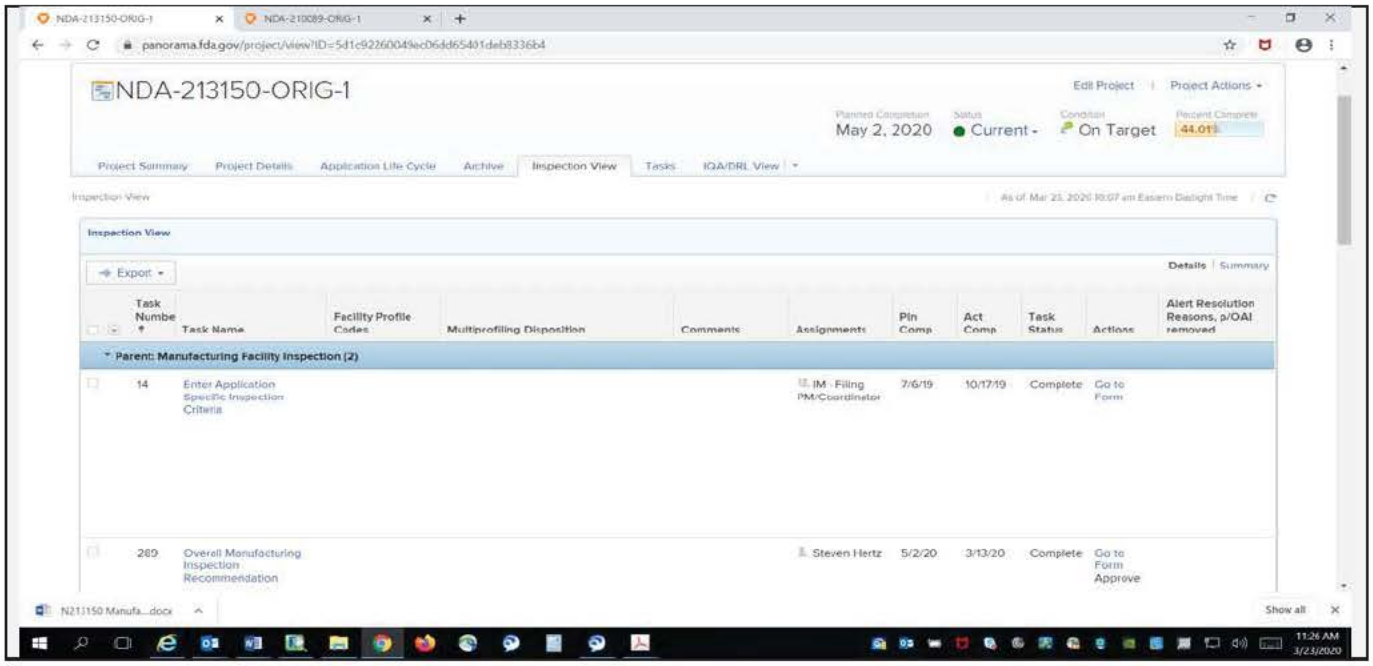
Fensolvi (leuprolide acetate) injection for suspension, is a combination product. It is a single injectable suspension for 6-month administration in two prefilled syringes. An expiry of 24 months under long term storage conditions of 5°C is granted.

Labeling: Adequate

Pending final labeling which will be completed after the time of this review.

Manufacturing: Adequate

The application includes 16 facilities. Panorama reports an overall manufacturing recommendation of APPROVE for the application, dated 13-Mar-2020, entered by Steven Hertz. See snapshot below.



Biopharmaceutics: Choose an item.

Not applicable

Microbiology (if applicable): Adequate

The drug product specifications for endotoxins were tightened to accommodate the new pediatric patient population.

C. <u>Risk Assessment</u>: N/A. The proposed product is identical to the approved product Eligard (leuprolide acetate) for injectable suspension, for subcutaneous injection (45mg).

