CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208088Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	208088
PDUFA Goal Date	August 28, 2020
OSE RSM	2020-486
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Laura Zendel, PharmD
Division Director	Cynthia LaCivita
Review Completion Date	August 17, 2020
Subject	Evaluation of Need for a REMS
Established Name	Testosterone undecanoate oral
Trade Name	Tlando
Name of Applicant	Lipocine, Inc.
Therapeutic Class	Androgen for testosterone replacement therapy
Formulation(s)	112.5 mg oral capsules
Dosing Regimen	225 mg orally twice daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Tlando (testosterone undecanoate oral) is necessary to ensure the benefits outweigh its risks. Lipocine, Inc. (Lipocine) submitted a New Drug Application (NDA 208088) for Tlando with the proposed indication of testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The most serious risk associated with Tlando is an increase in blood pressure which can increase the risk of major adverse cardiovascular events (MACE). The Applicant did not submit a proposed REMS with this application.

The Division of Risk Management (DRM) and the Division of Urology, Obstetrics, and Gynecology (DUOG) agree that a REMS is not necessary to ensure the benefits of Tlando outweigh its risks. The 24-hour average increase in systolic blood pressure (SBP) in subjects taking Tlando as measured by ambulatory blood pressure monitor (ABPM) was 4.3 mmHg (95% CI 2.1, 6.5 mmHg) and the 24-hour average increase in diastolic blood pressure (DBP) as measured by ABPM was 1.4 mmHg (0.5, 2.3 mmHg). The increase in blood pressure is concerning, as increased blood pressure can increase the risk of MACE. The risk of increased blood pressure and the effect that it can have on increasing MACE will be mitigated by communicating the risks through labeling including a boxed warning, warnings and precautions, and a Medication Guide. Tlando is expected to be prescribed by endocrinologists, urologists, and primary care providers, who typically monitor blood pressure at patient visits. Elevated blood pressure is a treatable condition that likely prescribers should be able to recognize and manage. Labeling will instruct prescribers that prior to initiating treatment to consider the patients' baseline cardiovascular risk, ensure that blood pressure is adequately controlled and to monitor blood pressure periodically while patients received treatment with Tlando.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Tlando (testosterone undecanoate) is necessary to ensure the benefits outweigh its risks. Lipocine, Inc. (Lipocine) submitted a New Drug Application (NDA 208088) for Tlando with the proposed indication of testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. This application is under review in the Division of Urology, Obstetrics, and Gynecology (DUOG). The Applicant did not submit a proposed REMS with this application.

2 Background

2.1 PRODUCT INFORMATION

Tlando, a 505(b)(2) application, is an androgen proposed for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Testosterone undecanoate, a fatty acid ester of testosterone, is an inactive prodrug hydrolyzed by esterases to testosterone. When taken orally, testosterone undecanoate avoids first pass metabolism as it is

absorbed by the intestinal lymphatics.[1] Tlando is proposed as an oral capsule to be taken as 225 mg twice daily and available in 112.5 mg capsules. Tlando is likely to be initiated on an outpatient basis.

Aveed, an injectable testosterone undecanoate, is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risk of pulmonary oil embolism and anaphylaxis. Oral testosterone undecanoate is available as Andriol Testocaps in Canada and Europe. Both Xyosted, a subcutaneous testosterone enanthate product approved on September 28, 2018, and Jatenzo, an oral testosterone undecanoate product approved on March 28, 2019 have a boxed warning due to an increase in blood pressure that can increase the risk of MACE. Xyosted or Jatenzo are not approved with a REMS. A table detailing the currently approved testosterone replacement therapies is included in Section 10.2, Appendix 1.

2.2 REGULATORY HISTORY

This application had received a Complete Response on June 28, 2016, May 8, 2018, and November 8, 2019. DRM previously completed reviews dated March 22, 2018, and October 18, 2019,[2,3] for each of these review cycles for this NDA. The following is a summary of the regulatory history for NDA 208088 relevant to the Complete Response dated November 8, 2019:

• **11/08/2019:** Complete Response issued due to the number of subjects with testosterone C_{max} excursions above the Agency's acceptable range as well as the unknown amount of time subjects spend outside the acceptable range, the use of pharmacokinetic data from a short-term study, and the unknown clinical implications of these excursions.

• **01/16/2020:** Type A Post-Action Meeting held as requested by the Applicant to address deficiencies noted in the CR letter and ask the Agency to reconsider the CR decision. A path forward was discussed, including the potential of modifying the standard testosterone C_{max} thresholds based on the Applicant's laboratory's upper limit of normal, and incorporating the up to 8% *ex vivo* conversion of testosterone undecanoate to testosterone to reflect actual *in vivo* exposure.[4]

• **01/21/2020:** Lipocine submitted a proposal to the Agency to adjust the testosterone C_{max} by 3%, 5%, and 8% and use an upper limit of normal as 1080 ng/dL.

• **02/19/2020:** The Agency sent an information request (IR) recommending the Applicant derive new testosterone C_{max} thresholds using the upper limit of normal proposed at the January 16, 2020 meeting, adjust individual patient testosterone C_{max} values by 3%, 5%, and 8%, then analyze the proportion of patients within target ranges.[5]

• **02/28/2020:** Resubmission of NDA 208088.

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.[6] 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.[7] 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.[8] 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.[9]

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. 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. Xyosted, a subcutaneous formulation of testosterone enanthate, was approved in September of 2018 and carries a boxed warning for an increased risk of MACE due to an increase in blood pressure. Jatenzo, an oral testosterone undecanoate formulation was approved on March 28, 2019 with the same boxed warning regarding increased risk of MACE due to increase in blood pressure. A table detailing the currently approved testosterone replacement therapies is included in Section 10.2, Appendix 1.

4 Benefit Assessment

The original submission's clinical development program included 6 studies; pivotal Phase 3 safety and efficacy 52-week LPCN 1021-13-001 (NCT02081300), as well as LPCN 1021-09-001, S361.1.001, M12-778 (NCT01346319), M13-293, and LPCN 1021-14-001. The first complete response added two new trials LPCN 1021-16-003 (NCT03242408) and LPCN 1021-16-002 (NCT03242590). These studies are discussed in a previous DRM review, dated March 22, 2018.[2] The primary efficacy endpoint of pivotal Phase 3 safety and efficacy trial LPCN 1021-13-001 was $\geq$75% of subjects' testosterone C_{ave} within the eugonadal range of 300-1140 ng/dL at week 13 of treatment, lower bound of the 95% confidence interval (CI) to be at least 65%. Secondary endpoints were defined as meeting the FDA goals of subjects with testosterone

C_{max} <1500ng/dL being ≥85%, subjects with C_{max} 1800-2500 ng/dL ≤5%, and no subject's C_{max} over 2500 ng/dL.

The second complete response added three new non-efficacy trials, LPCN 1021-18-001 (NCT03868059), LPCN 1021-18-002, and LPCN 1021-18-003. These trials included one for ambulatory blood pressure monitoring (ABPM), and two trials to evaluate the influence of blood collection tubes on serum testosterone. These studies are discussed in a previous DRM review from October 18, 2019.[3]

The May 8, 2018 complete response letter included the Agency's reasons for the complete response (CR), including that the Pivotal Phase 3 study did not prove that Tlando can maintain testosterone levels in the eugonadal range (300-1140 ng/dL) without excursions beyond acceptable upper limits of testosterone C_{max}. A second CR was issued on November 8, 2019 and included DUOG's continuing concerns over the number of subjects' testosterone C_{max} levels that exceeded the Agency's acceptable thresholds, the unknown amount of time that subjects were above acceptable C_{max} threshold daily, the use of pharmacokinetic data from a short-term study to determine clinical safety implications, and the lack of long-term adverse event data in subjects who exceed acceptable testosterone C_{max} levels.

