CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

NON-CLINICAL REVIEW(S)

Memorandum

PHARMACOLOGY/TOXICOLOGY LABELING MEMO

Date:	September 24, 2018
IND or NDA #	NDA 209863
Sponsor:	Antares Pharma Inc
Drug/Indication:	Testosterone Enanthate (XYOSTED); Hypogonadism
Reviewer:	Miyun Tsai-Turton, PhD, MS

Background:

The Applicant, Antares Pharma, Inc., resubmitted NDA 209863 for Testosterone Enanthate Injection (XYOSTED™) to treat adult male patients with hypogonadism. QuickShot™ Testosterone (QST) is a new single-use auto-injector, prefilled with TE solution. It is designed for subcutaneous self-administration at 50, 75, 100 mg of TE weekly.

NDA 209863 is a 505(b)(2) application and the applicant chose to reference Delatestryl® as the Listed Drug (LD). Xyosted is a preservative free single use product. Delatestryl® contains chlorobutanol, which is used as an antimicrobial preservative.

NDA 209863 was first submitted in December 2016. In their first submission, the NDA submission contained no nonclinical studies. Published literature was provided under the nonclinical section. The Applicant also referred to the Agency's findings for the nonclinical pharmacology, pharmacokinetics, and toxicology of Delatestryl® injectable. Pharm/tox recommended approval. The division did not approve this NDA and issued a CR (Complete Response) letter in October 2017. In the CR letter, the Applicant was asked to address the effect of Xyosted on blood pressure and the impact on cardiovascular risk in the hypogonadal populations anticipated to use Xyosted.

The sponsor resubmitted the NDA 209863 in March 2018. The resubmission again did not contain any nonclinical information.

The pharm/tox review of Xyosted is in a separate memo. This memo is for labeling only.

Summary of Nonclinical Data:

As stated in September 15, 2017 pharm/tox review, the original NDA submission contained no nonclinical studies. Published literature was provided under nonclinical section in Module 4 of the eCTD file. The Applicant referred to the Agency's previous findings for the nonclinical pharmacology, pharmacokinetics, and toxicology of Delatestryl® injectable (NDA 009165).

The resubmission also did not contain any nonclinical information.

Label:

Delatestryl Label	Antares proposed	PT proposed (2018)
Pregnancy: Teratogenic Effects Category X (see CONTRAINDICATIONS). CONTRAINDICATIONS Androgens are contraindicated in men with carcinomas of the breast or with known or suspected carcinomas of the prostate and in women who are or may become pregnant. When administered to pregnant women, androgens cause virilization of the external genitalia of the female fetus. This virilization includes clitoromegaly, abnormal vaginal development, and fusion of genital folds to form a scrotal-like structure. The degree of masculinization is related to the amount of drug given and the age of the fetus and is most likely to occur in the female fetus when the drugs are given in the first trimester. If the patient becomes pregnant while taking androgens, she should be apprised of the potential hazard to the fetus. This preparation is also contraindicated in patients with a history of hypersensitivity to any of its components. Nursing Mothers It is not known whether androgens are excreted in human	8. USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Risk Summary Xyosted is contraindicated in pregnant women. (b) (4) [redacted] These studies did not meet current standards for nonclinical development toxicity studies. Data *Animal Data* In developmental studies	8. USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Risk Summary[1] ~~Xyosted~~ XYOSTED is contraindicated in pregnant women (b) (4) [redacted] Testosterone is teratogenic and may cause fetal harm. Based on data from animal studies and its mechanism of action, (b) (4) [redacted] *[see Contraindications (4) and Clinical Pharmacology (12.1)]*. Exposure of a female fetus to androgens may result in varying degrees of virilization.[3] In animal developmental studies, (b) (4) exposure to testosterone in utero resulted in hormonal and behavioral changes and structural impairments of reproductive tissues in female and male offspring (b) (4) [redacted] These studies did not meet current standards for nonclinical development toxicity studies. [4] Data *Animal Data* In developmental studies

milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pediatric Use Androgen therapy should be used very cautiously in pediatric patients and only by specialists who are aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every six months by an X-ray of the hand and wrist (see INDICATIONS AND USAGE, and WARNINGS).	conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used in testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes. Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant females and offspring in rats exposed to doses approximately twice those used in testosterone replacement therapy.	conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used in testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes. Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant females and offspring in rats exposed to doses approximately twice those used in testosterone replacement therapy.
	8.2 Lactation Risk Summary XYOSTED is not indicated for use in females.	8.2 Lactation[5] Risk Summary XYOSTED is not indicated for use in females (b) (4)

	[redacted] (b) (4)	
	8.3 Females and Males of Reproductive Potential Infertility During treatment with large doses of exogenous androgens, including XYOSTED, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis [see Warnings and Precautions (5.8)]. Reduced fertility is observed in some men taking testosterone replacement therapy. [redacted] (b) (4) the impact on fertility [redacted] (b) (4)	**8.3 Females and Males of Reproductive Potential** Infertility During treatment with large doses of exogenous androgens, including XYOSTED, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis [see Warnings and Precautions (5.8)]. Reduced fertility is observed in some men taking testosterone replacement therapy. [redacted] (b) (4) The impact on fertility may be [redacted] (b) (4) irreversible [redacted] (b) (4)
Carcinogenesis	**13 NONCLINCIAL TOXICOLOGY** **13.1 Carcinogenesis,**	

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.	Mutagenesis, Impairment Fertility *Carcinogenicity* Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. *Mutagenicity* Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. *Impairment of Fertility* The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.	No proposed changes.

