

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208088Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TLANDO™ safely and effectively. See full prescribing information for TLANDO.

TLANDO (testosterone undecanoate) capsules, for oral use, CIII
Initial U.S. Approval: 1953

WARNING: BLOOD PRESSURE INCREASES

See full prescribing information for complete boxed warning

- TLANDO can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death (5.1, 5.3, 6.1).
- Before initiating TLANDO, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled (5.1, 5.3).
- Periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension and re-evaluate whether the benefits of TLANDO outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease on treatment (5.1, 5.3).
- Due to this risk, use TLANDO only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies (1, 4).

INDICATIONS AND USAGE

TLANDO is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (1).

Limitations of Use

- Safety and efficacy of TLANDO in males less than 18 years old have not been established (1).

DOSAGE AND ADMINISTRATION

- Prior to initiating TLANDO, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range (2.2).
- Recommended dosage is 225 mg orally twice daily with food (2.3).
- Monitor serum testosterone after initiating TLANDO to determine if TLANDO should be continued or discontinued (2.3).

DOSAGE FORMS AND STRENGTHS

Capsules: 112.5 mg (3)

CONTRAINDICATIONS

- Carcinoma of the breast or known or suspected carcinoma of the prostate (4)
- Women who are pregnant. Testosterone may cause fetal harm (4, 5.7, 8.1)
- Hypersensitivity to TLANDO or any of its ingredients (4)
- Hypogonadal conditions not associated with structural or genetic etiologies (4)

WARNINGS AND PRECAUTIONS

- **Polycythemia:** Monitor hematocrit approximately every 3 months during the first year after beginning TLANDO and then every 6 months thereafter during treatment. Discontinue TLANDO if necessary (5.2).
- **Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer:** Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. Evaluate patients for prostate cancer, including monitoring prostate specific antigen (PSA) prior to initiating and during treatment with androgens (5.4).
- **Venous thromboembolism (VTE):** VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Discontinue TLANDO if VTE is suspected and initiate appropriate workup and management (5.5).
- **Abuse of Testosterone and Monitoring of Serum Testosterone:** If testosterone use at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids is suspected, check serum testosterone concentration (5.6).
- **Potential for Adverse Effects on Spermatogenesis:** TLANDO may cause azoospermia (5.8, 8.3).
- **Edema:** Edema, with or without congestive heart failure (CHF) may occur in patients with preexisting cardiac, renal, or hepatic disease. Discontinue TLANDO and initiate appropriate workup (5.10).
- **Sleep Apnea:** TLANDO may potentiate sleep apnea in those with risk factors (5.11).
- **Lipid Changes:** Testosterone may affect serum lipid profile. Monitor patient lipid concentrations; if necessary, adjust dosage of lipid lowering drug(s) or discontinue TLANDO (5.13).
- **Increases in Prolactin:** Monitor serum prolactin levels prior to initiation of TLANDO and 3 to 4 months after starting TLANDO. Discontinue TLANDO if serum prolactin levels remain elevated (5.16).

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 2\%$): increased blood prolactin, hypertension, increased hematocrit, upper respiratory tract infection, weight increased, headache, and musculoskeletal pain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Antares at 1-855-287-7476 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Insulin:** In patients with diabetes, concomitant use with TLANDO may decrease blood glucose and insulin requirements (7.1).
- **Oral Anticoagulants:** Concomitant use with TLANDO may cause changes in anticoagulant activity. Monitor International Normalized Ratio and prothrombin time frequently (7.2).
- **Corticosteroids:** Concomitant use with TLANDO may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3).
- **Drugs that May Also Increase Blood Pressure:** Concomitant use with TLANDO may lead to additional increases in blood pressure (7.4).

USE IN SPECIFIC POPULATIONS

Geriatric Patients: Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH and hypertension (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2022

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FULL PRESCRIBING INFORMATION

WARNING: BLOOD PRESSURE INCREASES

- **TLANDO can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with greater risk in patients with established cardiovascular disease or risk factors for cardiovascular disease [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].**
- **Before initiating TLANDO, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled [see Warnings and Precautions (5.3)].**
- **Three weeks after initiating therapy monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension [see Warnings and Precautions (5.1)].**
- **Re-evaluate whether the benefits of TLANDO outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease on treatment [see Warnings and Precautions (5.3)].**
- **Due to this risk, use TLANDO only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies [see Indications and Usage (1) and Contraindications (4)].**

1 INDICATIONS AND USAGE

TLANDO is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle stimulating hormone (FSH), luteinizing hormone (LH)) above the normal range [see Dosage and Administration (2.2)].
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range [see Dosage and Administration (2.2)].