A post-action meeting was held with the Applicant on January 16, 2020 to discuss a path forward and further clarification was provided to the Applicant on February 19, 2020. On February 28, 2020, the Applicant resubmitted, providing a Complete Response to the Action letter dated November 8, 2020. Because phase 3 efficacy study LPCN 1021-16-002 did not meet its secondary endpoints, the Applicant completed a reanalysis of the testosterone C_{max} data. The Applicant conducted a testosterone C_{max} distribution analysis after adjustment of testosterone C_{max} thresholds based on the pivotal study's testosterone assay upper limit of normal (ULN) of 1080 ng/dL. This also changed the testosterone C_{max} goal secondary endpoint thresholds to > 85% of subjects with testosterone C_{max} <1620ng/dL, < 5% of subjects with C_{max} 1944-2700 ng/dL, and no subjects with a C_{max} over 2700 ng/dL. To account for ex vivo testosterone undecanoate to testosterone conversion under different test tube conditions and processing times, individual subjects' testosterone C_{max} values were adjusted by 3%, 5%, and 8%. The adjusted values were used in a dataset of daily total excursion time (in minutes), and a testosterone C_{max} distribution analysis of transient (≤60 minutes/24 hours) excursions above testosterone C_{max} thresholds. Using the 5% to capture an average of adjusted testosterone C_{max} values, the reanalysis resulted in 82% of subjects' testosterone C_{max} <1620ng/dL, 5% of subjects with C_{max} 1944-2700 ng/dL, and no subjects over 2700 ng/dL. These values closely resemble those of approved oral testosterone product Jatenzo.[10] The clinical reviewer states in the current review cycle that with the above reanalysis of the data, Tlando met the primary endpoint and two of three secondary endpoints. The third endpoint was missed by a small amount, which is not expected to affect the efficacy of the drug.[11]

5 Risk Assessment & Safe-Use Conditions

The original pooled safety analysis included 6 studies; pivotal Phase 3 safety and efficacy 52-week study LPCN 1021-13-001, as well as LPCN 1021-09-001, S361.1.001, M12-778, M13-293, and 1021-14-001. The first resubmission safety database included all the above plus new trials LPCN 1021-16-003 and LPCN 1021-16-002. The second resubmission includes all the previous trials and new studies LPCN 1021-18-

001 and LPCN 1021-18-003. The safety databases are hereafter referred to as Original Integrated Safety Summary (ISS1), second ISS (ISS2), and third ISS (ISS3), in accordance with the Applicant's nomenclature. The Original ISS (ISS1) included data from 381 subjects, and the first Resubmission ISS (ISS2) includes 525 subjects. The second resubmission ISS (ISS3) is comprised of data from 654 subjects and is the subject of this risk assessment, as the third resubmission did not include any additional subjects or new Tlando safety data.

The most commonly seen treatment-emergent related adverse events in ISS3 were headache, increase in hematocrit, and acne. Headache was the most commonly occurring treatment-related treatment-emergent adverse event, occurring in 1.5% of Tlando subjects, 2.9% of Andriol 80 mg subjects, 3.8% of Androgel 1.62% subjects, and no placebo subjects in ISS3. No deaths and no major adverse cardiac events were noted in any of the trials.

Six (4.6%) subjects experienced an increase in hematocrit from normal range at baseline of study LPCN 1021-18-001 to levels that were above the acceptable range of 35% to 54%. This effect was seen with Tlando therapy for approximately 110 days and the clinical reviewer stated in their review it may demonstrate insufficient exposure for long term safety data.

Due to findings of minimal to moderate diffuse adrenal cortical vacuolation in all treated male rats and moderate to marked adrenal cortical atrophy in all treated male dogs potentially causing adrenal insufficiency in the first submission, an ACTH stimulation test was performed on 68 subjects at baseline at three weeks after treatment on FDA recommendation for ISS2. Sixty-two subjects had normal levels both at baseline and end of study, one had a normal baseline, but was abnormal at the end of study, and five had abnormal ACTH at baseline, making the results uninterpretable. The Applicant will be advised to resubmit further assessment in a Post Marketing Requirement that includes a longer length of study to properly assess adrenal function.[10]

5.1 Increase in Blood Pressure that may cause an Increase in Major Cardiac Events (MACE)

In all trials in ISS2, only cuff measurements were taken of subjects' blood pressure. All cuff readings were done at the morning visit with subjects at rest for 5 minutes and no blood pressure measurements from any other time of day are known. The outcomes of the cuff pressures from ISS2 demonstrated that the systolic blood pressure (SBP) increased 0.9 mmHg (SD +/- 13.21), and diastolic blood pressure (DBP) decreased 0.2 mmHg (SD +/- 8.10).[2] As cuff pressure readings may not always provide accurate longitudinal data, the Applicant was required to conduct ambulatory blood pressure monitoring (ABPM) studies.

In the ABPM study LPCN1021-18-001, 140 hypogonadal men were enrolled, and the Safety Set included all who received at least 1 dose of Tlando (N = 138), while the Full Analysis Set included only those with valid ABPM at visits 3 (baseline) and 5 (post treatment). The study demonstrated clinically significant increases in 24-hour systolic, diastolic, and average blood pressure, and clinically significant increases in heart rate. The Division of Cardiovascular and Renal Products (DCRP) review of the data of LPCN 1021-

18-001 noted that several subjects' data had not been included in the final analysis due to the subject starting the ABPM measurements after the selected 7 AM start time. DCRP was in favor of including all collected data as the trial protocol allowed for an evening ABPM start time.[12] This review contains the data as interpreted in DCRP's review. The 24-hour average increase in systolic blood pressure (SBP) as measured by ABPM was 4.3 mmHg (95% CI 2.1, 6.5 mmHg). During this study, the corresponding cuff measured increase in 24-hour SBP was 4.8 mmHg (2.7 mmHg, 6.9 mmHg). The 24-hour average increase in DBP as measured by ABPM was 1.4 mmHg (0.5, 2.3 mmHg). During this study, the corresponding cuff measured increase in 24-hour DBP was 1.6 mmHg (0.3 mmHg, 2.9 mmHg). This study also measured mean change in 24-hour heart rate. Upon ABPM measurement, it was noted to increase 2.1 bpm (1.0, 3.1 bpm), and with cuff measurement, 2.0 bpm (0.4, 3.6 bpm). During this study, 3 subjects changed antihypertensive medications, and 2 subjects started a new antihypertensive medication while on Tlando therapy.