[1] The risk summary should be all one paragraph.

[2] Regardless of whether it was indicated or not for females, we would still consider testosterone to be contraindicated in a pregnant woman. It is not indicated for use in females which is mentioned in warnings and precautions – contraindication in "women who are or may become pregnant or breastfeeding women". In addition, per PLLR guidance, it needs to be stated the reason why the drug is contraindicated.

[3] Since this is a 505b2, pharm/tox believes the risk summary should be all one paragraph. It's important to use some of the class language in the risk summary, along with the sponsor's summary of the animal data that shows teratogenicity and virilization. We think by incorporating it together, it communicates the risk and also gives the reason why based on the animal studies.

[4] Pharm/Tox proposes to keep this statement since this is supported by the draft PLLR guidance: "The risk statement must state when animal studies do not meet current standards for nonclinical developmental toxicity studies, or when there are no animal data (§ 201.57(c)(9)(i)(B)(2)).

[5] COMMENT TO THE SPONSOR: Xyosted is not indicated in females. The data section is omitted. DPMH agreed. The data for lactation are very limited (a single case of nursing mom using 100 mg

testosterone implant from LactMed). Very high doses of testosterone may decrease milk production, but such doses are unlikely to be relevant to prescription testosterone. We do not give recommendations regarding use (e.g., contraindication) if there are no data to inform the recommendation.

[6] The Clinical Team agreed with the changes in this sentence.

Outstanding Nonclinical Issue:

N/A

Conclusion(s):

Below is the FINAL label language.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

XYOSTED is contraindicated in pregnant women. Testosterone is teratogenic and may cause fetal harm when administered to a pregnant woman. Based on data from animal studies and its mechanism of action *[see Contraindications (4) and Clinical Pharmacology (12.1)]*. Exposure of a female fetus to androgens may result in varying degrees of virilization. In animal developmental studies, exposure to testosterone in utero resulted in hormonal and behavioral changes and structural impairments of reproductive tissues in female and male offspring. These studies did not meet current standards for nonclinical development toxicity studies.

Data

Animal Data

In developmental studies conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used for testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes.

Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant females and offspring in rats exposed to doses approximately twice those used for testosterone replacement therapy.

8.2 Lactation

Risk Summary

XYOSTED is not indicated for use in females.

8.3 Females and Males of Reproductive Potential

Infertility

During treatment with large doses of exogenous androgens, including XYOSTED, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis *[see Warnings and Precautions (5.8)]*. Reduced fertility is observed in some men taking testosterone replacement therapy. The impact on fertility may be irreversible.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Mutagenicity

Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays.

Impairment of Fertility

The administration of exogenous testosterone suppresses spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

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/

MIYUN M TSAI-TURTON
09/24/2018

KIMBERLY P HATFIELD
09/24/2018

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209863
Supporting document/s:	SDN32, 03-29-2017
Applicant's letter date:	March 29, 2018
CDER stamp date:	March 29, 2018
Product:	Xyosted (testosterone enanthate, injection)
Indication:	Testosterone replacement therapy in hypogonadal males
Applicant:	Antares Pharma Inc.
Review Division:	DBRUP
Reviewer:	Miyun Tsai-Turton, MS, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	Hylton V. Joffe, M.D., M.M.Sc.
Project Manager:	Jeannie Roule

PDUFA: 9/29/2018

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209863 are owned by Antares or are data for which Antares has obtained a written right of reference. Any information or data necessary for approval of NDA 209863 that Antares does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209863.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

The Applicant, Antares Pharma, Inc., submitted NDA 209863 for Testosterone Enanthate Injection (XYOSTED) to treat adult male patients with hypogonadism. Hypogonadism, associated with low levels of serum testosterone, is a clinical syndrome characterized by decreased bone mineral density, increased fat mass, decreased muscle mass/strength, hot flashes, decreased sexual activity, depression, and linking to metabolic syndrome such as insulin resistance.

Testosterone enanthate (TE) is the common standard of care for hypogonadism. It is usually given as an intramuscular (IM) bolus injection every 2-4 weeks, but this regimen could lead to fluctuations of testosterone levels in patients (overexposure or underexposure occurring early and late after injection, respectively). There are other formulations and routes of administration on the market or under development (topical solutions, patches, buccal devices, oral pills, and nasal applications) that are partially successful in addressing this issue.

