CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	209863
PDUFA Goal Date	September 29, 2018
OSE RCM #	2018-657
Reviewer Name(s)	Courtney Cunningham, PharmD
Acting Team Leader	Laura Zendel, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	September 28, 2018
Subject	Evaluation of Need for a REMS
Established Name	Testosterone Enanthate Injection
Trade Name	Xyosted
Name of Applicant	Antares Pharma Inc.
Therapeutic Class	Androgen for testosterone replacement therapy for adult male hypogonadism
Formulation(s)	Subcutaneous Injection
Dosing Regimen	50 mg, 75 mg, or 100 mg subcutaneously once weekly

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Xyosted (testosterone enanthate) is necessary to ensure the benefits outweigh its risks. Antares Pharma Inc. (Antares) submitted a New Drug Application (NDA 209863) for Xyosted with the proposed indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (primary hypogonadism or hypogonadotropic hypogonadism). The major risks associated with Xyosted include an increase in blood pressure that may increase major cardiovascular events (MACE), an increase in depression and suicide, and an increase in hematocrit. The applicant submitted a REMS consisting of a Communication Plan, Medication Guide, and a timetable for assessments with this application.

DRISK and the Division of Bone, Reproductive, and Urologic Products (DBRUP) agree that a REMS is not necessary to ensure the benefits of Xyosted outweigh its risks. While an increase in blood pressure is concerning, the REMS options considered by the review team, such as prescriber and patient education, are not likely to promote a change in behavior to decrease the risk of MACE. REMS that would require monitoring of blood pressure or ensuring only patients with low cardiovascular risk or certain diagnoses were prescribed Xyosted were deemed too burdensome for both prescribers and patients for this indication and risk. Therefore, the risks of this product will be communicated through labeling including a boxed warning, contraindications and specific indications, and a Medication Guide.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Xyosted (testosterone enanthate) is necessary to ensure the benefits outweigh its risks. Antares Pharma Inc. (Antares) submitted a New Drug Application (NDA 209863) for Xyosted with the proposed indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (primary hypogonadism or hypogonadotropic hypogonadism). This application is under review in the Division of Bone, Reproductive, and Urologic Products (DBRUP). The applicant submitted a REMS consisting of a Communication Plan, Medication Guide, and a timetable for assessments with this application.

2 Background

2.1 PRODUCT INFORMATION

Xyosted, (testosterone enanthate), a 505 (b)(2) application, is a subcutaneous testosterone enanthate product proposed for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (primary hypogonadism or hypogonadotropic hypogonadism). Testosterone enanthate undergoes ester cleavage to form testosterone and heptanoic acid.[1] Xyosted is proposed as a 50 mg, 75 mg, or 100 mg once weekly subcutaneous injection. Delatestryl, an intramuscular testosterone enanthate injection (the reference product for Xyosted), was approved in the United States in 1953. Currently approved topical testosterone products have REMS consisting of a Medication Guide to mitigate the risk of potential skin to skin transfer to minors causing virilization. Aveed, an injectable testosterone undecanoate, is approved with an ETASU REMS to

mitigate the risk of pulmonary oil embolism and anaphylaxis. A table detailing the currently approved testosterone replacement therapies is included in Appendix 1.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for Xyosted (NDA 209863) relevant to this review:

- 12/20/2016: NDA 209863 submitted for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone received.
- 10/20/2017: Complete Response (CR) letter issued to the applicant due to a clinically meaningful increase in blood pressure and the Agency's inability to exclude Xyosted from causality in two cases of suicide attempt (including one completed suicide) and two cases of depression in the clinical development program.
- 02/21/2018: Type A Post CR Meeting held with the applicant to discuss their approach for addressing the issues raised in the CR Letter, including the possibility of the inclusion of a Communication Plan REMS proposed by the applicant.
- 03/29/2018: Resubmission of NDA 209863 received.
- 06/14/2018: Medical Policy and Program Review Council (MPPRC) meeting to discuss risk mitigation strategies to address the risk of increase in blood pressure seen in Xyosted that may increase the risk of MACE.
- 07/12/2018: REMS Oversight Committee (ROC) meeting with CDER Center Director input to discuss risk mitigation strategies for Xyosted. The ROC advised the risk of MACE can be mitigated with a boxed warning, contraindications, and a medication guide for patients.
- 07/16/2018: The Agency notified the Applicant via an Information Request (IR) email a REMS is not required for Xyosted at this time.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Hypogonadism in males can occur during fetal development, before puberty, or during adult life. Causes range from genetic disorders such as Klinefelter syndrome, diseases such as cancer and mumps orchitis, hemochromatosis, and testicular injury that can be physical, chemical, or radiation induced.[2] Normal male aging can also cause decreases in testosterone that are clinical meaningful. It is estimated that 20% of men over 60 years old and 30-40% of those over 80 years old have testosterone levels that are clinically subnormal due to the aging process.[3] As common as the decrease in testosterone is in the typical aging male, Klinefelter syndrome affects 1/500-1,000 male births in the US.[4] If hypogonadism occurs before puberty, genitals are typically undeveloped, secondary sexual characteristic development is delayed, and arm and leg length are often excessive when compared to trunk size. Social and cognitive developmental delays may also result. As males age, gynecomastia, difficulty concentrating, infertility, decrease in muscle mass, and osteoporosis may be observed.