D. <u>List of Deficiencies for Complete Response:</u> N/A

Application Technical Lead Name and Date:
Anne Marie Russell, Ph.D. OPQ/ONDP/DNDPII/Branch VI 24-Mar-2020

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Drug Substance Leuprolide Acetate US	adequate	10-Oct-2018	Reviewed by Govindaraj Kumaran
	II		Drug Substance Leuprolide Acetate US	adequate	08-Feb-2013	Reviewed by Sharon Kelly

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
CMC information (Module 3)	NDA 021731 Held by Tolmar	Eligard (Leuprolide acetate injection suspension 45mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	Complete	Approval	27-Mar-2020	Shanley M Chan
CDRH-OC				
Clinical	N/A			
Other	N/A			

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Anne Russell

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ENVIRONMENTAL

R REGIONAL INFORMATION
Environmental Assessment

Pursuant to 21 CFR § 25.31(a), Tolmar claims a categorical exclusion from the requirement for an Environmental Assessment. To Tolmar's knowledge, no extraordinary circumstances exist.

Assessment: Adequate

Primary Environmental Assessor Name and Date:
Anne Marie Russell, Ph.D. CMC reviewer OPQ/ONDP/DNDPIII/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Danae Christodoulou, Ph.D. Branch Chief OPQ/ONDP/DNDPIII/Branch 6

CHAPTER II: LABELING

1.0 PRESCRIBING INFORMATION: Acceptable pending acceptable response to the CMC labeling comment.

The following comment was sent to the applicant on 25-Mar-2020:

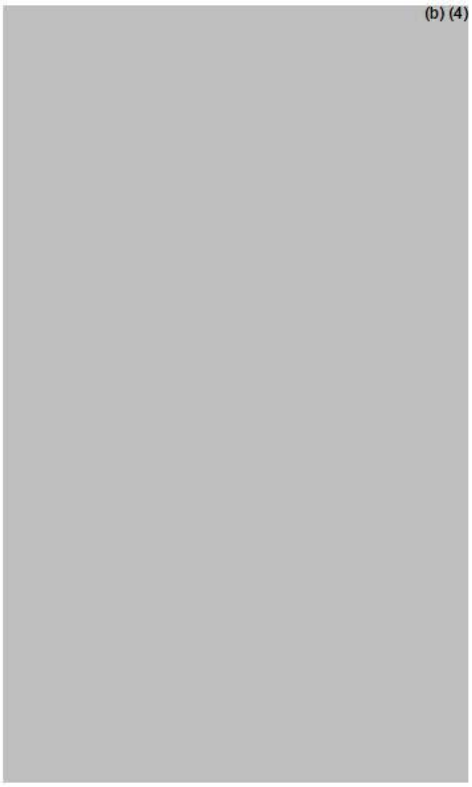
> "From a CMC standpoint, Fensolvi is the same product as your currently marketed Eligard 45mg. However, the description section of the two labels differ in the information provided, the language used and layout. Revise you Prescribing Information (PI) label Section 11 Description of the fensolvi (leuprolide acetate) for injection suspension product to replicate your existing product Eligard 45mg."

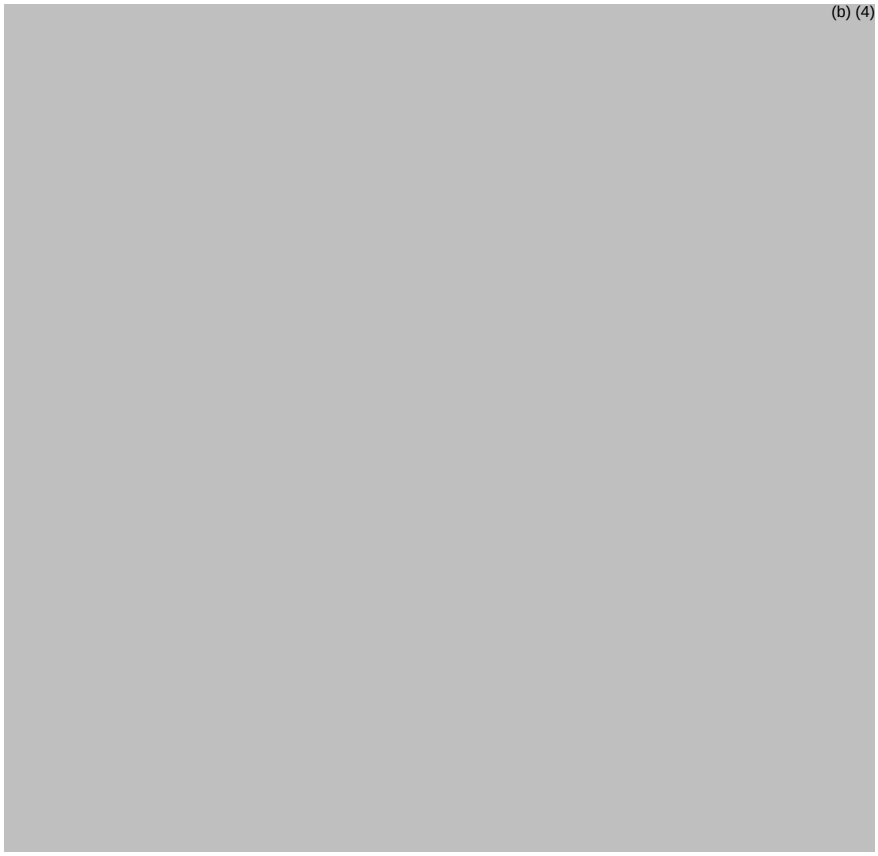
The CMC aspects of the Fensolvi Prescribing Information (PI) are similar to the approved Eligard label. This includes pertinent CMC information in the following sections of the PI: Highlights, Dosage and Administration (2), Dosage Form and Strengths (3), Description (11), How Supplied Storage and Handling (16).