The Applicant also conducted a subgroup analysis of men based upon their cardiac risk score determined by the Framingham Heart Study's algorithm. In their consult from July 2019, DCRP did not concur with the Applicant's subgroup validity. The Agency's analysis of this subgroup concluded the following: for low cardiovascular risk patients, average 24-hour SBP dropped 1.5 mmHg (95% CI -6.5, 3.6), for men at moderate cardiovascular risk, blood pressure increased 3.3 mmHg (-0.1, 6.7), and for those with high cardiovascular risk, the average 24- hour SBP increased 8.0 mmHg (4.4, 11.6). Also concerning is the difference in baseline diabetic subjects. Those with diabetes had a 24-hour average SBP increase of 9.3 mmHg (5.3, 13.3), while those without diabetes at baseline's increase was 2.2 mmHg (-0.4, 4.7 mmHg). Due to the noticeable differences, DCRP recommends placing the subgroup findings in Tlando's label.[12]

6 Expected Postmarket Use

Tlando, like other testosterone products, is likely to be prescribed by endocrinologists, urologists, and primary care providers, and will used by patients on an outpatient basis. Typically, blood pressure is a regularly checked vital sign at medical appointments, so prescribers are expected to be able to monitor the blood pressure of patients receiving Tlando and treat increases in blood pressure accordingly.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Tlando beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Tlando met study efficacy criteria with occasional excursions into the supratherapeutic serum testosterone range. After re-analysis, the C_{max} was similar to a currently approved testosterone replacement therapy product. The clinical reviewer recommends approval, as Tlando has met the efficacy goals without excursions of testosterone C_{max} into an unacceptably supratherapeutic range. The

Applicant considers Tlando an effective testosterone replacement therapy in men with conditions associated with a deficiency in endogenous testosterone. The clinical reviewer agrees and notes that this product has similar efficacy and safety to other currently approved treatments.

Due to the uncertainty that the increase in blood pressure seen in an oral testosterone product may be a class wide effect, the Agency notified all NDA holders of approved testosterone replacement therapies to conduct ABPM studies in May 2018 to further evaluate this risk. As measured by ABPM study, the 24-hour average increase in systolic blood pressure (SBP) was 4.3 mmHg (95% CI 2.1, 6.5 mmHg) and the 24-hour average increase in DBP was 1.4 mmHg (0.5, 2.3 mmHg) for Tlando. These changes in blood pressure were similar to those seen in Xyosted and Jatenzo.

The Agency has concerns regarding the blood pressure elevation seen in subjects in clinical trials who used Tlando. This change in blood pressure is expected to increase the risk of MACE in the overall population that is prescribed Tlando.[13] The Agency also has concerns regarding the potential off-label use of Tlando and other testosterone products, which may significantly increase the number of men with an increased risk of MACE,[14] and this concern was a consideration in developing labeling.

DRM and DUOG considered the benefit of treatment with Tlando, the risk of increases in blood pressure due to Tlando and the potential increase in MACE, and if a REMS was necessary to ensure the benefits outweigh these risks. The review team had thoughtful discussions during the review of the applications for Tlando, Xyosted, and Jatenzo on how best to mitigate the risk of increased blood pressure and MACE. These products and the risk of increases in blood pressure and whether a REMS was necessary to ensure the benefits of these products outweighed their risks were also discussed at the REMS Oversight Committee. No products currently have a REMS to mitigate the risk of an increase in blood pressure which may lead to MACE; however, some products 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. Blood pressure is typically assessed at nearly every medical appointment and DRM expects that the likely prescribers should know how to monitor for changes in blood pressure, that increases in blood pressure can potentially lead to increased cardiovascular events, and patients should be treated as appropriate for increases in blood pressure.

Similar to the other recently approved testosterone products, the team determined that the increased risk of blood pressure for Tlando will be mitigated by communicating the risk through labeling including a boxed warning, warnings and precautions, and a Medication Guide. Labeling will instruct prescribers to consider the patient's baseline cardiovascular risk prior to initiating treatment, ensure that blood pressure is adequately controlled, and to monitor blood pressure while patients receive treatment with Tlando. A Medication Guide for patients provides patient friendly language to explain the risks of increased blood pressure that can occur while taking Tlando.[15] Tlando is expected to be prescribed by endocrinologists, urologists, and primary care providers, who typically monitor blood pressure during

medical evaluations. We expect that these prescribers should know how to monitor for changes in blood pressure, that increases in blood pressure can potentially lead to increased cardiovascular events and, patients should be treated as appropriate for increases in blood pressure.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits of Tlando outweigh the risks of increased blood pressure which may increase the risk of MACE. These risks will be communicated in the labeling using a boxed warning including the risk of an increase in blood pressure that may increase MACE, and a contraindication for men with hypogonadal conditions not associated with structural or genetic etiologies as well as a Medication Guide for patients.

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

10 Appendices

10.1 References

1. Lipocine I. Summary of Clinical Efficacy of Tlando February 26, 2020. February 26, 2020.
2. Cunningham C. Evaluation for the Need for a REMS on Tlando (testosterone undecanoate) March 22, 2018.
3. Cunningham C. Evaluation of the Need for a REMS on Tlando (Tesosterone undecanoate) October 18, 2019.
4. Roule J. Type A Post-Action Meeting Minutes FDA and Lipocine, Inc. January 16, 2020. 2020.
5. Roule J. Information Request February 19, 2020. In: Lipocine I, ed2020.
6. Clinic M. Male Hypogonadism. https://www.mayoclinic.org/diseases-conditions/male-hypogonadism/doctors-departments/ddc-20354888. Published 2012. Updated 9/29/2016. Accessed 10 January, 2018.
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8. NIH-US. National Library of Medicine Genetics Home Reference - Klinefelter Syndrome. 2018.
9. Bhasin S, Cunningham, GR, Hayes, FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism.* 2010;95(6):2536-2559.
10. Lipocine I. Summary of Clinical Efficacy of Tlando February 26, 2020.
11. Kaufman M. Unireview of Tlando (testosterone undecanoate).
12. McDowell T-Y. Interdisciplinary Review Team for Ambulatory Blood Pressure Monitoring Study Consultation Review (DCRP) July 16, 2019.
13. Senatore F. NDA 208088: Review Applicant's Action Plan to address deficiency #2 (ABPM). 2018.
14. Mohamoud M. *Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveveillance and Epidemiology Division of Epidemiology II Drug Use Review "Testosterone and Cardiovascular Risk"*

15. US Food and Drug Administration Guidance for Industry: Warnings and Precaustions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format.

10.2 CURRENTLY APPROVED TESTOSTERONE 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
Androgel (testosterone) gel, 1%	TRT	50 mg TD daily	Skin to skin transfer to children-virilizing effects	Boxed Warning Medication Guide
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
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
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

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		
Xyosted (testosterone enanthate) subcutaneous injection, 50 mg, 75 mg, and 100 mg	TRT	50-100 mg injected once weekly	Increase in blood pressure	Boxed warning
Jatenzo (testosterone undecanoate) oral capsules, 158 mg, 198 mg, 237 mg	TRT	Starting dose 237 mg daily; may titrate to 396 mg twice daily	Increase in blood pressure	Boxed warning

APPEARS THIS WAY ON ORIGINAL

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

/s/

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Division of Risk Management (DRISK)
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Application Type	NDA
Application Number	208088
PDUFA Goal Date	November 9, 2019
OSE RCM #	2019-1010
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Laura Zendel, PharmD
Division Director	Jamie Wilkins, PharmD
Review Completion Date	October 18, 2019
Subject	Evaluation of Need for a REMS
Established Name	Testosterone undecanoate oral
Trade Name	Tlando
Name of Applicant	Lipocine, Inc.
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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Tlando (testosterone undecanoate) is necessary to ensure the benefits outweigh its risks. Lipocine, Inc. submitted a New Drug Application (NDA 208088) for Tlando with the proposed indication of testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The most serious risk associated with Tlando is major adverse cardiovascular events (MACE) resulting from increased blood pressure. The Applicant did not submit a REMS with this application.