Diagnosis is made via a physical exam and two separate serum testosterone levels. Diagnosis is typically made when levels are below 300 ng/dL, and symptoms are present. Testosterone replacement therapy is usually titrated to a therapeutic range of 400-700 ng/dL.[5]

3.2 Description of Current Treatment Options

Treatment involves testosterone replacement therapy. Testosterone is available commercially in the United States as intramuscular injections, a buccal formulation, topical solutions, patches, gels, an implantable slow release pellet, and a nasal gel. Methyltestosterone is available as an oral tablet. All formulations carry the risk of increasing hematocrit and prostate specific antigen (PSA) levels, venous thromboembolism, altering lipid levels, benign prostatic hyperplasia, increasing sleep apnea in those at risk, edema, the potential for myocardial infarction, and azoospermia. Topical formulations can cause local irritation, require drying time, and application sites should be rotated, nasal formulations require 3 times daily dosing, intramuscular injections are painful and may cause bruising, and injection sites should be rotated. The buccal formulation has been poorly received, and implantable pellets may become infected. The topical gels and solutions have a Medication Guide REMS to mitigate the risk of skin to skin transfer to children due to the potentially virilizing effect, and Aveed, an injectable formulation, has an ETASU REMS that includes prescriber certification and administration at a certified healthcare facility because of its risk of pulmonary oil microembolism (POME) and anaphylaxis. A table detailing the currently approved testosterone replacement therapies is included in the Appendix 1.

4 Benefit Assessment

The pivotal Phase 3 trial QST-13-003 (NCT 02159469) was the primary source to determine efficacy and provided supporting safety data. The pivotal Phase 3 trial QST-15-005 (NCT 02504541) was the primary source of safety data and provided supporting efficacy data as well. Phase 1 single dose Trial QST-14-004 (NCT 02233751), and Phase 2 Trials QST-13-002 (NCT 01887418) and QST-16-006 (NCT 02777242) provided supporting safety data.

QST-13-003 was a double blind to dose strength, multiple-dose, 52-week study. The study included a screening phase, a 12-week treatment titration phase, and a 40-week extended treatment phase for evaluation of long-term safety. Patients were trained on proper use of Xyosted to self-administer the initial dose of 75 mg once each week on the same day of the week and at approximately the same time (e.g. 7:00 am ± 2 hours). The dose was increased by 25 mg at Week 7 if the Week 6 serum total testosterone (TT) concentration at the end of the dosing interval (C_{trough}) was < 350 ng/dL and was decreased by 25 mg if the C_{trough} was ≥ 650 ng/dL.

The primary endpoint was the percentage of patients with a time-averaged serum total testosterone concentration (C_{avg}) over the 7-day dosing interval (0-168 hours) within the normal range (300-1100 ng/dL) at Week 12. Secondary endpoints included the percentage of patients with a maximum total testosterone concentration (C_{max}) above three predetermined limits: < 1500 ng/dL, 1800-2500 ng/dL, and > 2500 ng/dL.

Trial QST-15-005 was a Phase 3, multiple-dose, 26-week study including a screening period, treatment titration period, and an extended treatment period for long-term safety evaluation. Unlike Study

QST-13-003, patients with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at baseline were excluded.[a] Dosing started at 75 mg per week, with dose adjustments at Weeks 7, 13, and 19, based on total testosterone trough concentration. Using a simulation model from study QST-13-003, C_{avg} and C_{max} values were extrapolated. Twenty-one subjects were enrolled in the PK sub-study and were held on a 75 mg weekly dose through Week 12 but were able to have dose adjustments at weeks 13 and 19 if necessary. For these sub-study subjects, TT C_{avg168} values were determined at Weeks 1, 6, and 12.

