CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***APPROVAL***

NDA 209863

Xyosted
(testosterone enanthate) Injection

Review #2

Drug Name/Dosage Form	Testosterone Enanthate Injection
Strength	50 mg, 75 mg, 100 mg
Route of Administration	subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Antares Pharma Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission (0032)	03/29/18	Labeling, Facilities
Labeling (0033)	04/16/18	Labeling
Labeling (0034)	08/20/18	Labeling
Labeling (0035)	08/29/18	Labeling
Labeling (0036)	09/06/18	Labeling
Labeling (0037)	09/19/18	Labeling

PREVIOUSLY REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0001)	12/20/16	All
Amendment (0003)	01/09/17	API
Amendment (0005)	01/26/17	EA
Amendment (0007)	02/13/17	CDRH-ODE, Facilities
Amendment (0009)	03/13/17	Micro
Amendment (0010)	04/07/17	CDRH-OC
Amendment (0012)	05/12/17	Micro, CDRH
Amendment (0013)	06/15/17	CDRH-ODE
Amendment (0014)	06/16/17	Product
Amendment (0018)	06/23/17	CDRH-ODE
Amendment (0020)	07/19/17	Labeling
Amendment (0023)	07/31/17	CDRH-ODE
Amendment (0024)	08/25/17	Product
Amendment (0027)	09/29/17	Labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance (API)	Ben Stevens	OPQ/ONDP/DNDPAPI/BII
Drug Product, Labeling, EA	Hamid Shafiei	OPQ/ONDP/DBRUP/BV
Process	James Norman	OPQ/OPF/DPAII/BV
Microbiology	Christine Craig	OPQ/OPF/DMA/BIII
Facility	Allison Aldridge	OPQ/OPF/DIA/BIII
Biopharmaceutics	Not Applicable	-
RBPM	Thao Vu	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Mark Seggel	OPQ/ONDP/DNDPII/BV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	Last reviewed 08/01/2012	See IQA Chapter 1, Drug Substance for additional information
	III			Adequate	11/29/16 V.Amspacher	Formerly DMF (b) (4)
	V			Adequate	08/11/16 W.G.Tan	
	III			Adequate	H.Ngai 08/29/16	
	V			Adequate	04/25/17 L.W.Moussa	
2193	MAF	Antares Pharma	QuickShot Auto-injector	-	-	See CDRH-ODE review for details

B. Other Documents: *IND, RLD, or sister applications*

APPLICATION NUMBER	DOCUMENT	DESCRIPTION
NDA 9165	NDA application, and FDA's findings of safety and efficacy (Endo Pharmaceuticals; AP 12/24/1953)	Delatestryl (Testosterone Enanthate)
IND 116022	IND application, associated reviews, and communications	Antares QuickShot TE Inj.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	n/a			
Pharmacology/Toxicology	n/a			
CDRH-ODE	Complete	Device constituents parts of the combination product are Approvable	08/08/17	Sarah Mollo
CDRH-OC	Complete	No deficiencies with Quality System documentation; Post-approval device GMP inspection (b) (4) recommended	08/17/17	Felicia Brayboy
Clinical	n/a			
Other	n/a			

Executive Summary

I. Recommendations and Conclusion on Approvability

Antares Pharma's 505(b)(2) New Drug Application #209863, for Xyosted (testosterone enanthate) Injection, 50 mg/0.5 mL, 75 mg/0.5 mL and 100 mg/0.5 mL, as resubmitted in response to the October 20, 2017 Complete Response Letter, is now recommended for APPROVAL from the OPQ perspective.

Agreement has been reached on the drug product aspects of the labeling (package insert, container/carton). The labeling now complies with the requirements under 21 CFR 201.

This NDA does contain adequate drug substance, drug product, manufacturing process, product quality microbiology, and device (auto-injector) engineering data and information to support approval of this drug-device combination product.

The commercial drug substance and drug-device product manufacturing, packaging and testing facilities have acceptable CGMP status.

The claimed categorical exclusion from the environmental assessment requirements is granted.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	XYOSTED (testosterone enanthate injection) is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Duration of Treatment	As needed.
Maximum Daily Dose	100 mg/0.5 mL, administered subcutaneously into the abdomen once weekly.
Alternative Methods of Administration	Not applicable.

Numerous products are currently available for testosterone replacement therapy. These products range from topically applied testosterone gels to implanted pellets to injectable formulations of testosterone esters. Testosterone cypionate injection and testosterone enanthate injection are approved for intramuscular injection. Testosterone enanthate (TE) is the heptanoic acid ester of testosterone.

Hydrolysis *in vivo* releases testosterone. TE is insoluble in water, but is soluble in vegetable oils. Delatestryl (testosterone enanthate injection), 200 mg/mL, was approved in 1953 (see NDA 9165). It and the approved generic copies contain testosterone enanthate in sesame oil with chlorobutanol as a preservative. These products are supplied in multi-dose vials. Doses are typically administered by a healthcare provider every two to four weeks.

Xyosted (testosterone enanthate injection) is a sterile, preservative-free formulation of TE in sesame oil. It is a drug-device combination product consisting of an auto-injector and a pre-filled, single-dose syringe containing 50-, 75- and 100-mg of TE in 0.5 mL solution. Patients administer the product subcutaneously in the abdomen once a week. Administration of a lower dose on a weekly basis may result in improved consistency of testosterone exposure. This product therefore promises to offer a convenient and safer alternative to products already on the market.

B. Quality Assessment Overview

See OPQ IQA #1, dated October 13, 2017 and OPQ IQA #1 Addendum #1 dated October 20, 2017 for a detailed assessment of the original NDA submission and subsequent amendments. Two approvability issues were noted in the October 13, 2017 review.

1. Labeling negotiations had not been completed and there was no agreement on the content and format of the final product labeling. The proposed product labeling currently did not comply with the requirements for labels and labeling in 21 CFR 201.

2. During an inspection of the (b) (4) (FEI # (b) (4)) drug product manufacturing facility for this NDA, the FDA field investigator observed objectionable conditions at the facility. The facility was placed on potential Official Action Indicated (pOAI) status.

As noted in Addendum #1, the pOAI classification (b) (4) was upgraded to Voluntary Action Indicated (VAI), and an overall facilities recommendation of APPROVE was issued on October 20, 2017.

In addition to clinical deficiencies, the October 20, 2017 Complete Response Letter (CRL) noted the lack of agreement on the proposed prescribing information, and requested submission of draft carton and container labeling based on revisions proposed by FDA on May 18, 2017.

Antares Pharma responded to the CRL on March 29, 2018. No changes have been made to the drug substance chemistry, manufacturing and controls (CMC), or in drug-device manufacturing and controls. Antares confirmed that no changes have been made to the Xyosted device.

The current review thus focuses on labeling and determining if any changes in the CGMP status of the manufacturing facilities has occurred since the October 20, 2017.

Labeling

Preliminary revisions to the prescribing information (PI) were conveyed to the Applicant on September 22, 2017. Preliminary CMC and DMEPA comments regarding the container and carton labels were conveyed to the applicant May 18, 2017. See OPQ IQA #1 Chapter III for the drug product reviewer's initial labeling review.

Deficiencies noted included lack of prominence of the established name, absence of the statement "Protect from Light" on the carton and of a similar warning in Section 16 of the PI, incorrect of expression of strength.