XYOSTED is a single-use auto-injector, prefilled with TE solution. It is designed for subcutaneous self-administration of 50, 75, or 100 mg of TE weekly. Testosterone Enanthate Injection, is contained within a single-dose syringe with a 27-gauge, ½-inch needle with a soft needle shield within an autoinjector, which is equipped with a needle safety guard and safety cap.

NDA 209863 was first submitted in December 2016. In their first submission, the NDA contained no nonclinical studies. Published literature was provided under the nonclinical module. The Applicant also referred to the Agency's findings for the nonclinical pharmacology, pharmacokinetics, and toxicology of Delatestryl® injectable. Pharm/tox recommended approval. The division did not approve this NDA and issued a CR (Complete Response) letter. The sponsor resubmitted the NDA in March 2018. The resubmission does not contain any nonclinical information and refers to the information submitted in the initial submission.

1.2 Brief Discussion of Nonclinical Findings

This NDA resubmission contains no nonclinical studies. The Applicant refers to the Agency's previous findings for the nonclinical pharmacology, pharmacokinetics, and toxicology of Delatestryl® injectable (NDA 009165).

Upon initial submission of this NDA, the pharmacology/toxicology review team recommended approval of Xyosted. This determination has not changed. We reference the previous NDA review submitted to DARRTS on 09/15/2017 for a nonclinical review.

1.3 Recommendations

1.3.1 Approvability

Pharm/tox recommends approval.

1.3.2 Additional Non Clinical Recommendations

There are no additional nonclinical comments.

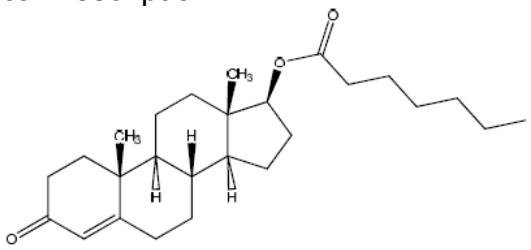
1.3.3 Labeling

The labeling below is proposed by the sponsor. There will be a separate memo for the final labeling.

2 Drug Information

2.1 Drug

- CAS Registry Number: 315-37-7
- Generic Name: Testosterone Enanthate (TE)
- Code Name: Testosterone Enanthate (TE); Antares QuickShot (QST)
- Chemical Name: (17β)-17-[(1-oxoheptyl)oxy]-androst-4-en-3-one or 17 β-heptanoyloxy-4-androsten-3-one
- Molecular Formula/Molecular Weight: 400.6 g/mol / $C_{26}H_{40}O_3$
- Structure or Biochemical Description:



- Pharmacologic Class: Androgen

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 116022 (associated IND for this product)
NDA 009165 (Delatestryl®; testosterone enanthate intramuscular injection; approved December 1953)

2.3 Drug Formulation

Each single-use prefilled autoinjector contains sterile, preservative-free testosterone enanthate (TE) for subcutaneous administration at a fixed volume of 0.5 mL, yielding final delivered doses equivalent to 50, 75 and 100 mg TE. Note: Delatestryl® (their

listed drug) has chlorobutanol as preservative. Since Xyosted is a single use product, it is preservative free.

Table 1 Drug Composition.

Ingredients	Quality Standard	Function of Components	Dose Strength		
			50 mg /0.5 mL	75 mg/ 0.5 mL	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

Testosterone Enanthate Injection, is contained within a single-dose syringe with a 27-gauge, ½-inch needle with a soft needle shield within an autoinjector, which is equipped with a needle safety guard and safety cap.

Container/Closure and Delivery System for Testosterone Enanthate Injection USP

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)	(b) (4)
Plunger Stopper	(b) (4)	
Autoinjector	single-use disposable, (b) (4) (non-product contact)	Antares Pharma, Inc. Medical Device Division MAF 2193

(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern.

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2.6 Proposed Clinical Population and Dosing Regimen

Testosterone Enanthate Injection is an androgen indicated for the treatment of adult males with hypogonadism. It comes with three strengths – 50, 75, and 100 mg in a fixed volume of 0.5 mL. This is a once per week subcutaneous administration.

Delatestryl® is the listed drug which provides 200 mg TE via intramuscular administration. In Study No QST-13-002, the comparative bioavailability of QST and Delatestryl® was studied. The data showed that 2 weekly QST 100 mg injections would provide the same drug exposure as 200 mg Delatestryl, but also results in a total testosterone (TT) level that varies less over the dosing interval, thereby achieving the desired physiological TT levels of 300-1100 ng/dL in the majority of treated subjects.