Results of QST-13-003

Ninety-seven out of 150 randomized subjects completed study QST-13-003. Results are summarized in Table 1 and Table 2 below.[1]

Table 1 – Percentage of Subjects on Xyosted with Testosterone C_{avg} in Normal Range at Week 12

Week 12 C_{avg} 300-1100 ng/dL	Xyosted 50 mg n = 25	Xyosted 75 mg n= 104[b]	Xyosted 100 mg n = 21	Total n = 150
n (%)	25 (100.0 %)	94 (90.4 %)	20 (95.2 %)	139 (92.7 %)
95% Exact Binomial CI	(86.3 %, 100.0 %)	(83.0 %, 95.3 %)	(76.2 %, 99.9 %)	(87.3 %, 96.3 %)

Table 2 provides a breakdown of the secondary endpoints of Study QST-13-003.

Table 2 – Percentage of Subjects on Xyosted with Supratherapeutic Testosterone C_{avg} at Week 12

Week 12 C_{max}	Xyosted 50 mg n = 25 (%)	Xyosted 75 mg n= 104 (%)	Xyosted 100 mg n = 21 (%)	Overall n = 150 (%)
<1500 ng/dL	25 (100.0 %)	93 (89.4 %)	19 (90.5 %)	137 (91.3 %)
1800 to 2500 ng/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>2500 ng/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing Week 12 C_{max}	0 (0.0)	11 (10.6 %)	2 (9.5 %)	13 (8.7 %)

[a] A 24-hour ambulatory blood pressure monitoring (ABPM) study was performed on subjects in Study QST-15-005 at baseline and after weeks 6 and 12 dosing was completed. Data will be discussed in Section 5.2.1.

[b] Subjects are included in the 75 mg dose category in the chart if they discontinued the study prior to Week 7.

Results of QST-15-005

Of 133 randomized subjects, 113 completed the study. The TT C_{avg168} at Week 12 was 552.5 (+/- 94.64) ng/dL. For patients in the PK population, the TT C_{avg168} at Week 12 was 797.5 (+/- 196.08) ng/dL, still within the eugonadal range. The clinical reviewer concurs with the applicant that Xyosted met its efficacy criteria.

5 Risk Assessment & Safe-Use Conditions

Safety data from Phase 3 Studies QST-13-003 and QST-15-005 as well as several Phase 1 and 2 studies provided safety data for Xyosted. A total of 380 subjects received at least 1 dose of Xyosted, 144 received Xyosted for at least 6 months, and 99 subjects received a full year of therapy. The most common treatment emergent adverse events (TEAEs) were increased hematocrit (32 subjects, 11.3%), increased prostate specific antigen (PSA) (22 subjects, 7.8%), upper respiratory infection (22 subjects, 7.8%), hypertension (22 subjects, 7.8%), and injection site bruising (15 subjects, 5.3%).[6]

5.1 DEATH

One case of completed suicide was reported in Study QST-13-003. The patient was a 71-year old Caucasian male who received his last dose of Xyosted on study day 169 and failed to report for his scheduled study visit on day 176.[7] After numerous contact attempts, his son reported that the patient had committed suicide on study day 182. While the subject's past medical history was negative for depression, his concomitant medicine list included St. John's Wort, 5-hxydroytryptophan, valerian, multiple B vitamins, and melatonin. At the last visit, the subject's serum testosterone levels were in the eugonadal range. The investigator ruled this suicide was not related to study drug. The risk of suicide will be addressed in warnings and precautions in Xyosted's labeling and events will be sent in quarterly for the first three years after approval in Periodic Adverse Drug Event Reports, which the clinical reviewer noted is appropriate to address the risk.[8]

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Increase in Blood Pressure That May Increase MACE