The revised prescribing information and the revised immediate container (pen injector) and carton labels as submitted on March 29, 2018 and August 29, 2018, respectively, are now acceptable. The resubmission is now recommended for APPROVAL from the product labeling perspective. See attached review for details.

Note that the September 6, 2018 and September 19, 2018 revisions to the labels and labeling are relatively minor from the chemistry perspective (e.g., capitalization, punctuation, deletion of references to the (b) (4) etc.).

Facilities

Allison Aldridge, OPQ/OPF/Division of Inspectional Assessment, has determined that all facilities associated with the manufacture, packaging and testing of the drug substance and the finished product, including (b) (4) (b) (4) continue to have acceptable cGMP status (see attached OPF/DIA review). An overall inspection recommendation of APPROVE was issued on May 2, 2018. Note that CDRH-OC recommends a post-approval inspection within six months that covers the medical device QS requirements should be covered.

Per the Panorama Submission Facility Status View accessed on September 21, 2018, no changes in facility status have occurred.

C. Special Product Quality Labeling Recommendations

Not Applicable.

D. Final Risk Assessment

See OPQ IQA #1 Addendum #1.

E. List of Deficiencies for Complete Response

Not Applicable.

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
Acting CMC Lead (for DBRUP)

Mark Seggel

Digitally signed by Mark Seggel
Date: 9/24/2018 04:18:20PM
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MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTARTION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: **August 31, 2018**

FROM: **Hamid R. Shafiei, Ph.D.**
Review Chemist (Branch V/DNDP II/ONDP)

Moo-Jhong Rhee, Ph.D.
Branch Chief (Branch V/DNDP II/ONDP)

TO: **Labeling/Label review # 1 for NDA 209863**

SUBJECT: **Final Approval Recommendation for the Labeling/Label Review**

In the review #1 of NDA 209863, the application was not deemed ready for approval due to the deficiencies noted in PI labeling as well as immediate container and carton labels (see **Attachment II**), however, since this application received CR action from the clinical perspective on October 20, 2017, resolution of those deficiencies were deferred to the next review cycle.

This application was resubmitted to Agency with revised PI labeling and immediate container/carton labels on March 29, 2018 and August 29, 2018, respectively.

Recommendation:

The resubmitted PI and labels (**Attachment I**) are deemed to have addressed the previously noted deficiencies satisfactorily. Therefore, this resubmission is now recommended for **Approval** from the labeling/labels perspective.

Attachment I: Final PI and Labels

A. PI

a) Highlight Section

These highlights do not include all the information needed to use XYOSTED safely and effectively. See full prescribing information for XYOSTED.
XYOSTED (testosterone enanthate) injection, for subcutaneous use
CIII
Initial US approval of testosterone enanthate: 1953

---------- DOSAGE FORMS AND STRENGTHS ----------

- XYOSTED (testosterone enanthate) Injection is supplied as 0.5mL of sterile solution in an autoinjector for subcutaneous administration in three strengths:

- 50mg/0.5mL
- 75mg/0.5mL
- 100mg/0.5mL

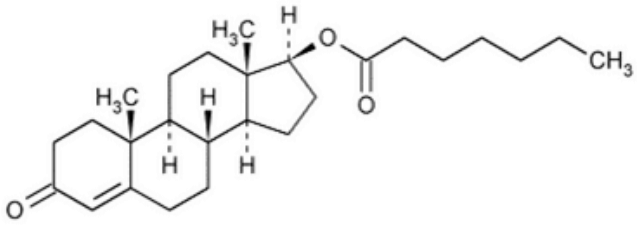
b) Full Prescribing Information

#3: Dosage Forms and Strengths

XYOSTED injection is available as 0.5 mL of a sterile, preservative-free, and nonpyrogenic clear colorless to yellow solution containing testosterone enanthate. It is supplied in a single-dose syringe assembled in an autoinjector for subcutaneous administration. Xyosted injection is available in three dosage strengths:
50 mg/0.5 mL
75 mg/0.5 mL
100 mg/0.5 mL

#11: Description

XYOSTED Injection contains testosterone enanthate, an ester derivative of an endogenous androgen, testosterone. Testosterone enanthate is a white to creamy white crystalline powder described by the chemical name (17 β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one. Testosterone enanthate has the molecular formula C26H40O3, the molecular weight 400.59, and the molecular structure with the chemical formula:



XYOSTED (testosterone enanthate) Injection is a sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution supplied in a single-dose syringe assembled in a [redacted](b) (4) pressure-assisted autoinjector for subcutaneous administration. Each XYOSTED autoinjector contains 50 mg, 75mg, or 100 mg of testosterone enanthate dissolved in 0.5mL of sesame oil providing three product strengths of 50mg/0.5mL, 75mg/0.5mL, and 100mg/0.5mL.

#16: How Supplied/Storage and Handling

16.1 How Supplied

XYOSTED (testosterone enanthate) Injection is provided as 0.5mL of a sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution in a single-dose syringe pre-assembled in an auto-injector for a single subcutaneous administration. XYOSTED is packaged in cartons containing four (4) autoinjectors. XYOSTED is available in the following strengths and configurations.

- XYOSTED Testosterone Enanthate Injection, USP 50 mg/0.5 mL
  - Carton of 4 autoinjectors NDC 54436-250-04
    - Autoinjector NDC 54436-250-02
- XYOSTED Testosterone Enanthate Injection USP 75 mg/0.5 mL
  - Carton of 4 autoinjectors NDC 54436-275-04
    - Autoinjector NDC 54436-275-02
- XYOSTED Testosterone Enanthate Injection USP 100 mg/0.5 mL
  - Carton of 4 autoinjectors NDC 54436-200-04
    - Autoinjector NDC 54436-200-02

Before use, each autoinjector should be visually inspected. XYOSTED should be clear to light yellow in color and be free of visible particles. DO NOT use if the liquid is cloudy or if visible particles are present. You may notice an air bubble, this is normal.

16.2 Storage and Handling

Do Not refrigerate or freeze. Use at room temperature.

- Store at controlled room temperature, 20°C to 25°C (68°F -77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
- Protect from light (keep in carton until time of use).

B. Container/Carton Labels:

1) Immediate Container Labels:

50mg/0.5mL

(b) (4)

75mg/0.5mL

(b) (4)

100mg/0.5mL

(b) (4)

Carton Labels:

50mg/0.5mL

75mg/0.5mL

100mg/0.5mL

(b) (4)

Attachment II: Previosly Noted Deficiencies and Resolved in this Resubmission

A. Regarding PI

a) Highlight Section

1) Revise the Highlights Title as shown below:

These highlights do not include all the information needed to use Xyosted (b) (4) (b) (4) *safely and effectively. See full prescribing information for XYOSTED* (b) (4)

Xyosted (testosterone enanthate) Injection, for subcutaneous use
CIII
Initial U.S. Approval: 1953

2) Add "Dosage Form and Strengths" section to the Highlights as shown below:

----------Dosage Form and Strengths----------
Xyosted (testosterone enanthate) Injection is supplied as 0.5mL of sterile solution in an autoinjector for subcutaneous administration in three strengths:
50mg/0.5mL
75mg/0.5mL
100mg/0.5mL

b) Full Prescribing Information

#3: Dosage Forms and Strengths

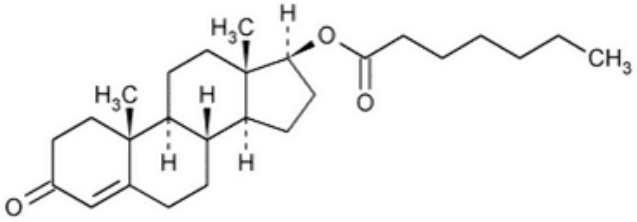
- Revise the dosage and strength section to:

XYOSTED injection is available as 0.5 mL of a sterile, preservative-free, and nonpyrogenic clear colorless to yellow solution containing testosterone enanthate. It is supplied in a single-dose syringe pre-assembled in an autoinjector for subcutaneous administration. Xyosted injection is available in three dosage strengths:
50 mg/0.5 mL
75 mg/0.5 mL
100 mg/0.5 mL

#11: Description

- Revise Description section as shown below:

BRAND NAMEXYOSTED Injection contains testosterone enanthate, an ester derivative of an endogenous androgen, testosterone. Testosterone enanthate is a white to creamy white crystalline powder described by the chemical name (17β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one . Testosterone enanthate has the molecular formula $C_{26}H_{40}O_3$, the molecular weight 400.59, and the molecular structure:



XYOSTED (testosterone enanthate) Injection is a sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution supplied in a single-dose syringe pre-assembled in a (b) (4) *pressure-assisted autoinjector for subcutaneous administration. Each XYOSTED autoinjector contains 50 mg, 75 mg, or 100 mg of testosterone enanthate dissolved in 0.5mL of sesame oil providing three product strengths of 50mg/0.5mL, 75mg/0.5mL, and 100mg/0.5mL.*

#16: How Supplied/Storage and Handling

- Revise HOW SUPPLIED/STORAGE AND HANDLING as shown below:

XYOSTED (testosterone enanthate) Injection is provided as 0.5mL of a sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution in a single-dose syringe pre-assembled in an autoinjector for a single subcutaneous administration. Xyosted is packaged in cartons containing four (4) autoinjectors. XYOSTED is available in the following strengths and configurations.

- *XYOSTED Testosterone Enanthate Injection, USP 50 mg/0.5 mL*
  - *Carton of 4 autoinjectors NDC 54436-250-04*
    - *Autoinjector NDC 54436-250-02*
- *XYOSTED Testosterone Enanthate Injection USP 75 mg/0.5 mL*

    - *Carton of 4 autoinjectors NDC 54436-275-04*
        - *Autoinjector NDC 54436-275-02*
- *XYOSTED Testosterone Enanthate Injection USP 100 mg/0.5 mL*
    - *Carton of 4 autoinjectors NDC 54436-200-04*
        - *Autoinjector NDC 54436-200-02*

B. Regarding the Container/Carton Labels:

1) Immediate Container Label:

- Display the barcode on the immediate container label.
- The strengths should be correctly expressed as 50mg/0.5ml, 75mg/0.5ml, and 100mg/0.5ml.

2) Carton Label

- The strengths should be correctly expressed as 50mg/0.5ml, 75mg/0.5ml, and 100mg/0.5ml

Hamid Shafiei

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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 8/31/2018 01:06:57PM
GUID: 502d0913000029f9798ca689a802fa55

Memorandum DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **October 20, 2017**

From: **Mark R. Seggel, Ph.D.**
Application Technical Lead and Acting CMC Lead
Office of New Drug Products
Branch V / DNDP II

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Office of New Drug Products
Branch V / DNDP II

To: **OPQ Integrated Quality Assessment #1 of NDA 209863 for Xyosted (testosterone enanthate injection)**

Subject: **Final Recommendation – *COMPLETE RESPONSE***

Background: OPQ's Integrated Quality Assessment #1 for NDA 209863, dated October 13, 2017, noted, "[a]s of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8) and 21 CFR 314.125(b)(13)." Specifically:

• During a recent inspection of the (b) (4) (FEI # (b) (4)) drug product manufacturing facility for this NDA, the FDA field investigator observed objectionable conditions at the facility. The facility currently is under potential Official Action Indicated (pOAI) status. Satisfactory resolution of the observations is required before this NDA may be approved.

• Labeling negotiations have not been completed and there is no agreement on the content and format of the final product labeling. The proposed product labeling currently does not comply with the requirements for labels and labeling in 21 CFR 201.

Current Status: FDA, and in particular the Office of Manufacturing Quality (OMQ) in CDER's Office of Compliance, has been working with (b) (4) to resolve the GMP issues at the (b) (4) site. OMQ has determined that the facility has adequately corrected the deficiencies, and on October 19, 2017, the pOAI status was revised to Voluntary Action Indicated (VAI). The Division of Inspectional Assessment (DIA) in OPQ's Office of Process and Facilities has therefore revised the overall recommendation of Withhold for this application to Adequate (see the attached Addendum to the Facility review).

With resolution of the facility-related deficiencies, the OPF Process review team's previous recommendation of "adequate pending resolution of facility-related deficiencies" is now satisfied.

No further labeling negotiations have been conducted in the interim.

Recommendation: In accordance with 21 CFR 314.125(b)(8), a ***Complete Response*** for Antares Pharma's NDA 209863, Xyosted (testosterone enanthate injection) is recommended from the OPQ perspective.

APPLICATION TECHNICAL LEAD SIGNATURE:

Mark R. Seggel, Ph.D.
CMC Lead (Acting)
ONDP / DNDP II / Branch V

FACILITIES

IQA Review Guide Reference

NDA: 209863

Concise Description Outstanding Issues Remaining: None

3.2.P.3 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)		DP manufacturing, testing and packaging into prefilled syringes (SVS)	• Medium	• Acceptable

Reviewer's Assessment: *Adequate*

(b) (4) ***FEI #*** (b) (4)

The final classification of the most recent GMP/post-approval inspection completed on (b) (4) was VAI. OMQ has determined the facility adequately corrected the deficiencies.

The facility appears to be acceptable for the intended operations stated in the application.

Primary Facilities Reviewer Name and Date: Allison Aldridge, Ph.D., 10/19/17
Secondary Reviewer Name and Date (and Secondary Summary, as needed): Juandria Williams, PhD; DIA/B3 ; 10/19/2017

Allison Aldridge

Digitally signed by Allison Aldridge
Date: 10/19/2017 03:44:39PM
GUID: 508da7170002981da764ca33dfb39a19

Juandria Williams

Digitally signed by Juandria Williams
Date: 10/19/2017 03:44:04PM
GUID: 513b65ab0005b7cb48614cd3d341d717

Mark Seggel

Digitally signed by Mark Seggel
Date: 10/20/2017 10:43:35AM
GUID: 507572b5000036176969356148025bae

Recommendation: ***As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8) and 21 CFR 314.125(b)(13).***

NDA 209863

Xyosted
(testosterone enanthate injection)