Limitations of Use

Safety and efficacy of TLANDO in males less than 18 years old have not been established [see Use in Specific Populations (8.4)].

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

TLANDO is not substitutable with other oral testosterone undecanoate products.

2.2 Confirmation of Hypogonadism Before Initiation of TLANDO

Prior to initiating TLANDO, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

2.3 Recommended Dosage

The recommended dosage of TLANDO is 225 mg (taken as two 112.5 mg capsules), orally twice daily, once in the morning and once in the evening. Take with food.

Monitoring for Continued Use or Discontinuation

Monitor serum testosterone (8 to 9 hours after the morning dose) 3 to 4 weeks after initiating TLANDO, and periodically thereafter. Based on serum testosterone measurements, determine if TLANDO should be continued or discontinued:

- Serum testosterone 300 - 1080 ng/dL: continue TLANDO
- Serum testosterone < 300 ng/dL: discontinue TLANDO
- Serum testosterone > 1080 ng/dL: discontinue TLANDO

3 DOSAGE FORMS AND STRENGTHS

Capsules: 112.5 mg, white opaque body imprinted with “112” in black ink and grey opaque cap, banded with a colorless gelatin band.

4 CONTRAINDICATIONS

TLANDO is contraindicated in:

- Patients with carcinoma of the breast or known or suspected carcinoma of the prostate [*see Warnings and Precautions (5.4)*].
- Women who are pregnant. Testosterone can cause virilization of the female fetus when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].
- Known hypersensitivity to testosterone undecanoate or any of TLANDO’s ingredients [*see Description (11)*].
- Men with hypogonadal conditions, such as “age-related hypogonadism”, that are not associated with structural or genetic etiologies. The efficacy of TLANDO has not been established for these conditions, and TLANDO can increase BP that can increase the risk of MACE [*see Boxed Warning and Warning and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Blood Pressure

In Study 18-001, TLANDO increased systolic BP after 4 months of treatment by an average of 4.3 mmHg based on ambulatory blood pressure monitoring (ABPM) and 4.8 mmHg from baseline based on blood pressure cuff measurements [*see Adverse Reactions (6.1)*].

These BP increases can increase the risk of major adverse cardiovascular events (MACE), with greater risk in patients with established cardiovascular disease or risk factors for cardiovascular disease.

In some patients, the increase in BP with TLANDO may be too small to detect but can still increase the risk for MACE.

Before initiating TLANDO, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled. Check BP approximately 3 weeks after initiating TLANDO and periodically thereafter. Treat new-onset hypertension or exacerbations of pre-existing hypertension. Re-evaluate whether the benefits of continued treatment with TLANDO outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease.

5.2 Polycythemia

Increases in hematocrit levels, reflective of increases in red blood cell mass, may require discontinuation of TLANDO. Check hematocrit prior to initiating TLANDO. Evaluate hematocrit approximately every 3 months during the first year of treatment, and then every 6 months thereafter while the patient is taking TLANDO. If hematocrit becomes elevated, stop TLANDO until hematocrit decreases to an acceptable concentration. If TLANDO is restarted and again causes hematocrit to become elevated, stop TLANDO permanently. An increase in red blood cell mass may increase the risk of thromboembolic events [see *Warnings and Precautions (5.5)*].

5.3 Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men.

TLANDO can cause BP increases that can increase the risk of MACE [see *Boxed Warning and Warnings and Precautions (5.1)*]. Patients should be informed of this possible risk when deciding whether to use or to continue to use TLANDO.

5.4 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

- Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer, including measurement of prostate specific antigen (PSA), prior to initiating and during treatment with androgens [see *Contraindications (4)*].

5.5 Venous Thromboembolism

There have been post marketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone replacement products such as TLANDO. Evaluate patients who report symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue TLANDO and initiate appropriate workup and management [see *Adverse Reactions (6.2)*].