At this time, the benefits of Tlando do not outweigh its risks. The review division has concerns regarding the number of subjects with C_{max} excursions above the Agency's acceptable range as well as the clinical implications of these excursions, the unknown amount of time those subjects spend in excursion, the use of pharmacokinetic data from a short-term study, and the use of that data to determine that C_{max} excursions are not clinically significant. Therefore, a final REMS determination cannot be made on this product. However, if the Applicant was to resubmit the application, they will be advised to propose detailed strategies in labeling that will adequately address the concern of MACE resulting from increased blood pressure.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Tlando (testosterone undecanoate) is necessary to ensure the benefits outweigh its risks. Lipocine, Inc. (Lipocine) submitted a New Drug Application (NDA 208088) for Tlando with the proposed indication of testosterone replacement therapy in males for conditions associated with a deficiency in endogenous testosterone. This application is under review in the Division of Bone, Reproductive, and Urologic Products (DBRUP). The Applicant did not submit a proposed REMS with this application.

2 Background

2.1 PRODUCT INFORMATION

Tlando, a 505(b)(2) application, is an androgen proposed for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Testosterone undecanoate, a fatty acid ester of testosterone, is an inactive prodrug hydrolyzed by esterases to testosterone. When taken orally, testosterone undecanoate avoids first pass metabolism as it is absorbed by the intestinal lymphatics.[1] Tlando is proposed as an oral capsule to be taken as 225 mg twice daily and available in 112.5 mg capsules. Tlando is likely to be initiated on an outpatient basis.

Aveed, an injectable testosterone undecanoate, is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risk of pulmonary oil embolism and anaphylaxis. Oral testosterone undecanoate is available as Andriol Testocaps in Canada and Europe. Both Xyosted, a subcutaneous testosterone enanthate product approved on September 28, 2018, and Jatenzo, an oral testosterone

undecanoate product approved on March 28, 2019 have a boxed warning due to a potential increase in MACE due to an increase in blood pressure. A table detailing the currently approved testosterone replacement therapies is included in Appendix 10.2.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208088 relevant to this review:

- **08/25/2015:** NDA 208088 submission for testosterone undecanoate replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone (primary hypogonadism and hypogonadotropic hypogonadism).
- **06/28/2016:** Complete response (CR) letter issued due to impractical dose titration scheme that would provide improper dosing to patients and a nonclinical adrenal adverse signal in dogs and rats.
- **10/06/2016:** Type A Post Action meeting held between DBRUP and Applicant. The excessive testosterone C_{max}, high trial dropout rate, and dihydrotestosterone (DHT) and estrogen level testing were discussed. The difference in testosterone assays from screening to trial and the limitations of dosing titrations were also brought up.
- **08/08/2017:** Resubmission of NDA 208088.
- **11/13/2017:** Amendment dated 11/10/2017 received, required a Division of Cardiovascular and Renal Products (DCRP) consult due to blood pressure measurements in trials taken only by cuff, not ambulatory blood pressure monitor (ABPM) and at all morning visits.
- **11/14/2017:** Major amendment acknowledgement letter sent to the Applicant in response to the Applicant's amendment dated 11/10/2017 containing information in response to IR questions on sample collection method, accounting for testosterone undecanoate to testosterone *ex vivo* conversion, detailed descriptions of blood pressure monitoring methods, along with demographic breakdowns and subgroup analysis of blood pressure data, as well as hypertension and increased blood pressure adverse event and discontinuation narratives; PDUFA goal date extended to May 8, 2018.
- **01/10/2018:** Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting was convened to discuss whether the safety of Tlando has been adequately characterized in regard to cardiovascular risk factors, supraphysiologic DHT concentrations, subjects with maximum testosterone concentrations exceeding prespecified targets, and adrenal findings. The need for added safety data to be pro-approval or post-approval is also discussed. The appropriateness of the dosing titration regimen to identify patients requiring titration or discontinuation was highlighted, as was the appropriateness of the use of NaF/EDTA blood collection tubes. The AC voted 13-6 against approval. The committee discussed the use of a REMS and the need for an ambulatory blood pressure monitor (ABPM) study pre-approval as reasons to their votes.
- **05/08/2018:** Complete response letter issued due to questions as to the extent of *ex vivo* conversion of testosterone undecanoate to testosterone using the recommended sample collection method, and because of this conversion disparity, the percentage of patients who had

an unacceptably high testosterone C_{max} may be skewed, which may change the results of a pivotal efficacy study. Due in part to the potentially unreliable data, as well as other concerns regarding the questionable calculation T concentrations, the Agency had concerns that a sample time of 7-9 hours post dose was in fact acceptable in determining who should discontinue Tlando. Also, the Agency had concerns that Tlando, along with another oral twice-daily dosed testosterone had clinically meaningful increases in blood pressure. Tlando lacked the ABMP study that the other product submitted, therefore true cardiovascular risk could not be determined, and the Agency noted the need for this study to be completed prior to resubmission

- **07/19/2018:** Type A Post-Action Meeting was held to address the deficiencies in the May 2018 CR letter.
- **05/09/2019:** Resubmission of NDA 208088.

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. Xyosted, a subcutaneous formulation of testosterone enanthate, was approved in September of 2018 and carries a boxed warning for an increased risk of MACE due to an increase in blood pressure. Jatenzo, an oral testosterone undecanoate formulation was approved on March 28, 2019 with the same boxed warning regarding increased risk of MACE due to increase in blood pressure. A table detailing the currently approved testosterone replacement therapies is included in Appendix 10.2.

4 Benefit Assessment

The original submission's clinical development program included 6 studies; pivotal Phase 3 safety and efficacy 52-week LPCN 1021-13-001 (NCT02081300), as well as LPCN 1021-09-001, S361.1.001, M12-778 (NCT01346319), M13-293, and LPCN 1021-14-001. The first complete response added two new trials LPCN 1021-16-003 (NCT03242408) and LPCN 1021-16-002 (NCT03242590). These studies are discussed in a previous DRISK review from March 22, 2018.[6]

The second complete response added three new non-efficacy trials, LPCN 1021-18-001 (NCT03868059), LPCN 1021-18-002, and LPCN 1021-18-003. These trials included one for ambulatory blood pressure monitoring, and two trials to evaluate the influence of blood collection tubes on serum testosterone.

LPCN 1021-18-001 (NCT03868059) was an open-label, single arm, multicenter ABPM trial of hypogonadal men treated with Tlando for an average of 4 months. The study included a collection of 24-four ABPM data at both baseline and at visit 5 (approx. 4 months after first dose). The primary safety endpoint of the study was the average increase in 24-hour systolic blood pressure (SBP), as well as determining the average 24-hour increase in diastolic blood pressure (DBP), and heart rate (HR). The study contained an exploratory subgroup of patients with higher baseline cardiovascular risk based on their Framingham Risk Score.