Review #1

Drug Name/Dosage Form	Testosterone Enanthate Injection
Strength	50 mg, 75 mg, 100 mg
Route of Administration	subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Antares Pharma Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0001)	12/20/16	All
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Amendment (0005)	01/26/17	EA
Amendment (0007)	02/13/17	CDRH-ODE, Facilities
Amendment (0009)	03/13/17	Micro
Amendment (0010)	04/07/17	CDRH-OC
Amendment (0012)	05/12/17	Micro, CDRH
Amendment (0013)	06/15/17	CDRH-ODE
Amendment (0014)	06/16/17	Product
Amendment (0018)	06/23/17	CDRH-ODE
Amendment (0020)	07/19/17	Labeling
Amendment (0023)	07/31/17	CDRH-ODE
Amendment (0024)	08/25/17	Product
Amendment (0027)	09/29/17	Labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance (API)	Ben Stevens	OPQ/ONDP/DNDPAPI/BII
Drug Product, Labeling, EA	Hamid Shafiei	OPQ/ONDP/DBRUP/BV
Process	James Norman	OPQ/OPF/DPAII/BV
Microbiology	Christine Craig	OPQ/OPF/DMA/BIII
Facility	Allison Aldridge	OPQ/OPF/DIA/BIII
Biopharmaceutics	Not Applicable	-
RBPM	Thao Vu	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Mark Seggel	OPQ/ONDP/DNDPII/BV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	Last reviewed 08/01/2012	See IQA Chapter 1, Drug Substance for additional information
	III			Adequate	11/29/16 V.Amspacher	Formerly DMF (b) (4)
	V			Adequate	08/11/16 W.G.Tan	
	III			Adequate	H.Ngai 08/29/16	
	V			Adequate	04/25/17 L.W.Moussa	
2193	MAF	Antares Pharma	QuickShot Auto-injector	-	-	See CDRH-ODE review for details

B. Other Documents: *IND, RLD, or sister applications*

APPLICATION NUMBER	DOCUMENT	DESCRIPTION
NDA 9165	NDA application, and FDA's findings of safety and efficacy (Endo Pharmaceuticals; AP 12/24/1953)	Delatestryl (Testosterone Enanthate)
IND 116022	IND application, associated reviews, and communications	Antares QuickShot TE Inj.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	n/a			
Pharmacology/Toxicology	n/a			
CDRH-ODE	Complete	Device constituents parts of the combination product are Approvable	08/08/17	Sarah Mollo
CDRH-OC	Complete	No deficiencies with Quality System documentation; Post-approval device GMP inspection (b) (4) recommended	08/17/17	Felicia Brayboy
Clinical	n/a			
Other	n/a			

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, Antares Pharma's 505(b)(2) New Drug Application #209863, for Xyosted (testosterone enanthate injection), 50 mg/0.5 mL, 75 mg/0.5 mL and 100 mg/0.5 mL, is not ready for approval.

During a recent inspection of the [redacted] (b) (4) (FEI # [redacted] (b) (4)) drug product manufacturing facility for this NDA, the FDA field investigator observed objectionable conditions at the facility. The facility currently is under potential Official Action Indicated (pOAI) status. Satisfactory resolution of the observations is required before this NDA may be approved.

Labeling negotiations have not been completed and there is no agreement on the content and format of the final product labeling. The proposed product labeling currently does not comply with the requirements for labels and labeling in 21 CFR 201.

This NDA does contain adequate drug substance, drug product, manufacturing process, product quality microbiology, and device (auto-injector) engineering data and information to support approval of this drug-device combination product pending resolution of the facility and labeling issues.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	XYOSTED (testosterone enanthate injection) is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Duration of Treatment	As needed.
Maximum Daily Dose	100 mg/0.5 mL, administered subcutaneously into the abdomen once weekly.
Alternative Methods of Administration	Not applicable.

Numerous products are currently available for testosterone replacement therapy. These products range from topically applied testosterone gels to implanted pellets

to injectable formulations of testosterone esters. Testosterone cypionate injection and testosterone enanthate injection are approved for intramuscular injection. Testosterone enanthate (TE) is the heptanoic acid ester of testosterone. Hydrolysis *in vivo* releases testosterone. TE is insoluble in water, but is soluble in vegetable oils. Delatestryl (testosterone enanthate injection), 200 mg/mL, was approved in 1953 (see NDA 9165). It and the approved generic copies contain testosterone enanthate in sesame oil with chlorobutanol as a preservative. These products are supplied in multi-dose vials. Doses are typically administered by a healthcare provider every two to four weeks.

Xyosted (testosterone enanthate injection) is a sterile, preservative-free formulation of TE in sesame oil. It is a drug-device combination product consisting of an auto-injector and a pre-filled, single-dose syringe containing 50-, 75- and 100-mg of TE in 0.5 mL solution. Patients administer the product subcutaneously in the abdomen once a week. Administration of a lower dose on a weekly basis may result in improved consistency of testosterone exposure. This product therefore promises to offer a convenient and safer alternative to products already on the market.

B. Quality Assessment Overview

Drug (b) (4)

Testosterone enanthate (TE) is a derivative of testosterone, the primary endogenous androgen. *In vivo*, hydrolysis of TE releases testosterone. TE is prepared by (b) (4)

The manufacture of testosterone enanthate (b) (4) is documented in Type II DMF # (b) (4). TE manufactured (b) (4) is well characterized. Antares Pharma's specification for TE is based on the (b) (4) specification as well as the USP and EP monographs for this API. Limits for organic impurities are adequately justified.

The information on the API supports approval of the NDA. This application is therefore recommended for approval from the drug substance perspective.

Drug Product

Xyosted (testosterone enanthate injection) is a sterile, preservative-free formulation of TE in sesame oil. It is a drug-device combination product consisting of an auto-injector and a pre-filled, single-dose syringe. The product will be available in three strengths: 50-, 75- or 100-mg of TE in each 0.5 mL dose.

The pre-filled syringe (PFS) consists of a 1-mL (b) (4) clear, long glass syringe barrel with a fixed, 27 gauge, 12.7 mm (1/2") staked (b) (4) needle, a rubber needle shield, and a plunger stopper. The 'QuickShot' auto-injector is a single use, (b) (4) fixed dose, disposable device. The delivery volume is fixed by syringe fill volume. Priming is not required.

Sesame oil used in the manufacture of the drug product meets NF compendial requirements. Additional tests ensure minimal amounts of residual (b) (4)

Testosterone enanthate injection is the subject of a USP monograph, however the tests and acceptance criteria therein represent minimum quality standards. Two sets of specifications have been established by the applicant. The first covers the pre-filled syringe while the second covers the assembled auto-injector. The former includes tests for appearance, identification, assay of TE, organic impurities, foreign particulate matter, sterility, endotoxins volume in container, and uniformity of dosage units. The tests on the assembled auto-injector include appearance, delivery volume, uniformity of dosage unit, and photo-degradation products.

Tests for photo-degradation products were added to the specification (b) (4) Using an HPLC/MS/MRM method, the photo-degradants were identified (b) (4) Testing for these photo-degradants will be discontinued after several batches unless levels above (b) (4)% are detected.

The suitability for use of the analytical procedures for identification, assay and organic impurities has been demonstrated.

The stability of the formulation in pre-filled syringes and assembled auto-injectors was characterized at 25°C/60% RH through 24 months, at 30°C/65% RH for 12 months and at 40°C/75% RH for 6 months. No significant changes in any of the product quality attributes were observed under these conditions.

Leachables and extractables testing supports use of the primary container closure system (syringe).

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product at release and throughout the proposed expiration dating period of 24 months. Therefore, this application is recommended for approval from the drug product perspective. See IQA Chapter II for details.

Environmental Assessment

The applicant has requested a categorical exclusion from the preparation of the environmental assessment in accordance with 21 CFR §25.3l(a). Approval of this 505(b)(2) application will not increase the use of the active moiety. The applicant also states that, to the best of their knowledge, no extraordinary circumstances exist which would preclude the categorical exclusion. The categorical exclusion is therefore granted.

Labeling

Preliminary comments regarding the package insert and the container and carton labels have been conveyed to the applicant. Deficiencies with the originally proposed labels and labeling are detailed in IQA Chapter III. The proposed product labeling currently does not comply with the requirements for labels and labeling in 21 CFR 201. Labeling negotiations have not been completed and there is no agreement on the content and format of the final product labeling.