The Integrated Summary of Safety noted that 7.8% of patients experienced a TEAE of hypertension. In the phase 3 studies, the mean systolic blood pressure (SBP) increase was 4.4 mmHg at week 26, and 3.3 mmHg at week 52. Mean diastolic blood pressure (DBP) increase from baseline peaked at week 26 at 1.3 mmHg, and at week 52, the increase from baseline was 0.5 mmHg. In study QST 15-005, 106 subjects took part in an ABPM study, with ABPM measurement taken at baseline and the end of weeks 6 and 12 dosing. The ABPM study participants also had a mean SBP increase by week 13 of 4 mmHg and a mean DBP increase at weeks of 1 mmHg, verifying the cuff blood pressure findings of study QST-13-003.[6]

As the results of the studies demonstrated an elevation in BP, the Division of Cardiovascular and Renal Products (DCRP) was consulted. In their consult dated May 25, 2018, DCRP noted that, "the hypertensive effect of this drug will increase the risk of cardiovascular death, myocardial infarction, stroke, and heart failure, albeit modestly," and recommended appropriate risk conveyance language in

the product information.[9] The clinical reviewer noted 10% of subjects in study QST-13-003 and 3% of subjects in study QST-15-005 needed to start or change their antihypertensive medication.[10] The Agency determined the appropriate method of risk messaging for Xyosted at this time to be a boxed warning, a concise medication guide for patients, as well as a specific indication and contraindications for the product. Labeling will include the study results. See further discussion in Section 8.

5.2.2 Increased Risk of Suicide and Depression

Suicidal ideation and depression may occur in subjects who are using testosterone replacement therapies, and in men who have low serum testosterone levels. In the Xyosted development program, in addition to the completed suicide narrative above, there were 3 TEAEs of depression, including a suicidal ideation with suicide attempt. Six days after the first Xyosted dose, a 67-year old subject with a past medical history of depressive disorder and 8 previous years of paroxetine use ingested 25-50 tramadol 50 mg tablets that were not prescribed to him following a fight with his spouse. He was hospitalized and later discharged with symptom resolution with outpatient psychiatric care. Study medication was discontinued. The Division of Pharmacovigilance (DPV) was consulted due to the cases of attempted and completed suicide and depression in the clinical trials. DPV noted in an August 30, 2017 review of testosterone products, that most of the cases in FAERS of suicide attempts, suicidal ideations, and completed suicides did not provide enough background data to ascertain a specific trend or drug-event association. DPV recommended in its review that Antares submit all reports of depression and suicidality-type events as part of the quarterly Periodic Adverse Event Report (PADER) for the first three years of Xyosted marketing.[11] The risk will be addressed in warnings and precautions in Xyosted's labeling.

5.2.3 Increased Hematocrit

While an increase in hematocrit[c] is expected in users of testosterone replacement therapy, the increase seen in Xyosted users is noteworthy. In Phase 3 studies, 9.9% of subjects using Xyosted experienced a TEAE of increased hematocrit. Within the first 6 months of therapy, 4.5% of subjects on Xyosted in Phase 3 studies reached a study-ending threshold of a >55% increase in hematocrit. The risk will be addressed in labeling in warnings and precautions by recommending testing hematocrit levels every 3 months while patients are on Xyosted. The clinical reviewer proposed increased monitoring of hematocrit in patients using Xyosted.

6 Expected Postmarket Use

Xyosted, like other testosterone products, is likely to be prescribed by endocrinologists, urologists, and primary care providers, and can be used by patients on an outpatient basis. Prescribers are likely to familiar with the risks of suicidality and depression as depression is a labeled adverse reaction with other injectable testosterone products. Prescribers should note the incremental, long-term increase in blood pressure, especially in patients with hypertension, might lead to an increase in MACE; however, blood pressure is a regularly checked vital sign at medical appointments, so prescribers will be able to

[c] Increased hematocrit was defined as a shift in hematocrit levels from the normal range to above normal range

closely monitor the blood pressure of patients receiving Xyosted, and treat increases according to current guidelines.

7 Risk Management Activities Proposed by the Applicant

Antares proposed risk management activities for Xyosted beyond routine pharmacovigilance and labeling including a proposed REMS to mitigate the potential risk of increases in blood pressure associated with the administration of Xyosted.

7.1 Review of Applicant's Proposed REMS

Antares submitted a REMS proposal including a REMS document and appended materials with their NDA submission dated March 29, 2018. The REMS consists of a Medication Guide (MG), Communication Plan (CP), and a timetable for submission of assessments. The submission did not include a supporting document.