2.7 Regulatory Background

IND 116022

- Dec 2012 - Type B pre-IND meeting.
  - A nonclinical bridging study was conducted and adequate justification to bridge the Antares product to the reference product should be submitted for a 505(b)(2) pathway.
  - Sesame oil as excipient was acceptable.
- July 2013 – IND submission
  - Nonclinical review can be found in DARRTS dated 8/16/13.
- May 2014 – Type C meeting (no nonclinical question)
- Feb 2015 – Agreed iPSP (full waiver for pediatric studies)
- Nov 2016 – Pre-NDA meeting scheduled (no nonclinical question)

NDA 209863

- Dec 2016 – NDA submission
- Feb 2017 – Internal filing meeting – Fileable (pharm/tox perspective)

Pharm/Tox Comment for the 74-day Letter (Recommended)
You have not adequately informed the Pregnancy and Lactation Labeling Rule (PLLR) format for Sections 8.1, 8.2, and 8.3. In order to comply with PLLR format for Sections 8.1, 8.2, and 8.3, provide human or animal data or published literature, that support the conclusions in the Risk Summary and Clinical Considerations. If published literature is used in support of PLLR labeling, provide the scientific rationale to justify the basis for such reliance. For guidance on labeling in PLLR format, consult the labeling review resources on the *Pregnancy and Lactation Labeling Final Rule* website and the draft Guidance for Industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf

- March 2017 – Filing letter sent to the Applicant.
- April 2017 – Response to 74 day letter sent to the FDA (PLLR white paper with proposed labeling language included)
- October 2017 – Complete Response (CR) letter issued.
- March 2018 – NDA resubmission
- May 2018 – Internal filing meeting and no filing issue was identified.

3 Studies Submitted

3.1 Studies Reviewed

No new or updated nonclinical information was submitted.

3.2 Studies Not Reviewed

n/a

3.3 Previous Reviews Referenced

NDA 209863, SD#1 (eCTD #001), 12/20/16 (Reviewed by Miyun Tsai-Turton, PhD, MS)

11 Integrated Summary and Safety Evaluation

The Applicant, Antares Pharma, Inc., submitted NDA 209863 for Testosterone Enanthate Injection (QuickShot™ Testosterone; proprietary name of XYOSTED™) to treat adult male patients with hypogonadism. XYOSTED™ is a single-use auto-injector, prefilled with TE solution. It is designed for subcutaneous self-administration at 50, 75, or 100 mg of TE weekly.

NDA 209863 is a 505(b)(2) application and Delatestryl® is the Listed Drug. Delatestryl is also a Testosterone Enanthate Injection, providing TE for intramuscular administration. Delatestryl is a sterile, colorless to pale yellow solution where each 1 mL injection provides 200 mg TE in sesame oil with 5 mg chlorobutanol (chloral derivative) as a preservative.

The comparative bioavailability of QST and the Listed Drug (generic for Delatestryl) was studied in Study No. QST-13-002. The data showed that the absorption curves of two weekly doses of QST vs. one dose of LD over 366 hours were different. Both C_{max} and C_{avg168} values for TT after administration of QST 50 mg and QST 100 mg were below the values observed for Delatestryl at all time points. In order to explore the possibility of differing relative bioavailability, an $AUC_{0\text{-}inf}$ was extrapolated. The $AUC_{0\text{-}inf}$ values of TT for two doses of 100 mg QST starting at Week 5 and 200 mg Delatestryl were comparable with a ratio of approximately 1.05. These data suggest that 2 weekly QST 100 mg injections provide the same drug exposure as 200 mg Delatestryl, but also results in a TT level that varies less over the dosing interval, thereby achieving the desired physiological TT levels of 300-1100 ng/dL in the majority of treated subjects.

These data provide a justification of the reliance on the FDA's previous nonclinical findings for Delatestryl in support of this 505(b)(2) NDA for QST.

The initial NDA submission contained no nonclinical studies. Published literature is provided under the nonclinical section in Module 4 of the eCTD file. The Applicant refers to the Agency's previous findings for the nonclinical pharmacology, pharmacokinetics, and toxicology of Delatestryl® injectable (NDA 009165), and no further studies were necessary. The NDA resubmission was responding to the FDA's Complete Response Letter (CRL) dated October 20, 2017 and post CRL responding communications. There is no new or updated nonclinical information.

Below is the sponsor proposed label comparing to Delatestryl label. The nonclinical related label changes will be addressed in a separate memo. Of note, the Delatestryl label is in pre-PLR format (no numbered sections).

PROPOSED XYOSTED LABEL VS. DELATESTRYL LABEL

Delatestryl Label	Xyosted Proposed Label
Pregnancy: Teratogenic Effects Category X (see **CONTRAINDICATIONS**). **CONTRAINDICATIONS** Androgens are contraindicated in men with carcinomas of the breast or with known or suspected carcinomas of the prostate and in women who are or may become pregnant. When administered to pregnant women, androgens cause virilization of the external genitalia of the female fetus. This virilization includes clitoromegaly, abnormal vaginal development, and fusion of genital folds to form a scrotal-like structure. The degree of masculinization is related to the amount of drug given and the age of the fetus and is most likely to occur in the female fetus when the drugs are given in the first trimester. If the patient becomes	8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Risk Summary Xyosted is contraindicated in pregnant women. (b) (4) [redacted] These studies did not meet current standards for nonclinical development toxicity studies. Data *Animal Data* In developmental studies conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used in testosterone replacement

pregnant while taking androgens, she should be apprised of the potential hazard to the fetus.