Process

Conceptually, the drug product manufacturing process is relatively straightforward. (b) (4)

Those aspects of the manufacturing process (b) (4) are addressed in the product quality microbiology review (see summary below).

The Process review (IQA Chapter V) identified processes and process parameters that could impact product quality, and the steps taken to mitigate those risks. Consideration was given (b) (4)

While there are no outstanding deficiencies from the manufacturing process review perspective, the application, as amended, is adequate pending resolution of facility-related deficiencies (see below). Recommendations for coverage areas during a future inspection of (b) (4) are provided as part of lifecycle management considerations.

Facilities

With the exception of the [redacted] drug product manufacturing site (FEI [redacted]), all other facilities associated with the manufacture, packaging and testing of the drug substance and the finished product, have acceptable cGMP status.

An FDA Form 483 was issued at the closeout of a GMP / post-approval inspection [redacted] Due to significant deviations from cGMPs, the inspection was classified as potential Official Action Indicated (pOAI). While the Office of Manufacturing Quality (OMQ) within CDER's Office of Compliance continues to work [redacted] to resolve the GMP issues, and the pOAI may be upgraded to Voluntary Action Indicated (VAI), as of this review the OPF / Division of Inspectional Assessment review team is recommending withhold for this application. See IQA Chapter VI for details.

Biopharmaceutics

Because the product is a simple solution of active ingredient dissolved in a sesame oil vehicle, review of the NDA by the Biopharmaceutics team was not required.

Microbiology

The drug product is a sterile, preservative-free solution for subcutaneous injection. Assurance of product sterility at release and throughout the shelf-life is therefore critical for ensuring patient safety.

The suitability of the container closure system for maintaining product sterility has been demonstrated. An appropriate test for container closure integrity has been established.

The drug product is manufactured [redacted] The applicant provided an acceptable description of the manufacturing process and production parameters for commercial production. The facility design and floorplans demonstrate adequate flow of material, product and personnel to reduce the risk of contamination.

Regulatory expectations for validation of the processes [redacted] have been met.

The applicant has met also regulatory expectations with regard to the test methods, acceptance criteria and verification of the suitability of use of the tests for bacterial endotoxins and sterility.

This NDA is recommended for approval from the product quality microbiology perspective (see IQA Chapter VIII).

CDRH-ODE

The syringe and "QuickShot" auto-injector are described in module P.7. The design, manufacture and control of the auto-injector are documented in Antares' device master file MAF 2193. Note that the phase III study utilized the to-be-marketed device. While numerous deficiencies were identified during the initial device engineering review, the applicant has adequately addressed these issues.

An apparent discrepancy between the label claim (0.5 mL) and the proposed acceptance criteria for volume in container / delivery volume / dose accuracy ((b) (4) mL) was identified. According to the injector standard (ISO 11608-1), the dose accuracy should be ±5% of the labeled dose (which in this case is (b) (4) mL). Concerns were raised about the potential clinical impact of doses of (b) (4) mL. Based on subsequent discussions, the NDA review team determined that the differences in standards would have minimal impact on delivered dose.

From the device engineering perspective, the device constituent parts of the combination product are approvable (see S. Mollo's consult review dated August 8, 2017).

CDRH-OC

Two facilities were identified as being subject to applicable Quality System requirements under 21 CFR part 820. (b) (4) Based on a recent inspection, (b) (4) has acceptable medical device GMP status. Although the last medical device GMP inspection (b) (4) was classified as No Action Indicated (NAI), given the current pOAI (b) (4) (see Facilities comments above), the CDRH Office of Compliance recommends a medical device inspection of (b) (4) months of approval of the NDA.

Documentation demonstrating compliance with the Quality System regulation under 21 CFR 820, as required under 21 CFR Part 4 for drug-device combination products, has been submitted to the NDA. See Felicia Brayboy's consult reviewed dated August 17, 2017 for details.

C. Special Product Quality Labeling Recommendations

Not Applicable

D. Final Risk Assessment (see Attachment 1)

E. List of Deficiencies for Complete Response

During a recent inspection of the [redacted] (b) (4) (FEI # [redacted] (b) (4)) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
Acting CMC Lead (for DBRUP)

Mark Seggel

Digitally signed by Mark Seggel
Date: 10/13/2017 12:21:20PM
GUID: 507572b5000036176969356148025bae

ATTACHMENT I: Drug Product Risk Assessment

Final Risk Assessment for NDA 209863, Testosterone Enanthate Injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Appearance	• Raw Materials • Formulation • Process • Stability	9	100% visual inspection	Adequate	Breakage of syringes
Identification	• CGMPs	5		Adequate	
Physical Stability	• Raw Materials • Formulation • Process	6		Adequate	True solution of TE in sesame oil (b) (4)
pH					*Non-aqueous formulation*
Osmolality					*Non-aqueous formulation*
Assay (active) / Stability	• Formulation • Raw materials • Process • Container closure • Storage conditions • Site	6		Adequate	
Uniformity of Dose (Fill Volume / deliverable volume)	• Formulation • Raw materials • Process • Equipment • Site	4	(b) (4)	Adequate	(b) (4)
Related Substances Impurities / Degradants	• Formulation • Raw materials • Process • Container/Closure • Equipment • Site	18		Adequate	
Foreign Particulate Matter	• Raw materials • Process • Container/Closure • Equipment • Site	16		Adequate	
Leachables / Extractables	• Formulation • Container/closure system • Equipment	20	(b) (4)	Adequate	Evaluate any changes to syringe components and manufacturing equipment
Antioxidant Assay					(b) (4)
Preservative Assay					*Single-dose product without preservative*
Endotoxins	• Raw Materials • Formulation • Process • Equipment • Site	32	(b) (4)	Adequate	
Sterility	• Raw Materials • Formulation • Process • Equipment • Site	60		Adequate	Non-aqueous system Preservative-free formulation, but single-dose system

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

######

Mark Seggel

Digitally signed by Mark Seggel
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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4)

BRAND NAME (testosterone enanthate) injection, for subcutaneous use
CIII
Initial U.S. Approval: 1953

2) DOSAGE FORMS AND STRENGTHS

Not provided.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	BRAND NAME (testosterone enanthate)	Provided. The brand name will be Xyosted. **Satisfactory**
Dosage form, route of administration	injection, for subcutaneous use	Provided. Satisfactory
Controlled drug substance symbol (if applicable)	CIII	Provided. **Satisfactory**
Dosage Forms and Strengths (201.57(a)(8))	This section is not included in the Highlights section.	Not provided. **Unsatisfactory**
Whether the drug product is scored	Not applicable.	Not applicable.