The Applicant proposed the following goal for the Xyosted REMS:

(b) (4)

Antares proposed to include a MG as part of the REMS. The proposed MG includes (b) (4)

The Applicant proposed a Communication Plan (b) (4)

The proposed REMS website will include all the REMS materials, prescribing information, MG, (b) (4)

Antares proposes to submit assessments to the FDA (b) (4)

Reviewer's Comments: *After internal Agency discussion, the Agency determined the appropriate risk mitigation at the time of this review for Xyosted is a boxed warning, concise indications and contraindications, and a comprehensive medication guide for patients. See Section 8 for further discussion.*

7.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

Antares proposed the following risk management activities to mitigate the risk of depression/suicide:

- Enhanced Pharmacovigilance including expedited reporting of all completed suicides based on MedDRA preferred terms to the Agency within 15 days of receipt regardless of expectedness, enhanced follow-up on all post-marketing reports of suicidality-type events and depression with Antares staff providing phone initial case review, then a phone or mail follow up. If initial intake is insufficient, a minimum of 3 written attempts to contact reporter will be made, followed by a fourth phone attempt. Antares will provide periodic and cumulative summaries and analysis of depression and suicidality-type event reports since approval of Xyosted as part of the quarterly Periodic Adverse Drug Event Report (PADER) for the first 3 years of Xyosted marketing. Xyosted will discuss and then recommend labeling changes based on these reports.

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to Division of Pharmacovigilance (DPV) for review and input. DPV recommended Antares submit all reports of depression and suicidality-type events as part of the quarterly Periodic Adverse Event Report (PADER) for the first three years of Xyosted marketing.*

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of Xyosted based on the efficacy and safety information currently available.

Xyosted met study efficacy criteria without demonstrating supratherapeutic serum testosterone levels in subjects in clinical trials. The Applicant considers Xyosted an effective testosterone replacement therapy in men with primary/hypogonadotropic hypogonadism and the clinical reviewer concurs.

The most commonly reported TEAEs were increased hematocrit, increased PSA, upper respiratory infection, hypertension, and injection site bruising. In clinical trials, Xyosted showed an increase in blood pressure that may lead to an increase in MACE, as an average increase in systolic blood pressure of 4-5 mmHg is expected to increase the risk of MACE in the overall population.[12] Because of the universal concern of the health consequences of hypertension and the significant documented off-label use of testosterone products in men, the Agency has concern regarding the blood pressure elevation seen in subjects in clinical trials who used Xyosted and testosterone products in general.

No products currently have a REMS to mitigate the risk of an increase in blood pressure which may lead to MACE; however, some products do have boxed warnings and warnings and precautions in labeling to convey this risk. These products include nonsteroidal anti-inflammatory medications, which use a boxed warning to convey their increased risk of cardiovascular events and mirabegron, which has

recommendations for periodic blood pressure determinations and a statement that it may increase blood pressure in the warnings and precautions section of its labeling.

To further discuss this risk, the Agency engaged in internal discussions.[d] Discussion concentrated about the potential increase in MACE due to Xyosted's increase in blood pressure, and if in fact, a REMS should be required to mitigate this risk. In determining whether a REMS would be appropriate and if so what type, limitations and burden of REMS were considered. A restrictive REMS that could potentially ensure only the indicated population would receive the drug or mitigate MACE would require elements which were determined to be unduly burdensome for this prescriber and patient population. For example, a REMS that only educates prescribers may not mitigate the risk of MACE as education does not always facilitate a change in behavior, however, a REMS that requires blood pressure monitoring or that patients have a calculated low cardiovascular risk was deemed too burdensome to both patients and prescribers. Therefore, it was determined the risk will be communicated through labeling via a boxed warning including the risk of an increase in blood pressure that may increase MACE and the need to monitor for and treat hypertension, concise indications for Xyosted, a contraindication for men with hypogonadal conditions not associated with structural or genetic etiologies, and a Medication Guide for patients that is distinguished from all other testosterone MG's so that the increase in BP and associated increased risk of MACE risk message is clearly communicated. Xyosted is expected to be prescribed by endocrinologists, urologists, and primary care providers, who monitor blood pressure at visits, and should be familiar with the risk of increase in blood pressure potentially leading to an increase in MACE events.