2.0 PATIENT LABELING: Not reviewed. See DMEPA review.

3.0 CARTON AND CONTAINER LABELING: Acceptable

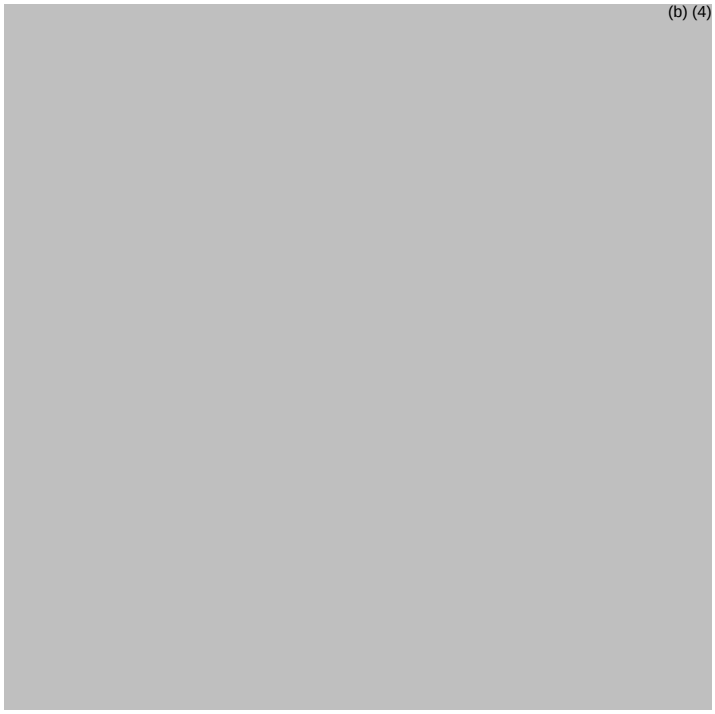
3.1 Container Labels: The carton contains two syringes, Syringe A and Syringe B, each held in a thermoformed tray, Syringe A Tray and Syringe B Tray. The four labels are reviewed below.





Assessment: Adequate. Dosage form, strength, established name, Rx, NDC#, Lot # and expiry are adequately described in the container label. The storage condition is not included on the syringe, but is included on the syringe tray.

3.2 Carton Labeling



Assessment: Adequate. Dosage form, strength, established name, manufacturer name, storage conditions, Rx, NDC#, Lot # and expiry are adequately described in the carton label.

Assessment of Carton and Container Labeling: Adequate

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Acceptable. Final label revisions will be completed during OND labeling review.