1) The Highlights Title needs to be revised as shown below:
2) (b) (4) should be removed in the Highlighted section (b) (4)

These highlights do not include all the information needed to use Xyosted [redacted] safely and effectively. See full prescribing information for XYOSTED [redacted]

Xyosted (testosterone enanthate) Injection, for subcutaneous use
CIII
Initial U.S. Approval: 1953

3) "Dosage .Form and Strengths" section should be added to the Highlights as shown below:

----------Dosage Form and Strengths----------
Xyosted (testosterone enanthate) Injection is supplied as 0.5mL of sterile solution in an autoinjector for subcutaneous administration in three strengths:
50mg/0.5mL
75mg/0.5mL
100mg/0.5mL

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

[redacted]

50 mg/0.5 mL
75 mg/0.5 mL
100 mg/0.5 mL

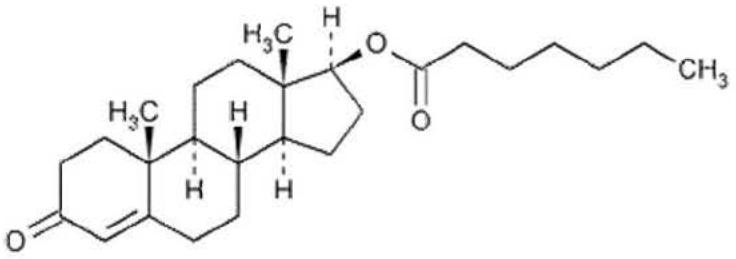
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	BRAND NAME injection	Provided. **Satisfactory**
Strengths: in metric system	50 mg/0.5 mL 75 mg/0.5 mL 100 mg/0.5 mL	Provided. Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	[redacted]	Incomplete. **Unsatisfactory**

The Dosage and Strength section needs to be revised to:

XYOSTED injection is available as 0.5 mL of a sterile, preservative-free, and nonpyrogenic clear colorless to yellow solution containing testosterone enanthate. It is supplied in a single-dose syringe pre-assembled in an autoinjector for subcutaneous administration. Xyosted injection is available in three dosage strengths:
50 mg/0.5 mL
75 mg/0.5 mL
100 mg/0.5 mL

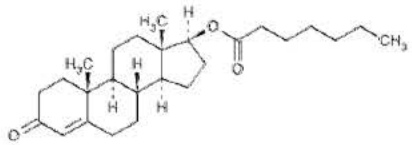
2) #11: DESCRIPTION

BRAND NAME contains testosterone enanthate (b) (4) Testosterone enanthate is a white to creamy white crystalline powder (b) (4):



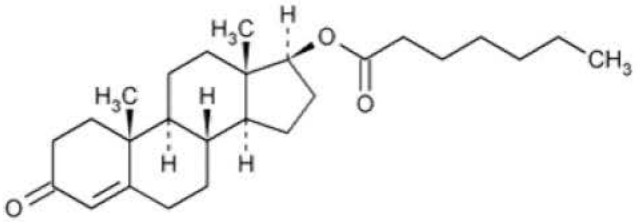
(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	BRAND NAME contains testosterone enanthate	Provided. Brand name will be Xyosted. **Satisfactory**
Dosage form and route of administration	BRAND NAME Testosterone Enanthate Injection	Provided. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Not applicable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not provided	Not provided. **Unsatisfactory**

Statement of being sterile (if applicable)	(b) (4) [redacted]	Provided. **Satisfactory**
Pharmacological/ therapeutic class	Not provided	Not provided. **Unsatisfactory**
Chemical name, structural formula, molecular weight	(17β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one  $C_{26}H_{40}O_3$ 400.59	Provided. **Satisfactory**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Testosterone enanthate is a white to creamy white crystalline powder. (b) (4) [redacted]	Provided. **Satisfactory**

Description section needs to be revised as shown below:

BRAND NAMEXYOSTED Injection contains testosterone enanthate, an ester derivative of an endogenous androgen, testosterone. Testosterone enanthate is a white to creamy white crystalline powder described by the chemical name (17β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one . Testosterone enanthate has the molecular formula $C_{26}H_{40}O_3$, the molecular weight 400.59, and the molecular structure:



XYOSTED (testosterone enanthate) Injection is a sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution supplied in a single-dose syringe (b) (4) [redacted] pressure-assisted autoinjector for subcutaneous administration. Each XYOSTED autoinjector contains 50 mg, 75 mg, or 100 mg of testosterone enanthate dissolved in 0.5mL of sesame oil providing three product strengths of 50mg/0.5mL, 75mg/0.5mL, and 100mg/0.5mL.

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

BRAND NAME is available in the following strengths and configurations.

- BRAND NAME Testosterone Enanthate Injection USP (b) (4)
  - Carton of 4 autoinjectors NDC 54436-250-04
    - Autoinjector NDC 54436-250-02

- BRAND NAME Testosterone Enanthate Injection USP (b) (4)
  - Carton of 4 autoinjectors NDC 54436-275-04
    - Autoinjector NDC 54436-275-02

- BRAND NAME Testosterone Enanthate Injection USP (b) (4)
  - Carton of 4 autoinjectors NDC 54436-200-04
    - Autoinjector NDC 54436-200-02

Before use, each autoinjector should be visually inspected. BRAND NAME should be clear to light yellow in color and be free of visible particles. DO NOT use if the liquid is cloudy or if visible particles are present. You may notice an air bubble, this is normal.

Do Not refrigerate or freeze. Use at room temperature.
Store at controlled room temperature, 20°C to 25°C (68°F -77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light (keep in carton until time of use).

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	(b) (4)	Dosage form is provided. However, the strength should be revised as: 50mg/0.5mL 75mg/0.5mL 100mg/0.5mL **Unsatisfactory**
Available units (e.g., bottles of 100 tablets)	Carton of 4 autoinjectors	Provided. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Provided. The brand name will be Xyosted. **Satisfactory**
Special handling (e.g., protect from light)	Before use, each autoinjector should be visually inspected. BRAND NAME should be clear to light yellow in color and be free of visible particles. DO NOT use if the liquid is cloudy or if visible particles are present. You may notice an air bubble, this is normal. Do Not refrigerate or freeze. Use at room temperature.	Provided. **Satisfactory**
Storage conditions	Store at controlled room temperature, 20°C to 25°C (68°F -77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light (keep in carton until time of use).	Provided. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured For: Antares Pharma, Inc. Ewing, NJ 08628 BRAND NAME is a trademark of Antares Pharma, Inc.	Provided. **Satisfactory**

HOW SUPPLIED/STORAGE AND HANDLING section needs to be revised as shown below:

XYOSTED (testosterone enanthate) Injection is provided as 0.5mL of a sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution in a single-dose syringe pre-assembled in an autoinjector for a single subcutaneous administration. Xyosted is packaged in cartons containing four (4) autoinjectors. XYOSTED is available in the following strengths and configurations.

- XYOSTED Testosterone Enanthate Injection, USP 50 mg/0.5 mL
  - Carton of 4 autoinjectors NDC 54436-250-04
    - Autoinjector NDC 54436-250-02
- XYOSTED Testosterone Enanthate Injection USP 75 mg/0.5 mL
  - Carton of 4 autoinjectors NDC 54436-275-04
    - Autoinjector NDC 54436-275-02
- XYOSTED Testosterone Enanthate Injection USP 100 mg/0.5 mL