Further, there is uncertainty that the increase in blood pressure seen in Xyosted is a class wide effect. One currently unapproved oral testosterone product has recently demonstrated a clinically significant increase in blood pressure during an ABPM study, but not showing an equivalent increase in blood pressure cuff pressure measurements. As cuff measurements are the gold standard in clinical practice, small elevations in blood pressure may not be caught in the clinic setting. There has only been one completed ABPM trial that has used a single topical testosterone product as a small comparator arm. The topical testosterone product did not show the same elevation in SBP on ABPM study. Therefore, in May of 2018, the Agency notified all NDA holders of approved testosterone replacement therapies that each product would need to undergo an ABPM study to further evaluate the class effects of testosterone on blood pressure. The Cardiovascular Outcomes Trial is a randomized, placebo-controlled trial, with Androgel 1.62% as a comparator control, to determine if testosterone replacement therapies increase hypertension or MACE in hypogonadal men. Enrollment for this long-term trial began in May of 2018. The results of these trials may play a role in the future of risk mitigation for testosterone products regarding the risk of increased blood pressure potentially leading to an increase in MACE.

9 Conclusion & Recommendations

[d] Discussions included a Medical Policy and Program Review Council (MPPRC) Meeting and a REMS Oversight Committee (ROC) Meeting

Based on the available data a REMS is not necessary to ensure the benefits of Xyosted outweigh its risks. The safety concern of increased blood pressure which may increase MACE will be communicated in the labeling via a boxed warning including the risk of an increase in blood pressure that may increase MACE, concise indications for Xyosted, a contraindication for men with hypogonadal conditions not associated with structural or genetic etiologies, and a Medication Guide for patients that is distinguished from all other testosterone MG's so that the increase in BP and associated increased risk of MACE risk message is clearly communicated. Xyosted is expected to be prescribed by endocrinologists, urologists, and primary care providers, who monitor blood pressure at visits, and should be familiar with the risk of increase in blood pressure potentially leading to an increase in MACE events. Elevated blood pressure is a treatable condition that providers who are treating patients with Xyosted should be able to manage.

Should DBRUP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

1. Inc AP. Summary of Clinical Efficacy of Xyosted. December 20, 2016.
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11. Kapoor R. Division of Pharmacovigilance 2 Review of Enhanced Pharmacoviglance proposal for depression and suicide of Xyosted (testosterone enanthate) NDA 209863. 2018.
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10.2 Currently Approved Testosterone Replacement Therapies

Product Proprietary Name (Generic)	Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
Androgel (testosterone) gel, 1.62%	Testosterone replacement therapy (TRT)	40.5 mg transdermal(TD) daily	Skin to skin transfer to children-virilizing effects	Boxed Warning Medication Guide REMS
Androgel (testosterone) gel, 1%	TRT	50 mg TD daily	Skin to skin transfer to children-virilizing effects	Boxed Warning Medication Guide REMS
Axiron (testosterone) solution, 30 mg/1.5 ml	TRT	60 mg TD daily	Skin to skin transfer to children-virilizing effects	Boxed Warning Medication Guide REMS
Androderm (testosterone) film, s2 and 4 mg	TRT	4 mg TD daily	Application site reactions	
Testim (testosterone) gel, 1%	TRT	50 mg TD daily	Skin to skin transfer to children-virilizing effects	Boxed Warning Medication Guide REMS
Fortesta T-gel, (testosterone) gel, 10 mg/actuation	TRT	40 mg TD daily	Skin to skin transfer to children-virilizing effects	Boxed Warning Medication Guide REMS
Android (methyltestosterone) tablet, 10 and 25 mg	TRT	10-50 mg by mouth (PO) daily	Elevated liver enzymes	
Testred (methyltestosterone) capsule, 10 mg	TRT	10-50 mg PO daily	Elevated liver enzymes	
Aveed (testosterone undecanoate) injection, 750 mg/3 ml	TRT	750 mg intramuscularly (IM) q10 weeks	POME, anaphylaxis, injection site reactions.	Boxed Warning ETASU REMS

Delatestryl (testosterone enanthate) injection, 200 mg/ml	TRT	50-400 mg IM q2-4 weeks		
Depo-testosterone (testosterone cypionate) injection, 100 mg/ml, 200 mg/ml	TRT	50-400 mg IM q2-4 weeks		
Testopel (testosterone) pellet, 75 mg	TRT	150-450 mg under skin q3-6 months	Implantation site reaction	
Striant (testosterone) tablet ER, 30 mg	TRT	30 mg buccally twice daily	Stomatitis	
Natesto (testosterone) nasal gel (metered), 5.5 mg/actuation	TRT	2 actuations/nare 3 times daily		

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