This preparation is also contraindicated in patients with a history of hypersensitivity to any of its components.

Nursing Mothers
It is not known whether androgens are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Androgen therapy should be used very cautiously in pediatric patients and only by specialists who are aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every six months by an X-ray of the hand and wrist (see **INDICATIONS AND USAGE**, and **WARNINGS**).

therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes. Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant females and offspring in rats exposed to doses approximately twice those used in testosterone replacement therapy.

8.2 Lactation
Risk Summary
XYOSTED is not indicated for use in females.

(b) (4)

	8.3 Females and Males of Reproductive Potential Infertility During treatment with large doses of exogenous androgens, including XYOSTED, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic pituitary-testicular axis [see Warnings and Precautions (5.8)]. Reduced fertility is observed in some men taking testosterone replacement therapy. (b) (4) the impact on fertility (b) (4)
Carcinogenesis Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.	13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** *Carcinogenicity* Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. *Mutagenicity* Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. *Impairment of Fertility* The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

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/s/

MIYUN M TSAI-TURTON
08/20/2018

KIMBERLY P HATFIELD
08/20/2018
I concur with the conclusions and recommendations of Dr. Tsai-Turton, and recommend approval.

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 209863
Supporting document/s:	SD1, eCTD 001, 12/20/2016
	SD10, eCTD 010, 4/7/2017
Applicant's letter date:	12/20/2016
CDER stamp date:	12/20/2016
Product:	Xyosted (testosterone enanthate, injection)
Indication:	Testosterone replacement therapy in hypogonadal males
Applicant:	Antares Pharma Inc.
Review Division:	DBRUP
Reviewer:	Miyun Tsai-Turton, MS, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Jeannie Roule

PDUFA: 9/20/2017

Disclaimer

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Any information or data necessary for approval of NDA 209863 that Antares does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209863.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

The Applicant, Antares Pharma, Inc., submitted NDA 209863 for Testosterone Enanthate Injection (QuickShot™ Testosterone; pending proprietary name of XYOSTED™) to treat adult male patients with hypogonadism. Hypogonadism, associated with low levels of serum testosterone, is a clinical syndrome characterized by ↓ bone mineral density, ↑ fat mass, ↓ muscle mass/strength, hot flashes, ↓ sexual activity, depression, and linking to metabolic syndrome such as insulin resistance.

Testosterone enanthate (TE) is the common standard of care for hypogonadism. It is usually given as an intramuscular (IM) bolus injection every 2-4 weeks, but this regimen could lead to fluctuations of testosterone levels in patients (overexposure or underexposure occurring early and late after injection, respectively). There are other formulations and routes of administration on the market or under development (topical solutions, patches, buccal devices, oral pills, and nasal applications) that are partially successful in addressing this issue.

QuickShot™ Testosterone (QST) is a new single-use auto-injector, prefilled with TE solution. It is designed for subcutaneous self-administration at 50, 75, 100 mg of TE weekly.
NDA 209863 is a 505(b)(2) application and is referencing Delatestryl® as the approved listed drug, relying in part on the FDA's previous findings with respect to the nonclinical data for testosterone in the approved Delatestryl Injection product. Delatestryl® is also a Testosterone Enanthate Injection, providing TE for intramuscular administration. Delatestryl is a sterile, colorless to pale yellow solution where each 1 mL injection provides 200 mg TE in sesame oil with 5 mg chlorobutanol (chloral derivative) as a preservative. Delatestryl® Injection was approved under NDA 009165 on 23 Dec 1953, followed by subsequent supplements.

1.2 Brief Discussion of Nonclinical Findings

This NDA submission contains no nonclinical studies. Published literature is provided under nonclinical section in Module 4 of the eCTD file. The Applicant refers to the Agency's previous findings for the nonclinical pharmacology, pharmacokinetics, and toxicology of Delatestryl® injectable (NDA 009165).

1.3 Recommendations

1.3.1 Approvability

Pharm/tox recommends approval.

1.3.2 Additional Non Clinical Recommendations

There are no additional nonclinical comments.

1.3.3 Labeling

The labeling below is proposed by the sponsor. There will be a separate memo for the final labeling.

***** Note: The proposed labeling language below was submitted (along with PLLR literature review) in their response to the 74 day letter in April 2017.***

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Xyosted™ is contraindicated in pregnant women.

(b) (4)

These studies did not meet current standards for nonclinical development toxicity studies.

Data

Animal Data

In developmental studies conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used in testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes.

Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant females and offspring in rats exposed to doses approximately twice those used in testosterone replacement therapy.

8.2 Lactation

Risk Summary

Xyosted™ is not indicated for use in females.