5.6 Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions [see *Drug Abuse and Dependence (9)*].

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

5.7 Not for Use in Women

Due to lack of controlled studies in women and the potential for virilizing effects, TLANDO is not indicated for use in women [see *Use in Specific Populations (8.1, 8.2)*].

5.8 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including TLANDO, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) possibly leading to adverse effects on semen parameters including sperm count [see *Use in Specific Populations (8.3)*]. Patients should be informed of this possible risk when deciding whether to use or to continue to use TLANDO.

5.9 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. TLANDO is not a 17 alpha-alkyl androgen and is not known to produce hepatic adverse effects associated with 17-alpha-alkyl androgens. Nonetheless, patients should be instructed to report any signs or symptoms of hepatic dysfunction (e.g., jaundice). If these occur, promptly discontinue TLANDO while the cause is evaluated.

5.10 Edema

Androgens, including TLANDO, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease [see *Adverse Reactions (6.1)*]. In addition to discontinuation of the drug, appropriate work up and management of edema may be required.

5.11 Sleep Apnea

The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.

5.12 Gynecomastia

Gynecomastia may develop and persist in patients being treated for hypogonadism.

5.13 Lipid Changes

Changes in serum lipid profile may require dose adjustment of lipid lowering drugs or discontinuation of testosterone therapy. Monitor the lipid profile periodically after starting testosterone therapy.

5.14 Hypercalcemia

Androgens, including TLANDO, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Monitor serum calcium concentrations periodically in these patients.

5.15 Decreased Thyroxine-binding Globulin

Androgens, including TLANDO, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of triiodothyronine (T3) and thyroxine (T4). Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.16 Increases in Prolactin

Increases in serum prolactin have been reported in patients treated with TLANDO in clinical trials. Evaluate serum prolactin levels prior to initiating treatment with TLANDO. Re-evaluate serum prolactin levels 3 to 4 months after starting treatment. If serum prolactin remains elevated, discontinue TLANDO [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Increase in Blood Pressure [see *Warnings and Precautions (5.1)*]
- Polycythemia [see *Warnings and Precautions (5.2)*]
- Cardiovascular Risk [see *Warnings and Precautions (5.3)*]
- Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer [see *Warnings and Precautions (5.4)*]
- Venous Thromboembolism [see *Warnings and Precautions (5.5)*]
- Hepatic Adverse Effects [see *Warnings and Precautions (5.9)*]
- Edema [see *Warnings and Precautions (5.10)*]
- Sleep Apnea [see *Warnings and Precautions (5.11)*]
- Gynecomastia [see *Warnings and Precautions (5.12)*]
- Lipid Changes [see *Warnings and Precautions (5.13)*]
- Hypercalcemia [see *Warnings and Precautions (5.14)*]
- Decreased Thyroxine-binding Globulin [see *Warnings and Precautions (5.15)*]
- Increases in Prolactin [see *Warnings and Precautions (5.16)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TLANDO 225 mg twice daily, without dose titration, was evaluated in 233 hypogonadal males during two clinical studies: Study LPCN 1021-18-001 (18-001) and Study LPCN 1021-16-002 (16-002) [see *Clinical Studies (14)*].

In Study 18-001, an uncontrolled ambulatory blood pressure monitoring (ABPM) study, 138 hypogonadal males were treated with TLANDO 225 mg twice daily with morning and evening meals for approximately four months. Patients had a median age of 54 years (range 26-75), 79% were White, 18% were Black, and 2% were Asian. In 138 hypogonadal male patients, 70% (n=96) were obese (BMI ≥ 30 kg/m²), 24% (n=33) reported a history of type 2 diabetes, and 48% (n=66) reported a history of hypertension.

Table 1 summarizes adverse reactions ($\geq 2\%$) reported in patients receiving TLANDO in

Study 18-001.

Table 1. Adverse Reactions $\geq 2\%$ in Patients Receiving TLANDO in Study 18-001

Adverse Reaction	Overall (N=138) n (%)
Hypertension	7 (5.1)
Hematocrit increased	6 (4.3)
Upper respiratory tract infection	5 (3.6)

Four of the 138 patients (2.9%) in Study 18-001 reported adverse reactions that led to premature discontinuation from the study, including dizziness (n=1), weight increased (n=1), insomnia (n=1), and hypertension (n=2).