- Carton of 4 autoinjectors NDC 54436-200-04
  - Autoinjector NDC 54436-200-02

II. Labels

1. IMMEDIATE CONTAINER

1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

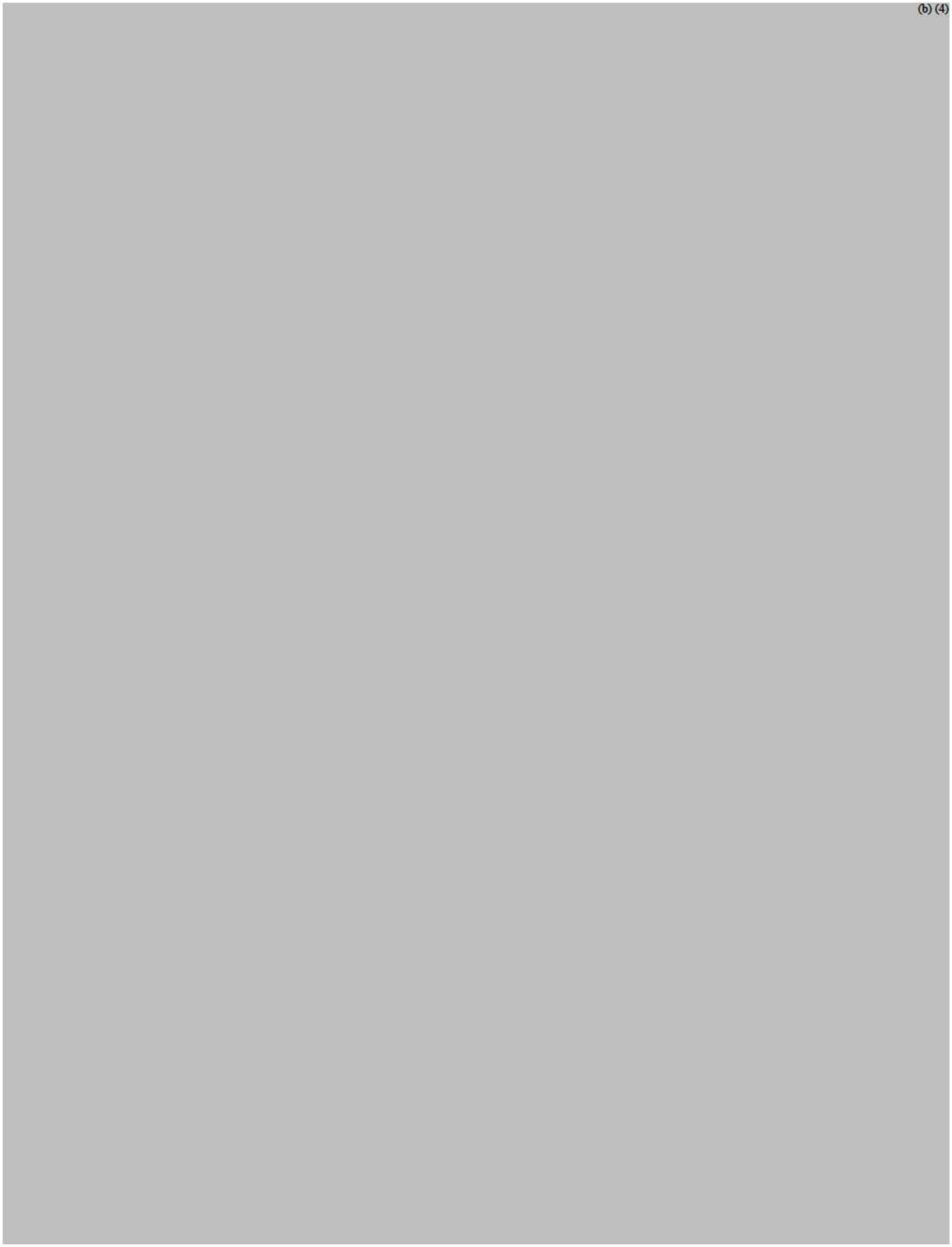
QUALITY ASSESSMENT

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	XYOSTED™ (testosterone enanthate)	Displayed. **Satisfactory**
Dosage strength	50mg/0.5mL 75mg/0.5mL 100mg/0.5mL	Provided. **Satisfactory**
Net contents		
"Rx only" displayed prominently on the main panel	Displayed	Displayed. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	 **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Displayed	Displayed. **Satisfactory**
Storage conditions	Store at 20°C to 25°C (68°F - 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (See USP controlled room temperature).	Provided. **Satisfactory**
Bar code (21CFR 201.25)	Not displayed	Not displayed. **Unsatisfactory**
Name of manufacturer/distributor	Mfd. for Antares Pharma, Inc. Ewing, NJ 08628	Provided. **Satisfactory**
And others, if space is available	Do Not Use if Seal is Broken Liquid Should Be Clear Protect from light. For subcutaneous injection only Single use auto-injector.. Do not reuse.	Provided. **Satisfactory**

1) The barcode on the immediate container label should be displayed. Also the strengths should be correctly expressed as 50mg/0.5ml, 75mg/0.5ml, and 100mg/0.5ml.

2. CARTON LABELS:

(b) (4)



2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

QUALITY ASSESSMENT

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	XYOSTED™ (testosterone enanthate)	Trade name and established name are provided. **Satisfactory**
Dosage strength	50mg/0.5mL 75mg/0.5mL 100mg/0.5mL	Provided. **Satisfactory**
Net contents	4 autoinjectors, each with a prefilled 0.5mL single-dose syringe	Provided Satisfactory
"Rx only" displayed prominently on the main panel	Displayed	Provided. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Provided. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Placeholder for the lot number and expiration is displayed.	Provided. **Satisfactory**
Storage conditions	Store at 20°C to 25°C (68°F - 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (See USP controlled room temperature). Protect from light (keep in carton until ready to use).	Provided. **Satisfactory**
Bar code (21CFR 201.25)	Placeholder for barcode is displayed	Provided. **Satisfactory**
Name of manufacturer/distributor	Mfd. for Antares Pharma, Inc. Ewing, NJ 08628	Provided. **Satisfactory**
And others, if space is available	For subcutaneous injection only.. Single use auto-injector. DO NOT reuse. Inactive ingredient: Sesame oil. Keep away from children..	Provided **Satisfactory**

The strengths should be correctly expressed as 50mg/0.5ml, 75mg/0.5ml, and 100mg/0.5ml.

III. LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

1) Revise the Highlights Title as shown below:

These highlights do not include all the information needed to use Xyosted (b) (4) safely and effectively. See full prescribing information for XYOSTED (b) (4)

Xyosted (testosterone enanthate) Injection, for subcutaneous use
CIII
Initial U.S. Approval: 1953

2) Add "Dosage .Form and Strengths" section to the Highlights as shown below:

----------Dosage Form and Strengths----------
Xyosted (testosterone enanthate) Injection is supplied as 0.5mL of sterile solution in an autoinjector for subcutaneous administration in three strengths:
50mg/0.5mL
75mg/0.5mL
100mg/0.5mL

b) Full Prescribing Information

#3: Dosage Forms and Strengths

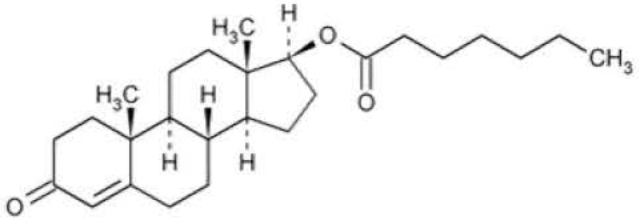
Revise the dosage and strength section to:

XYOSTED injection is available as 0.5 mL of a sterile, preservative-free, and nonpyrogenic clear colorless to yellow solution containing testosterone enanthate. It is supplied in a single-dose syringe pre-assembled in an autoinjector for subcutaneous administration. Xyosted injection is available in three dosage strengths:
50 mg/0.5 mL
75 mg/0.5 mL
100 mg/0.5 mL

#11: Description

Revise Description section as shown below:

BRAND NAMEXYOSTED Injection contains testosterone enanthate, an ester derivative of an endogenous androgen, testosterone. Testosterone enanthate is a white to creamy white crystalline powder described by the chemical name (17β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one . Testosterone enanthate has the molecular formula $C_{26}H_{40}O_3$, the molecular weight 400.59, and the molecular structure:



XYOSTED (testosterone enanthate) Injection is a sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution supplied in a single-dose syringe pre-assembled in a QuickShotTM pressure-assisted autoinjector for subcutaneous administration. Each XYOSTED autoinjector contains 50 mg, 75 mg, or 100 mg of testosterone enanthate dissolved in 0.5mL of sesame oil providing three product strengths of 50mg/0.5mL, 75mg/0.5mL, and 100mg/0.5mL.