(b) (4)

(b) (4)

8.3 Females and Males Reproductive Potential

Infertility

During treatment with large doses of exogenous androgens, including Xyosted™, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis [see Warnings and Precautions (5.6)]. Reduced fertility is observed in some men taking testosterone replacement therapy. (b) (4) the impact on fertility (b) (4) (b) (4)

13 NONCLINICAL TOXICOLOGY

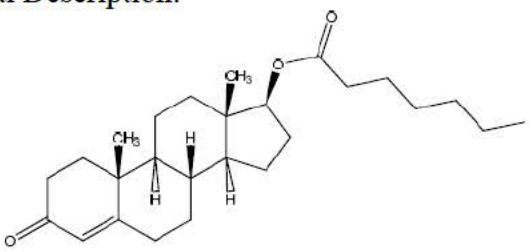
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

2 Drug Information

2.1 Drug

- CAS Registry Number: 315-37-7
- Generic Name: Testosterone Enanthate (TE)
- Code Name: Testosterone Enanthate (TE); Antares QuickShot (QST)
- Chemical Name: (17β)-17-[(1-oxoheptyl)oxy]-androst-4-en-3-one or 17 β-heptanoyloxy-4-androsten-3-one
- Molecular Formula/Molecular Weight: 400.6 g/mol / $C_{26}H_{40}O_3$
- Structure or Biochemical Description:



- Pharmacologic Class: Androgen

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 116022 (associated IND for this product)

NDA 009165 (Delatestryl®; testosterone enanthate intramuscular injection; approved December 1953)

2.3 Drug Formulation

Each single-use prefilled autoinjector contains sterile, preservative-free testosterone enanthate (TE) for subcutaneous administration at a fixed volume of 0.5 mL, yielding final delivered doses equivalent to 50, 75 and 100 mg TE. Note: Delatestryl® (their listed drug) has chlorobutanol as preservative. Since Xyosted is a single use product, it is preservative free.

Table 1 Drug Composition.

Ingredients	Quality Standard	Function of Components	Dose Strength		
			50 mg /0.5 mL	75 mg/ 0.5 mL	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

Testosterone Enanthate Injection, is contained within a single-dose syringe with a 27-gauge, ½-inch needle with a soft needle shield within an autoinjector, which is equipped with a needle safety guard and safety cap.

Container/Closure and Delivery System for Testosterone Enanthate Injection USP

Component	Specifications	Suppliers
Syringe	1 mL long syringe barrel (b) (4) glass (b) (4) with 27G thin-wall ½" (b) (4) 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

(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation.

2.5 Comments on Impurities/Degradants of Concern

The product meets USP standards for impurity levels. Known impurities are consistent with expected breakdown products for testosterone. Inorganic impurities, as well as residual solvents, are controlled by using the respective USP standards. These impurities are comparable to those in the listed drug and other approved testosterone products. In addition, no new degradants were found in the drug product primary stability tests.

2.6 Proposed Clinical Population and Dosing Regimen

Testosterone Enanthate Injection is an androgen indicated for the treatment of adult males with hypogonadism. It comes with three strengths – 50, 75, and 100 mg in a fixed volume of 0.5 mL. This is a once per week subcutaneous administration.

Delatestryl® is the listed drug which provides 200 mg TE via intramuscular administration. In Study No QST-13-002, the comparative bioavailability of QST and Delatestryl® was studied. The data showed that 2 weekly QST 100 mg injections would provide the same drug exposure as 200 mg Delatestryl, but also results in a TT level that varies less over the dosing interval, thereby achieving the desired physiological TT levels of 300-1100 ng/dL in the majority of treated subjects.

2.7 Regulatory Background

IND 116022

- Dec 2012 - Type B pre-IND meeting.
  - A nonclinical bridging study was conducted and adequate justification to bridge the Antares product to the reference product should be submitted for a 505(b)(2) pathway.
  - Sesame oil as excipient was acceptable.
- July 2013 – IND submission
  - Nonclinical review can be found in DARRTS dated 8/16/13.
- May 2014 – Type C meeting (no nonclinical question)
- Feb 2015 – Agreed iPSP (full waiver for pediatric studies)
- Nov 2016 – Pre-NDA meeting scheduled (no nonclinical question)

NDA 209863

- Dec 2016 – NDA submission
- Feb 2017 – Internal filing meeting – Fileable (pharm/tox perspective)

Pharm/Tox Comment for the 74-day Letter (Recommended)
You have not adequately informed the Pregnancy and Lactation Labeling Rule (PLLR) format for Sections 8.1, 8.2, and 8.3. In order to comply with PLLR format for Sections 8.1, 8.2, and 8.3, provide human or animal data or published literature, that support the conclusions in the Risk Summary and Clinical Considerations. If published literature is used

in support of PLLR labeling, provide the scientific rationale to justify the basis for such reliance. For guidance on labeling in PLLR format, consult the labeling review resources on the *Pregnancy and Lactation Labeling Final Rule* website and the draft Guidance for Industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf

- March 2017 – Filing letter sent to the sponror.
- April 2017 – Response to 74 day letter sent to the FDA (PLLR white paper with proposed labeling language included)

The following is a list of currently marketed testosterone products for reference.