The current submission also included LPCN 1021-18-002 and LPCN 1021-18-003, both open label, single dose studies in hypogonadal men to evaluate the influence of blood collection tubes on serum testosterone and testosterone concentrations in the presence of testosterone undecanoate following a single dose of Tlando given to healthy and hypogonadal males. In trial LPCN 1021-18-003, subject's blood was collected pre-dose and 3 and 3 hours post dose. It was collected in plasma EDTA (K2E), Serum Separation (SST), and NaF/Na_2EDTA (NaF) tubes. The tubes were either refrigerated, left at room temperature for 30-120 minutes, or sat on ice for 15-90 minutes. The percent difference of testosterone concentrations was compared to the control K2E tubes, and the bioequivalence of testosterone (T) concentration in SST was determined to be within the limits of 80% and 125% with a 90% confidence interval. The Applicant determined that SST tubes can have a clotting time up to 120 minutes in clinical

practice. The concentration of T increased at both 3 and 5 hours post dose, but the concentrations of T and testosterone undecanoate (TU) appeared to be lower in the NaFE tubes vs. the K2E and SST tubes. Trial LCPN 1021-18-002 blood samples drawn pre-dose and 3 hours post dose into serum tubes with NaF (an enzyme inhibitor), and 3 tubes without NaF: Plane Rapid Serum Tubes (RST), Plain Serum Separator Tubes (SST), and Plain Red Top Tubes (RTT). These were used to determine the impact of *ex vivo* TU to T conversion. The Applicant observed no meaningful difference seen in T concentrations processed under the same conditions in tubes with an enzyme inhibitor vs. those without, the post-TU dose and pre-TU dose trends observed with RST, RTT, and SST are not significantly different than NaF tubes (ex vivo TU to T conversion is not contributing to serum T concentrations), and a validation of their recommended clotting time of 30 minutes.

The pivotal Phase 3 safety and efficacy study LPCN 1021-13-001 was multicenter, open-label, active control, and parallel-group, with 210 hypogonadal males randomized to Tlando, and 105 randomized to AndroGel 1.62% for 52 weeks. Primary efficacy endpoint was >75% of subjects' testosterone C_{avg} within the normal range of 300-1140 ng/dL at week 13 of treatment, min lower bound of the 95% confidence interval (CI) to be at least 65%. Secondary endpoints were defined as meeting the FDA goals of subjects with testosterone C_{max} <1500ng/dL being >85%, subjects with C_{max} 1800-2500 ng/dL <5%, and no subjects over 2500 ng/dL. In the May 8, 2018, complete response letter to Lipocine, concerns over the findings of high testosterone C_{max} were outlined. In the clinical review dated March 12, 2018, it is noted that the Pivotal Phase 3 study did not prove that Tlando can maintain testosterone levels in the eugonadal range without excursions beyond acceptable upper limits of testosterone C_{max}.[7]

Study LPCN 1021-16-002 enrolled ninety-five hypogonadal adult males in the open-label, single-treatment, unblinded study at 2 centers around the United States. The subjects' serum testosterone had to be <300ng/dL in 2 successive morning samples after a washout period from any other androgen replacement therapy, as well as having undergone a physical exam. They received 225 mg Tlando twice daily with food, (no dietary restrictions), for 24 days +/- 4 days, and on day 24, subjects entered a 38 hour confinement and blood was drawn before the morning dose, at post-dose hours 2, 3, 4, 5, 6, 8, 12 (before pm dose), 14, 15, 16, 17, 18, 20, and 24. This pharmacokinetic data indicated the peak serum level of testosterone was reached at 4-6 hours after dosing.

The Applicant set an efficacy goal of 80% of subjects in eugonadal testosterone range of 300-1080 ng/dL, with lower limit of 95% confidence interval (CI) being 75%. Secondary endpoints were 85% of subjects' testosterone C_{max} <1500 ng/dL, <5% of subjects' testosterone C_{max} 1800-2500 ng/dL, and 0 subjects' testosterone C_{max} >2500 ng/dL. The Applicant met their primary efficacy goal, with 80% of subjects' testosterone levels between 300-1080 ng/dL, (95% CI 72%, 88%). However, only 74% of subjects had testosterone C_{max} of <1500 ng/dL; 14% of subjects' testosterone C_{max} was 1800-2500 ng/dL, and 1 subject had a level >2500 ng/dL. The single outlier was explained by the Applicant as being a protocol violation, as the subject had a prior cholecystectomy, which would have excluded him from participating in the study. It did not adequately explain the other outliers of the 1800-2500 ng/dL level, besides stating the maximum concentrations are transient.

Lipocine also submitted LPCN 1021-16-003, an open label, multicenter, single-treatment efficacy study of Tlando on 100 hypogonadal men using a 150 mg three times daily dosing scheme. It had the same

primary and secondary efficacy endpoints as LPCN 1021-16-002. While it only achieved 69% of subjects in the eugonadal range, all C_{max} values were within agency limits.

DBRUP has concerns over the number of subjects' testosterone C_{max} levels that exceeded the Agency's acceptable thresholds, the unknown amount of time that subjects were above acceptable C_{max} threshold daily, the use of pharmacokinetic data from a short-term study to determine clinical safety implications, and the lack of long-term adverse event data in subjects who exceed acceptable testosterone C_{max} levels. The May 8, 2018 complete response letter included the Agency's concerns over findings of high testosterone C_{max} and the clinical reviewer previously noted that the Pivotal Phase 3 study did not prove that Tlando can maintain testosterone levels in the eugonadal range without excursions beyond acceptable upper limits of testosterone C_{max}. The new information submitted from studies LCPN-1021-002 and LCPN 1021-18-003 is not reassuring in that when calculating for a testosterone to testosterone undecanoate conversion in test tubes, determined from the current submission's new pharmacokinetic studies, the efficacy studies still did not meet the secondary endpoint of the proportion of treated subjects with testosterone C_{max} (0-24 hours) within previously noted Agency predetermined limits.

5 Risk Assessment & Safe-Use Conditions

The original pooled safety analysis included 6 studies; pivotal Phase 3 safety and efficacy 52-week study LPCN 1021-13-001, as well as LPCN 1021-09-001, S361.1.001, M12-778, M13-293, and 1021-14-001. The first resubmission safety database included all the above plus new trials LPCN 1021-16-003 and LPCN 1021-16-002. The current resubmission includes all the previous trials and new studies LPCN 1021-18-001 and LPCN 1021-18-003. The safety databases are hereafter referred to as Original Integrated Safety Summary (ISS1), second ISS (ISS2), and third ISS (ISS3), in accordance with the Applicant's nomenclature. The Original ISS (ISS1) included data from 381 subjects, and the first Resubmission ISS (ISS2) includes 525 subjects. The current ISS (ISS3) is comprised of data from 654 subjects and is the subject of this review.

The most commonly seen treatment-emergent related adverse events in ISS3 were headache, increase in hematocrit, and acne. Headache was the most commonly occurring treatment-related treatment-emergent adverse event, occurring in 1.5% of Tlando subjects, 2.9% of Andriol 80 mg subjects, 3.8% of Androgel 1.62% subjects, and no placebo subjects in ISS3. No deaths and no major adverse cardiac events were noted in any of the trials.

The clinical reviewer has concerns regarding the 6 (4.6%) subjects who experienced an increase in hematocrit from normal range at baseline of study LPCN 1021-18-001 to levels that were above the acceptable range of 35% – 54%. This effect was seen with Tlando therapy for approximately 110 days and concerns the clinical reviewer as it may demonstrate insufficient exposure for long term safety data.