#16: How Supplied/Storage and Handling

Revise HOW SUPPLIED/STORAGE AND HANDLING as shown below:

XYOSTED (testosterone enanthate) Injection is provided as 0.5mL of a sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution in a single-dose syringe pre-assembled in an autoinjector for a single subcutaneous administration. Xyosted is packaged in cartons containing four (4) autoinjectors. XYOSTED is available in the following strengths and configurations.

- XYOSTED Testosterone Enanthate Injection, USP 50 mg/0.5 mL
  - Carton of 4 autoinjectors NDC 54436-250-04
    - Autoinjector NDC 54436-250-02
- XYOSTED Testosterone Enanthate Injection USP 75 mg/0.5 mL
  - Carton of 4 autoinjectors NDC 54436-275-04
    - Autoinjector NDC 54436-275-02
- XYOSTED Testosterone Enanthate Injection USP 100 mg/0.5 mL
  - Carton of 4 autoinjectors NDC 54436-200-04
    - Autoinjector NDC 54436-200-02

B. Regarding of the Container/Carton Labels:

1) Immediate Container Label:

- Display the barcode on the immediate container label.
- The strengths should be correctly expressed as 50mg/0.5ml, 75mg/0.5ml, and 100mg/0.5ml..

2) Carton Label

- The strengths should be correctly expressed as 50mg/0.5ml, 75mg/0.5ml, and 100mg/0.5ml.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

- Multiple PI labeling deficiencies are noted and they must be corrected before approval..

Recommendation:

From the ONDP perspective, this application is ***not*** recommended for approval per (CFR 314.125(b)(6) until the label/labeling deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Hamid Shafiei, Ph.D.
Reviewer, Branch V
DNDP II/ONDP/OPQ August 31, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Shafiei's assessment on the labels and labeling, and I concur with his recommendation that this application is not ready for approval as it is.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP August 31, 2017

Hamid Shafiei

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Moo Jhong Rhee

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MICROBIOLOGY

Product Background:

NDA: 209863

Drug Product Name / Strength: Testosterone Enanthane Injection USP, 50mg/0.5mL, 75mg/0.5mL, or 100mg/0.5mL

Route of Administration: Subcutaneous injection

Applicant Name: Antares Pharma Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Summary: Recommended for approval

List Submissions being reviewed: 12/20/2016, 3/13/2017

Highlight Key Outstanding Issues from Last Cycle: NA

Concise Description Outstanding Issues Remaining: None.

Supporting/Related Documents: The type III DMF (b) (4) was reviewed on 8/26/2016 by H. Ngai and deemed adequate (b) (4) The type V DMFs, (b) (4) was reviewed by D. Bateman on 6/29/2015 (b) (4) and W. Tan on 8/11/2016 (b) (4) and deemed adequate.

S Drug Substance

The drug product is (b) (4) The drug substance was not reviewed.

P Drug Product

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product is a sterile, clear to yellow solution, filled into a 1 mL syringe and assembled into an autoinjector.

- Drug product composition – The drug product composition is displayed in the applicant table below (Section 3.2.P.1, Description and Composition of the Drug Product).

Table 2: Unit Composition for Testosterone Enanthate Injection USP

Ingredients	Quality Standard	Function of Components	Dose Strength		
			50 mg /0.5 mL	75 mg/ 0.5	100 mg/ 0.5 mL
Testosterone Enanthate	USP	Active Pharmaceutical Ingredient	50 mg	75 mg	100 mg
Sesame Oil	NF	Solvent	q.s. to 0.5 mL	q.s. to 0.5 mL	q.s. to 0.5 mL

- Description of container closure system –Testosterone Enanthate Injection USP is supplied as a prefilled syringe in an autoinjector. The primary container closure is a prefilled syringe that is comprised of a (b) (4) clear glass syringe barrel with a fixed (b) (4) needle, a needle shield, and a plunger stopper. A description of the container closure system is included in the applicant table below (Section 3.2.P.1, Description and Composition of the Drug Product, Table 3).

Component	Specifications	Suppliers
Syringe	1 mL long syringe barrel (b) (4) glass (b) (4) with 27G thin-wall ½" needle and soft (b) (4) needle shield	(b) (4)
Plunger Stopper	(b) (4)	
Autoinjector	single-use disposable, (b) (4) (non-product contact)	Antares Pharma, Inc. Medical Device Division MAF 2193

Adequate

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

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity (section 3.2.P.2, Microbiological attributes)

The container closure integrity testing was conducted (b) (4)

(b) (4)

The applicant states that all acceptance criteria were met:

- (b) (4)
- (b) (4)

Adequate

Reviewer's Assessment: The applicant provided an acceptable description of the container closure integrity test.

P.3 Manufacture

P.3.1 Manufacturers

Drug product: (b) (4)

Overall Manufacturing Operation

(b) (4)

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(b) (4)

Adequate

Reviewer's Assessment: The applicant provided an acceptable description of the environmental monitoring program.

P. 3.5 Process Validation and/or Evaluation

(b) (4)

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(b) (4)

P.5 Control of Drug Product

(b) (4)

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P.7 Container Closure

See P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

The stability protocol for the drug product (prefilled syringe) is summarized in the table below (section 3.2.P.8.1, Stability Summary and Conclusion, pg. 2/10).

(b) (4)

The proposed shelf life for the three product presentations (50 mg/0.5 mL, 75 mg/0.5 mL and 100 mg/0.5 mL) is 24 months under storage conditions of 20-25°C.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to perform post-approval stability studies on the first three commercial batches of the drug product. In addition, stability studies will be performed on one batch for each calendar year that the drug product is manufactured.

P.8.3 Stability Data

The applicant provided bacterial endotoxin and sterility data for seven batches of the drug product: three lots each of the 50 mg/0.5 mL and 100 mg/0.5 mL presentations and one lot of the 75 mg/0.5 mL presentation. Data were provided for all storage conditions up to 24 months and all acceptance criteria were met.

Adequate

Reviewer's Assessment: The applicant provided acceptable microbiology stability data.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable.

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable.

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable.

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable.

R Regional Information

Executed Batch Records

(b) (4)

[redacted]

Comparability Protocols

Reviewer's Assessment: Not applicable.

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

2.A. Package Insert

The drug product is supplied as a single use prefilled syringe in an autoinjection device. There is no dilution or reconstitution step (section 1.14.1.3, spl) .

Reviewer's Assessment: The applicant provided acceptable instructions which are comparable to the RLD.

Post-Approval Commitments:

Reviewer's Assessment: NA

Lifecycle Management Considerations

Reviewer's Assessment: NA

Primary Microbiology Reviewer Name and Date: Christine M. Craig, Ph.D. May 16, 2017
Secondary Reviewer Name and Date: John W. Metcalfe, Ph.D.

Christine Craig

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John Metcalfe

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