Table 2 Marketed Testosterone Products.

FDA Approved Testosterone Products

Proprietary Name	Dosage Form	Application Number	Initial Approval Date / Supplement #	Latest Approval Date / Supplement #
Delatestryl®	Injectable	NDA 009165	24-DEC-1953 / 000	11-MAY-2015 / 033
Testopel®	Pellet	ANDA 080911	13-JUL-1972 / 000	08-APR-1996 / 013
Depo-Testosterone®	Injectable	ANDA 085635	25-JUL-1979 / 000	03-JUL-2002 / 015
Androderm®	Film (Patch)	NDA 020489	29-SEP-1995 / 000	11-MAY-2015 / 033
Testim®	Gel	NDA 021454	31-OCT-2002 / 000	11-MAY-2015 / 023
Striant®	Tablet (Buccal)	NDA 021543	19-JUN-2003 / 000	11-MAY-2015 / 011
Axiron®	Metered Solution	NDA 022504	23-NOV-2010 / 000	11-MAY-2015 / 012
Fortesta®	Metered Gel	NDA 021463	29-DEC-2010 / 000	10-MAR-2016 / 005
Androgel®	Gel	NDA 021015	28-FEB-2000 / 000	17-AUG-2015 / 041
		NDA 022309	29-APR-2011 / 000	17-AUG-2015 / 015
Aveed	Injectable	NDA 022219	4-MAR-2014 / 000	11-MAY-2015 / 005
Natesto	Metered Gel (Nasal)	NDA 205488	28-MAY-2014 / 000	11-MAY-2015 / 001
Vogelxo	Gel (Transdermal)	NDA 204399	4-JUN-2014 / 000	12-MAY-2016 / 003

3 Studies Submitted

3.1 Studies Reviewed

There were no studies reviewed. The Applicant provided published literature and reference to the listed drug Delatestryl to support their nonclinical section.

3.2 Studies Not Reviewed

n/a

3.3 Previous Reviews Referenced

n/a

4 Pharmacology

Testosterone is mainly synthesized in the testicles, and to a small extent in the adrenal cortex. Testosterone is responsible for the expression of masculine characteristics during fetal, early childhood, and pubertal development and thereafter for maintaining the masculine phenotype and androgen-dependent functions (e.g. spermatogenesis and accessory sexual glands). Dependent on the target organ, the spectrum of activities of testosterone is mainly androgenic (e.g. prostate, seminal vesicles, epididymis) or protein-anabolic (muscle, bone, haematopoiesis, kidney, liver). The effects of testosterone in some target organs arise after peripheral conversion of testosterone to estradiol, which binds to estrogen receptors in the target cell nucleus e.g. the pituitary, fat, brain, bone and testicular Leydig cells.

Insufficient secretion of testosterone results in male hypogonadism characterized by low serum testosterone concentrations. Signs and symptoms associated with male hypogonadism include but are not limited to, erectile dysfunction and decreased sexual desire, fatigue, depressive moods, as well as a lack of secondary sexual characteristics, their incomplete development, or their regression, an increased risk of osteoporosis, an increase of visceral fat and a decrease of lean body mass and muscle strength.

In hypogonadal men, exogenous androgens are given to improve the deficient endogenous testosterone levels and related signs and symptoms. Treatment with androgens decreases the body fat mass, increases the body lean mass and muscle strength, and prevents bone loss. Androgens may also improve sexual function and also may exert positive psychotropic effects by improving mood.

Nonclinical safety pharmacology studies with Antares QST product have not been completed or planned. Adequate data can be found in the published literature. Published toxicological studies have not revealed other effects than those which can be explained based on the hormone profile of Testosterone. See General Toxicity below for details on well-established adverse clinical cardiovascular events documented in the literature.

5 Pharmacokinetics/ADME/Toxicokinetics

Testosterone enanthate is an ester of the primary endogenous androgen testosterone (b) (4) hydrolysis to free testosterone occurs *in vivo*.

Delatestryl® USPI, 2015

- In men, approximately 98% of circulating testosterone binds to sex-hormone binding globulin (SHBG) and albumin and about 2% is free. Generally, the amount of SHBG in the plasma determines the distribution of testosterone between free and bound forms, whereas the free testosterone concentration determines its half-life.
- In responsive tissues, the activity of testosterone appears to depend on reduction to dihydrotestosterone (DHT), which binds to cytosol receptor proteins. The steroid-

receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

Aveed USPI, 2015

- Testosterone is metabolized to various 17-keto steroids through two different pathways. There are considerable variations of the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form.

6 General Toxicology

The toxicity of testosterone has been well-established in humans and nonclinical models. A common toxicity profile for testosterone is described across package inserts, regardless of route of administration.