Due to findings of minimal to moderate diffuse adrenal cortical vacuolation in all treated male rats and moderate to marked adrenal cortical atrophy in all treated male dogs potentially causing adrenal insufficiency in the first submission, an ACTH stimulation test was performed on 68 subjects at baseline at 3 weeks after treatment on FDA recommendation for ISS2. 62 subjects had normal levels both at baseline and end of study, 1 had a normal baseline, but was abnormal at the end of study, and 5 had

abnormal ACTH at baseline, making the results uninterpretable. The Applicant will be advised to resubmit further assessment. For Tlando, like other testosterone products, this may be accomplished via a Post Marketing Study Requirement upon product approval.

5.1 ADVERSE EVENT OF SPECIAL INTEREST

5.1.1 Increase in Blood Pressure That May Cause Increase in Major Adverse Cardiac Events (MACE)

In all trials in ISS2, only cuff measurements were taken of subjects' blood pressure. All cuff readings were done at the morning visit with subjects at rest for 5 minutes and no blood pressure measurements from any other time of day are known. The outcomes of the cuff pressures ISS2 are outlined in the DRISK review dated March 22, 2018. As cuff pressure readings may not always provide accurate longitudinal data, the Applicant was required to conduct ABPM studies.

In the ABPM study LPCN1021-18-001, 140 hypogonadal men were enrolled, and the Safety Set included all who received at least 1 dose of Tlando (N = 138), while the Full Analysis Set included only those with valid ABPM at visits 3 (baseline) and 5 (post treatment). The study demonstrated clinically significant increases in 24-hour systolic, diastolic, and average blood pressure, and clinically significant increases in heart rate. The Division of Cardiovascular and Renal Products (DCRP) review of the data of LPCN 1021-18-001 noted that several subjects' data had not been included in the final analysis due to the subject starting the ABPM measurements after the selected 7 AM start time. DCRP was in favor of including all collected data as the trial protocol allowed for an evening ABPM start time. This review contains the data as interpreted in DCRP's review. The 24-hour average increase in SBP as measured by ABPM was 4.3 mmHg (95% CI 2.1, 6.5 mmHg). During this study, the corresponding cuff measured increase in 24-hour SBP was 4.8 mmHg (2.7 mmHg, 6.9 mmHg). The 24-hour average increase in DBP as measured by ABPM was 1.4 mmHg (0.5, 2.3 mmHg). During this study, the corresponding cuff measured increase in 24-hour DBP was 1.6 mmHg (0.3 mmHg, 2.9 mmHg). This study also measured mean change in 24-hour heart rate. Upon ABPM measurement, it was noted to increase 2.1 bpm (1.0, 3.1 bpm), and with cuff measurement, 2.0 bpm (0.4, 3.6 bpm). During this study, 3 subjects changed antihypertensive medications, and 2 subjects started a new antihypertensive medication while on Tlando therapy.

The Applicant also conducted a subgroup analysis of men based upon their cardiac risk score determined by the Framingham Heart Study's algorithm. In their consult from July 2019, DCRP did not concur with the Applicant's subgroup validity. The Agency's analysis of this subgroup concluded the following: for low cardiovascular risk patients, average 24-hour SBP dropped 1.5 mmHg (95% CI -6.5, 3.6), for men at moderate cardiovascular risk, blood pressure increased 3.3 mmHg (-0.1, 6.7), and for those with high cardiovascular risk, the average 24- hour SBP increased 8.0 mmHg (4.4, 11.6). Also concerning as the difference in baseline diabetic subjects. Those with diabetes had a 24-hour average SBP increase of 9.3 mmHg (5.3, 13.3), while those without diabetes at baseline's increase was 2.2 mmHg (-0.4, 4.7 mmHg). Due to the noticeable differences, DCRP recommends placing the subgroup findings in Tlando's label.[8]

6 Expected Postmarket Use

Tlando, 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 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 should be able to closely monitor the blood pressure of patients receiving Tlando, and treat increases accordingly.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Tlando beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The clinical reviewer does not recommend approval of Tlando based on the efficacy and safety information currently available.

Tlando met study primary efficacy criteria with excursions into the supratherapeutic serum testosterone range. It did not meet secondary efficacy goals. Therefore, the clinical reviewer does not recommend approval at this time as Tlando has not met efficacy goals without excursions of testosterone C_{max} into an unacceptably supratherapeutic range. The use of short-term pharmacokinetic data to determine the clinical safety of Tlando is also of concern to the clinical reviewer.

The most commonly reported treatment-emergent related adverse events in ISS3 were headache, increase in hematocrit, and acne. In an ABPM trial, Tlando 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.[9] 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 Tlando and testosterone products in general.

The clinically significant increase in 24-hour SBP seen in Tlando's ABPM study is similar to that seen in another oral testosterone product as well as an injectable testosterone. Because of this, the risk of increase in blood pressure should be conveyed in the product's labeling by a boxed warning, a concise limitation of use, noted in Warnings and Precautions, and the inclusion of a Medication Guide for patients.

9 Conclusion & Recommendations

The review division recommends a complete response based on concerns regarding the number of subjects with C_{max} excursions outside of the Agency's acceptable range and the long term clinical

implications of these excursions, the unknown amount of time those subjects spend in excursion, the use of pharmacokinetic data from a short-term study, and the use of that data to determine that C_{max} excursions are not clinically significant in a drug that is expected to be used chronically. Because the overall unfavorable benefit vs. risk assessment at this time, we are unable to formulate further recommendations for risk management, specifically REMS.

10 Appendices

10.1 REFERENCES

1. Lipocine I. Summary of Clinical Efficacy of Tlando. May 9, 2019.
2. Clinic M. Male Hypogonadism. https://www.mayoclinic.org/diseases-conditions/male-hypogonadism/doctors-departments/ddc-20354888. Accessed January 12, 2018.
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6. Cunningham C. Evaluation for the Need for a REMS on Tlando (testosterone undeanoate). March 22, 2018.
7. Kauffman M. DBRUP Clinical Review of Tlando (tesoterone undecanoate oral capsules).
8. McDowell T-Y. Interdisciplinary Review Team for Ambulatory Blood Pressure Monitoring Study Consultation Review (DCRP). July 16, 2019.
9. Cunningham C, Nguyen, C. REMS Oversight Committee Meeting regarding Xyosted (testosterone enanthate) NDA 209863. In. Vol 20182018.

10.2 CURRENTLY APPROVED TESTOSTERONE 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		
Xyosted (testosterone enanthate) subcutaneous injection, 50 mg, 75 mg, and 100 mg	TRT	50-100 mg injected once weekly	Increase in blood pressure	Boxed warning
Jatenzo (testosterone undecanoate) oral	TRT	Starting dose 237 mg daily;	Increase in blood pressure	Boxed warning

capsules, 158 mg, 198 mg, 237 mg		may titrate to 396 mg twice daily		

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/s/

COURTNEY A CUNNINGHAM
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JAMIE C WILKINS PARKER on behalf of LAURA A ZENDEL
10/18/2019 03:55:12 PM

JAMIE C WILKINS PARKER
10/18/2019 03:55:45 PM

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	208088
PDUFA Goal Date	May 8, 2018
OSE RCM #	2017-1641
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Leah Hart, PharmD
Division Director	Jamie Wilkins-Parker, PharmD
Review Completion Date	March 22, 2018
Subject	Evaluation of Need for a REMS
Established Name	Testosterone undecanoate oral
Trade Name	TLANDO
Name of Applicant	Lipocine, Inc.
Therapeutic Class	Androgen for testosterone replacement therapy
Formulation(s)	112.5mg oral capsules
Dosing Regimen	225 mg orally twice daily

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tlando (testosterone undecanoate) is necessary to ensure the benefits outweigh its risks. Lipocine, Inc. submitted a New Drug Application (NDA 208088) for Tlando with the proposed indication of testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. These conditions are primary (congenital or acquired) hypogonadism and congenital or acquired hypogonadotropic hypogonadism. Lipocine, Inc. has proposed to limit the use of Tlando in men with "age related hypogonadism" by stating that safety and efficacy has not been established in this population.