Primary Environmental Assessor Name and Date:
Anne Marie Russell, Ph.D. CMC reviewer OPQ/ONDP/DNDPIII/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Danae Christodoulou, Ph.D. Branch Chief OPQ/ONDP/DNDPIII/Branch 6

Chapter III: Additional Quality Discipline
Summary of Consult to Center for Devices and Radiological Health (CDRH)

Fensolvi (leuprolide acetate) injection for suspension is a combination product – drug and device. The CDRH review of the device portion of this application is provided as a consult memo to OND and is archived in DARRTS. The final recommendation of the review memo is that Device Constituent Parts of the Combination Product are Approvable. See CDRH review, signed 26-Mar-2020, for complete details.

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	213150
Assessment Cycle Number	#1
Drug Product Name/ Strength	Leuprolide acetate for injectable suspension/ 45 mg
Route of Administration	Subcutaneous
Applicant Name	Tolmar International Limited 10 Earlsfort Terrace, Dublin Dublin 2, Ireland D02 T380
Therapeutic Classification/ OND Division	Idiopathic central precocious puberty (disorder)
Manufacturing Site	Tolmar, Inc. 701 Centre Avenue Fort Collins, CO 80526
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The submission references Agency approved NDA 021731 (ELIGARD 45 mg) for most of CMC. This submission is for a new indication (Idiopathic central precocious puberty disorder). No changes in Manufacturing are indicated except product labelling for the new indication.

Document(s) Assessed	Date Received
Seq 0001	**07/02/2019**
Seq 0009*	**02/11/2020**

***Response to Agency Information Request**

List Submissions being assessed (table): 07/02/2019 Orig-1, 02/11/2020

Highlight Key Issues from Last Cycle and Their Resolution: None.

Remarks: 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, and route of administration, manufacturing process, quality, and safety and performance characteristics. The two products differ only in terms of labeling and intended use. The submission is in eCTD format.
Applicant responded to Agency Information Request dated 01/17/2020 with Quality/Response to Information Request dated 02/11/2020 which was reviewed and found adequate.

Concise Description of Outstanding Issues- None.

Supporting Documents: NDA 021731, NDA 020263, MF (b) (4) & MF (b) (4)

S DRUG SUBSTANCE

S.2. MANUFACTURE

(b) (4)

Reviewer Guide:

LEUPROLIDE ACETATE FOR INJECTABLE SUSPENSION, 45 MG

Tolmar, Inc. (Tolmar) manufactures and markets four leuprolide acetate extended-release formulations for the palliative treatment of advanced prostate cancer under the brand name ELIGARD®. ELIGARD is available in doses of 7.5, 22.5, 30 and 45 mg that release the drug over 1, 3, 4, and 6 months, respectively. ELIGARD has been marketed for nearly 20 years in the US and is available in more than 92 other countries. In 2018, over (b) (4) units of ELIGARD were distributed worldwide. It is an effective product with a well-established safety profile.

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 (same as approved drug product), same mfg site, 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).

Leuprolide acetate for injectable suspension, 45 mg is defined as a drug/device combination product under 21 CFR 3.2.(e)(1). It is administrated subcutaneously and is supplied in two (2) prefilled syringes with a sterile safety needle. One syringe (Syringe A) contains the novel ATRIGEL® Delivery System and the other syringe (Syringe B) the lyophilized powder of the drug substance, leuprolide acetate. ATRIGEL is a polymeric delivery system consisting of a biodegradable polymer, 85:15 poly (DL-lactide-co-glycolide) (PLG), dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP).

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. Upon subcutaneous administration, (b) (4) forming a depot at the site of the injection. The entrapped drug is released at the site (b) (4)

The quantitative composition of the reconstituted product is given in Table 1. Leuprolide acetate is an USP/Ph. Eur material sourced from (b) (4) The two excipients PLG and NMP are controlled through in-house specifications. The drug product is (b) (4) (b) (4)

Table 1: Quantitative Composition of Reconstituted Drug Product: Leuprolide Acetate for Injectable Suspension, 45 mg

Component	Function	Reference to	Finished Product
Leuprolide Acetate[a]	API	USP/ Ph.Eur	45
85:15 Poly(DL-lactide-co-glycolide) (PLG)	(b) (4) polymer	In-house	165
N-methyl-2-pyrrolidone (NMP)	Solvent	In-house	165

API = Active Pharmaceutical Ingredient, USP = United States Pharmacopeia, Ph.Eur = European Pharmacopeia

[a]45 mg leuprolide acetate is equivalent to approximately 41.7 mg leuprolide free base.