Published literature has shown that exogenous augmentation of testosterone levels to physiologic or supra-physiologic levels may be associated with the occurrence of adverse events (IARC, 1979):

Reference: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Sex hormones (II). IARC Monogr Eval Carcinog Risk Chem Hum 1979; 21:11-561.

- Cardiovascular:
  - Fluid retention/edema can occur that may contribute to congestive heart failure.
  - Alteration in lipid profiles with increased cholesterol and Low Density Lipoprotein (LDL) with decreased High Density Lipoprotein (HDL) levels noted that may contribute to increased risk for heart disease.
  - Increases in red cells and hematocrit are often noted, and polycythemia may occur.
  - Cardiovascular damage and disease has been reported.

- Metabolic:
  - Weight gain through muscle and fat mass changes is often noted for both genders.
  - Changes in liver enzyme values occur; oral 17α-substituted testosterone is linked to liver failure and liver cancer.
  - Interactions with drugs metabolized by CYP3A4 and blood thinners have been reported.

- Androgenic:
  - Increased sebaceous gland activity and acne is common.
  - Prostatic hypertrophy and potentially prostate cancer may occur.
  - Testicular atrophy may occur, independent of fertility effects.
  - Menstrual irregularities (including amenorrhea) and virilization (hair growth, acne, muscle mass increase) in human women are common.

7 Genetic Toxicology

Testosterone was not mutagenic to bacteria and did not induce sperm abnormalities or micronuclei in mice treated in vivo (IARC, 1979)

8 Carcinogenicity

The carcinogenicity potential for testosterone has been previously established. The literature references provided support the findings in the testosterone Class Labeling (NDA 022504; Axiron).

Section 13.1 (Animal data) Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rat.

9 Reproductive and Developmental Toxicology

The reproductive and developmental risk potential for testosterone has been previously established through an extensive amount of experimental evidence in the literature. The presence of testosterone during male fetal development for all mammals is required for establishment of normal male gonadal and genitalia throughout development. In contrast, prenatal exposure during fetal development can cause abnormalities to females that include virilization of the external genitalia (clitoromegaly, labial fusion, increase in anogenital distances) and abnormal neurocrine or psychosexual development. Additionally, virilization of external genitalia and increased evidence of male secondary sexual characteristics (hair growth) and behaviors (aggression) have been noted in human children exposed to testosterone. These effects have been documented in humans through indirect transfer of drug product, i.e. below therapeutic levels. At supraphysiologic doses given to males, reversible oligo/azospermia, and infertility can occur (NDA 021463; Fortesta).

The current class labeling for testosterone products includes the following warning:
Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

10 Special Toxicology Studies

n/a

11 Integrated Summary and Safety Evaluation

The Applicant, Antares Pharma, Inc., submitted NDA 209863 for Testosterone Enanthate Injection (QuickShot™ Testosterone; pending proprietary name of XYOSTED™) to treat adult male patients with hypogonadism. QuickShot™ Testosterone (QST) is a new single-use auto-injector, prefilled with TE solution. It is designed for subcutaneous self-administration at 50, 75, 100 mg of TE weekly.

NDA 209863 is a 505(b)(2) application and Delatestryl® is the listed drug. Delatestryl is also a Testosterone Enanthate Injection, providing TE for intramuscular administration. Delatestryl is a

sterile, colorless to pale yellow solution where each 1 mL injection provides 200 mg TE in sesame oil with 5 mg chlorobutanol (chloral derivative) as a preservative.

The comparative bioavailability of QST and the Listed Drug (generic for Delatestryl) was studied in Study No. QST-13-002. The data showed that the absorption curves of two weekly doses of QST vs. one dose of LD over 366 hours were different. Both C_{max} and C_{avg168} values for TT after administration of QST 50 mg and QST 100 mg were below the values observed for Delatestryl at all time points. In order to explore the possibility of differing relative bioavailability, an $AUC_{0\text{-}inf}$ was extrapolated. The $AUC_{0\text{-}inf}$ values of TT for two doses of 100 mg QST starting at Week 5 and 200 mg Delatestryl were comparable with a ratio of approximately 1.05. These data suggest that 2 weekly QST 100 mg injections provide the same drug exposure as 200 mg Delatestryl, but also results in a TT level that varies less over the dosing interval, thereby achieving the desired physiological TT levels of 300-1100 ng/dL in the majority of treated subjects. These data provide a justification of the reliance on the FDA's previous nonclinical findings for Delatestryl in support of this 505(b)(2) NDA for QST.

This NDA submission contains no nonclinical studies. Published literature is provided under nonclinical section in Module 4 of the eCTD file. The Applicant refers to the Agency's previous findings for the nonclinical pharmacology, pharmacokinetics, and toxicology of Delatestryl® injectable (NDA 009165), and no further studies were necessary.

12 Appendix/Attachments

n/a

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

/s/

MIYUN M TSAI-TURTON
09/14/2017

KIMBERLY P HATFIELD
09/15/2017
I concur with Dr. Tsai-Turton's assessment.