The risks associated with Tlando include headache, acne, changes in lipids, and increases in hematocrit. Additionally, another oral testosterone undecanoate product currently under review demonstrated statistically significant increases in blood pressure measurements after a 24-hour ambulatory blood pressure monitor (ABPM) study. Tlando has no study using ABPM, and therefore the risk cannot be quantified. Therefore, the application will receive a Complete Response, and require the Applicant to conduct ABPM studies in their drug.

The regulatory decision regarding the need for a REMS is based on whether a REMS is necessary to ensure the benefits outweigh the risk of the drug. In the case of Tlando the analysis of the safety profile is incomplete due to lack of an ABPM study. At this time, a final determination has not been made regarding the potential risks of this application, and therefore this reviewer is not able to determine if a REMS would be needed to ensure that the benefits outweigh the risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tlando (testosterone undecanoate) is necessary to ensure the benefits outweigh its risks. Lipocine, Inc. (Lipocine) submitted a New Drug Application (NDA 208088) for Tlando with the proposed indication of primary (congenital or acquired) hypogonadism and congenital or acquired hypogonadotropic hypogonadism. This application is under review in the Division of Bone, Reproductive, and Urologic Products (DBRUP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Tlando, a 505(b)(2) application is an androgen proposed for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. These conditions are primary (congenital or acquired) hypogonadism and congenital or acquired hypogonadotropic hypogonadism. Testosterone undecanoate, a fatty acid ester of testosterone, is an inactive pro-drug hydrolyzed by esterases to testosterone. When taken orally, testosterone undecanoate avoids first pass metabolism as it is absorbed by the intestinal lymphatics.[1] Tlando is proposed as an oral capsule to be taken as 225mg twice daily and available in 112.5 mg capsules. Tlando will likely be initiated on an outpatient basis. Topical testosterone products currently have a Medication Guide REMS due to potential skin to skin transfer to minors causing virilization. Aveed, an

injectable testosterone undecanoate, has an ETASU REMS to mitigate the risk of pulmonary oil embolism and anaphylaxis. Oral testosterone undecanoate is available as Andriol Testocaps in Canada and Europe.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208088 relevant to this review:

- 08/25/2015: NDA 208088 submission for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone (primary hypogonadism and hypogonadotropic hypogonadism)
- 06/28/2016: Complete response (CR) letter issued due to impractical dose titration scheme that would provide improper dosing to patients and a nonclinical adrenal adverse signal in dogs and rats.
- 10/06/2016: Type A Post Action meeting held between DRBUP and Applicant. The excessive testosterone $C_{max,}$ high trial dropout rate, and dihydrotestosterone (DHT) and estrogen level testing were discussed. The difference in testosterone assays from screening to trial and the limitations of dosing titrations were also brought up.
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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 300ng/dL, and symptoms are present. Testosterone replacement therapy is titrated to a therapeutic range of 400-700ng/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, and 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 formulation 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.

4 Benefit Assessment

The original submission's clinical development program included 6 studies; pivotal Phase 3 safety and efficacy 52-week study LPCN 1021-13-001, as well as LPCN 1021-09-001, S361.1.001, M12-778, M13-

293, and 1021-14-001. The complete response adds two new trials LPCN 1021-16-003 and LPCN 1021-16-002.

The pivotal Phase 3 safety and efficacy study LPCN 1021-13-001 was multicenter, open-label, active control, and parallel-group, with 210 hypogonadal males randomized to Tlando, and 105 randomized to AndroGel 1.62% for 52 weeks. Primary efficacy endpoint was $\geq$75% of subjects' testosterone C_{ave} within the normal range of 300-1140 ng/dL at week 13 of treatment, min lower bound of the 95% confidence interval (CI) to be at least 65%. Secondary endpoints were defined as meeting the FDA goals of subjects with testosterone C_{max} <1500ng/dL being $\geq$85%, subjects with C_{max} 1800-2500 ng/dL $\leq$5%, and no subjects over 2500 ng/dL. In the June 28, 2016, complete response letter to Lipocine, concerns over the findings of high testosterone C_{max} were outlined. 10.2% of subjects had a 24 hour C_{max} of 1800-2500 ng/dL, and 3.8% of subjects had a 24 hour C_{max} of >2500 ng/dL. This exceeds the Agency's set limitations of $\leq$5% and 0%, respectively. However, due to the dose titration scheme deficiencies, this study was insufficient to review as per the clinical reviewer, Dr. Martin Kauffman, in a review dated June 7, 2016.

Study LPCN 1021-16-002 enrolled ninety-five hypogonadal adult males in the open-label, single-treatment, unblinded study at 12 centers around the United States. The subjects' serum testosterone had to be <300ng/dL in 2 successive morning samples after a washout period from any other androgen replacement therapy, as well as having undergone a physical exam. They received 225 mg Tlando twice daily with food, (no dietary restrictions), for 24 days +/- 4 days, and on day 24, subjects entered a 38 hour confinement and blood was drawn before the morning dose, at post-dose hours 2, 3, 4, 5, 6, 8, 12 (before pm dose), 14, 15, 16, 17, 18, 20, and 24. This pharmacokinetic data indicated the peak serum level of testosterone was reached at 4-6 hours after dosing.

The Applicant set an efficacy goal of 80% of subjects in eugonadal testosterone range of 300-1080 ng/dL, with lower limit of 95% confidence interval (CI) being 75%. Secondary endpoints were 85% of subjects' testosterone C_{max} $\leq$1500 ng/dL, $\leq$5% of subjects' testosterone C_{max} 1800-2500 ng/dL, and 0% of subjects' testosterone C_{max} >2500 ng/dL. The Applicant met their primary efficacy goal, with 80% of subjects' testosterone levels between 300-1080 ng/dL, (95% CI 72%, 88%). However, 14% of subjects' testosterone C_{max} was 1800-2500 ng/dL, and 1 subject had a level >2500 ng/dL. This was explained by the Applicant as being a protocol violation, as the single subject had a prior cholecystectomy, which would have excluded him from participating in the study. It did not explain the other outliers of lower levels, besides stating the maximum concentrations are transient. The clinical reviewer, noted that these excursions over accepted maximum values must be brought back to Agency standards before approval can occur.

Lipocine also submitted LPCN 1021-16-003, an open label, multicenter, single-treatment efficacy study of Tlando on 100 hypogonadal men using a 150 mg three times daily dosing scheme. It had the same primary and secondary efficacy endpoints as LPCN 1021-16-002. While it only achieved 69% of subjects in the eugonadal range, all C_{max} values were within agency limits.