The primary container-closure system for the drug product consists of two (2) sterile syringes:
Syringe A for the ATRIGEL delivery system and Syringe B for the lyophilized leuprolide acetate powder. Syringe A is 1.2 mL (b) (4) syringe moulded with a female Luer-Lok™ fitting capped with a (b) (4) Luer-Lok cover, with a (b) (4) plunger tip and (b) (4) rod. Syringe B is a 3 mL (b) (4) syringe moulded with a male Luer-Lok fitting with a (b) (4) tip and two (b) (4) grey stoppers. The second stopper behind the primary stopper is attached to a short blue plunger. A custom flange extender is attached to the syringe. A detailed diagram of Syringe B is given in Figure 1.

Syringe A and B are packed into two separate tray packs (Figure 2). In the Syringe A tray pack, a long polystyrene plunger rod for use with Syringe B is also included. The tray pack for Syringe B includes an off the shelf sterile safety needle. (b) (4) safety needle (18G x 5/8") which was recently approved for ELIGARD 45 mg (eCTD 0084, NDA 021731/S-039, approval date 04/17/2019) will be used for the proposed drug product. Prior to product mixing, the blue plunger rod with second stopper is removed from Syringe B and the white plunger rod (packaged in the Syringe

A Tray Pack) inserted for mixing. The tray packs are considered secondary packaging and are made of thermoformed (b) (4) with or without (b) (4) tray insert, with foil lidding material and heat sealed. Both trays also have a desiccant pack.

Figure 1: Detailed Diagram of Syringe B (not to scale)

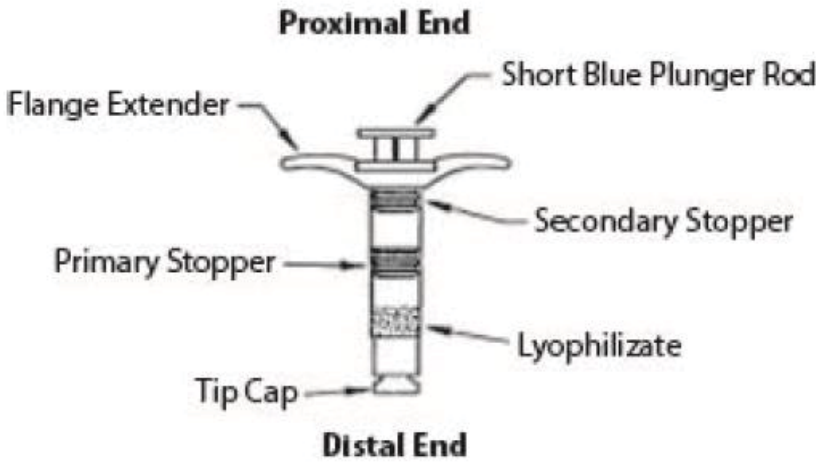
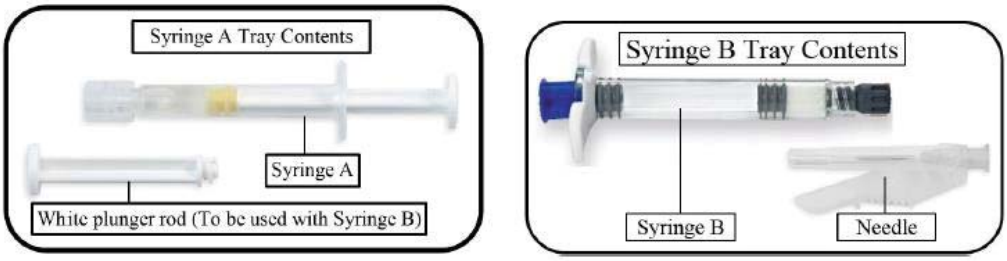


Figure 2: Contents of Syringe A Tray Pack and Syringe B Tray Pack



The Syringe A Tray Pack and Syringe B Tray Pack are placed together into a paperboard carton along with a package insert. The package insert and labels being submitted for the Syringe A, Syringe B, Syringe A tray pack, Syringe B tray pack and the container for the proposed drug product are in accordance with the labels recently approved for ELIGARD 45 mg (NDA021731/S-039 approval date 04/17/2019).

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/s/

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