DBRUP has concerns over the testosterone Cmax levels and stopping criteria, as Tlando is only studied as a single dose, and is not to be titrated to achieve eugonadal serum levels. It is also of importance that

Lipocine has used standard serum collection tubes, which do not account for potential ex vivo conversion of testosterone undecanoate to testosterone. This potentially invalidates the efficacy study, and the Applicant will be informed of the need to provide evidence that there is no ex vivo conversion in their complete response.

5 Risk Assessment & Safe-Use Conditions

In the June 28, 2016, complete response letter, it was noted that at that time, the safety database from the original submission was potentially sufficient, barring any further safety signals. The original pooled safety analysis included 6 studies; pivotal Phase 3 safety and efficacy 52-week study LPCN 1021-13-001, as well as LPCN 1021-09-001, S361.1.001, M12-778, M13-293, and 1021-14-001. The resubmission safety database included all the above plus new trials LPCN 1021-16-003 and LPCN 1021-16-002. They are hereafter referred to as Original Integrated Safety Summary (ISS) and Resubmission ISS, in accordance with the Applicant's nomenclature. The Original ISS included data from 381 subjects, and the Resubmission ISS includes 525 subjects. Therefore, information from both the OSS and ISS is included in this risk assessment, for a total of 906 patients in the safety database.

The most commonly seen adverse events were headache, acne, upper respiratory infection, and weight gain. Headache was the most commonly occurring treatment-related treatment-emergent adverse event, occurring in 1.7% of Tlando subjects, 2.9% of Andriol 80 mg subjects, 3.8% of Androgel 1.62% subjects, and no placebo patients in the Resubmission ISS. No deaths and no major adverse cardiac events were noted in any of the trials. In the Original ISS, 6 total patients (1.6%) had treatment-emergent hypertension, and 3 had an increase in blood pressure. In the Resubmission ISS, 7 total patients (1.3%) had treatment-emergent hypertension, and no additional were categorized with an increase in blood pressure. The hyperlipidemia rate in the Original ISS was 0.3%, and in Resubmission ISS, it fell to 0.2%. Rates of hematocrit increases were similar as well. In the Original ISS, the rate was 1%; it fell to 0.8% in the Resubmission ISS.

Due to findings of minimal to moderate diffuse adrenal cortical vacuolation in all treated male rats and moderate to marked adrenal cortical atrophy in all treated male dogs potentially causing adrenal insufficiency in the first submission, an ACTH stimulation test was performed on 68 subjects at baseline at 3 weeks after treatment on FDA recommendation. 62 subjects had normal levels both at baseline and end of study, 1 had a normal baseline, but was abnormal at the end of study, and 5 had abnormal ACTH at baseline, making the results uninterpretable. The Sponsor will be advised to resubmit further assessment.

5.1 Theoretical increase in blood pressure that may lead to an Increase in Major Adverse Cardiac Events

In all trials in the Resubmission ISS, only cuff measurements were taken of subjects' blood pressure. All cuff readings were done at the morning visit with subjects at rest for 5 minutes, so no blood pressure measurements from any other time of day are known. These cuff readings changed very little from baseline to trial exit. In the Original ISS, the mean baseline systolic blood pressure was 119.7 mmHg

(Standard Deviation [SD] +/- 12.96), and it fell 0.4 mmHg (SD +/- 14.19). In the Resubmission ISS, the baseline systolic blood pressure (SBP) was 124.4 mmHg (SD +/- 13.97), and it increased 0.9 mmHg (SD +/- 13.21). In the Original ISS, the mean baseline diastolic blood pressure was 77.1 mmHg (SD +/- 8.13), and it fell 0.6 mmHg (SD +/- 8.71). In the Resubmission ISS, the baseline diastolic blood pressure was 78.7 mmHg (SD +/- 8.93), and it decreased 0.2 mmHg (SD +/- 8.10).[6]

It is notable that a consult by DCRP found that one study, LPCN 1021-16-003, demonstrated a greater mean increase in systolic blood pressures. 98 subjects who completed this 25 day trial who received a dose of 150mg of Tlando three times daily had a mean increase in SBP of 4.3 mmHg (SD 12.00) (95% CI -3.0, 12.0) at the end of study.

It is important to note that only a slight increase in cuff pressure was noted with another oral testosterone undecanoate, however the ABPM studies demonstrated a statistically significant increase in 24-hour blood pressure readings. The lack of an ABPM study with Tlando is concerning and the Applicant will be directed to conduct an ABPM study for their resubmission. Due to this unknown, the safety of Tlando cannot be adequately expressed in regards to the increase in blood pressure at this time.

6 Expected Postmarket Use

Tlando is likely to be prescribed by endocrinologists, urologists, and general practitioners. It is expected to be dispensed and taken by patients in the outpatient setting. Prescribers have a major role in monitoring the testosterone blood levels of patients to ensure effectiveness, and The Endocrinology Society recommends monitoring testosterone and hematocrit at baseline, at 3-6 months post initiation, and annually afterwards.[5]

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for TLANDO beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Hypogonadism affects males of all ages, and can be a challenge to treat with the currently available therapies. Although there is an unmet need for a new route of administration, approved therapies are available, and new formulations must be safe and effective for patients to use, potentially for a lifetime.

The Clinical Reviewer does not recommend approval of TLANDO due to the lack of necessary safety information and unmet Agency standards regarding the maximum testosterone concentrations in clinical trial subjects. At the time of this review, it has not been determined that the benefits of the drug outweigh the risks, therefore DRISK is unable to assess whether a REMS for Tlando is necessary. The theoretical risk of an increase in blood pressure must be further characterized via an ABPM study before DRISK is able to make a determination of whether a REMS for Tlando is necessary to ensure the benefits outweigh the risks.

9 Conclusion & Recommendations

The review division recommends a complete response on the basis that the demonstrated benefit was insufficient to outweigh potential yet to be studied safety concerns. Evaluation of the need for a REMS for Tlando will be undertaken by DRISK after the Applicant addresses and responds to issues in the CR letter. Please send DRISK a new consult request at such time.

10 Appendices

10.1 References

1. Lipocine, Inc. TLANDO-Summary of Clinical Efficacy. July 25, 2017.
2. Clinic M. Male Hypogonadism. Vol 2018Updated 09/29/2016.
3. Faimen C. Male Hypogonadism. 2012.
4. NIH-US National library of Medicine Genetics Home Reference Klinefelter Syndrome. 2018.
5. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism.* 2010;95(6):2536-2559.
6. Lipocine, Inc. TLANDO Summary of CLincal Safety. July 27, 2017.

10.2 Currently Approved Testosterone Products

Product Trade 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	Box Warning Medication Guide REMS
Androgel (testosterone) gel, 1%	TRT	50 mg TD daily	Skin to skin transfer to children-virilizing effects	Box 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	Box Warning Medication Guide REMS
Androderm (testosterone) film, 2 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	Box 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	Box Warning Medication Guide REMS
Android (methyltestosterone) tablet, 10 and 25 mg	TRT	10-50 mg by mouth (PO) daily	Elevated liver enzyme	
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.	Box Warning ETASU REMS
Delatestryl (testosterone	TRT	50-400 mg IM q2-4 weeks		

enanthate) injection, 200 mg/ml				
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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/s/

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