In Study 16-002, 95 hypogonadal males were treated with TLANDO 225 mg twice daily with morning and evening meals for approximately 24 days. The dose of TLANDO was not titrated. Patients had a median age of 56 years (range 29-74), 81% were White, 16% were Black, 2% were mixed race, and 1% were Asian; 26% were Hispanic. In 95 hypogonadal male patients, 70% (n=66) were obese (BMI ≥ 30 kg/m²), 23% (n=22) reported a history of type 2 diabetes, and 50% (n=47) reported a history of hypertension.

Table 2 summarized adverse reactions ($\geq 2\%$) reported during Study 16-002 in patients receiving TLANDO.

Table 2. Adverse Reactions $\geq 2\%$ in Patients Receiving TLANDO in Study 16-002

Adverse Reaction	Overall (N=95) n (%)
Blood prolactin increased	6 (6.3)
Weight increased	2 (2.1)
Headache	2 (2.1)
Musculoskeletal pain	2 (2.1)

One of the 95 patients (1.1%) in the 24-day study reported an adverse reaction (gastric ulcer hemorrhage) that led to premature discontinuation from the study.

Blood Pressure Increases

In Study 18-001 24-hour ambulatory blood pressure monitoring (ABPM) was conducted in 138 male patients, 126 of whom completed the study. ABPM was conducted at 2 distinct 24-hour time periods: at baseline and following approximately 16 weeks of treatment with TLANDO. A total of 123 patients had acceptable 24-hour ABPM recordings at both time periods. In that group, the mean change in systolic BP from Baseline to End of Study was + 4.3 mmHg (95% CI 2.1, 6.5) and the mean change in diastolic BP was 1.4 mmHg (95% CI 0.5, 2.3).

The ABPM systolic and diastolic blood pressure increased in patients with a history of hypertension at baseline [4.8 mmHg (95% CI 1.0, 8.5) and 1.6 mmHg (95% CI 0.1, 3.0), respectively (n=60)]. In patients with no history of hypertension at baseline systolic and diastolic blood pressure increased [3.9 mmHg (95% CI 0.9, 6.8) and 1.2 mmHg (95% CI -0.1, 2.5), respectively (n =63)].

Increases in Hematocrit

Increases in hematocrit were reported in 6 of the 138 patients (4.3%) in Study 18-001. None of these increases led to premature discontinuation of TLANDO.

Increases in Prolactin

Increases in serum prolactin were reported in 6 (6.3%) of the 95 patients in the 24-day clinical study. The mean increase from baseline in serum prolactin was 7.0 ng/mL (n=93). The 4-month clinical study did not assess serum prolactin concentrations after the screening visit.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of testosterone replacement products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Disorders: myocardial infarction, stroke

Vascular Disorders: Venous thromboembolism

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens. Frequent monitoring of INR and prothrombin time may be necessary in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.

7.4 Drugs that May Also Increase Blood Pressure

Some prescription drugs and nonprescription analgesic and cold medications can increase blood pressure. Concomitant administration of these medications with TLANDO may lead to additional increases in blood pressure [*see Warnings and Precautions (5.1)*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TLANDO is contraindicated in pregnant women and not indicated for use in females [*see Contraindications (4)*]. Testosterone is teratogenic and may cause fetal harm when administered to a pregnant woman based on data from animal studies (see Data) and its mechanism of action [*see Clinical Pharmacology (12.1)*]. Exposure of a female fetus to androgens may result in varying degrees of virilization. In animal developmental studies, exposure to testosterone in utero resulted in hormonal and behavioral changes in offspring and structural

impairments of reproductive tissues in female and male offspring. These studies did not meet current standards for nonclinical development toxicity studies.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

TLANDO is not indicated for use in females.

8.3 Females and Males of Reproductive Potential

Infertility

Males

During treatment with large doses of exogenous androgens, including TLANDO, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis [see *Warnings and Precautions (5.8)*]. Reduced fertility is observed in some men taking testosterone replacement therapy. The impact on fertility may be irreversible. Testicular atrophy, subfertility, and infertility have also been reported in men who abuse anabolic androgenic steroids [see *Drug Abuse and Dependence (9.2)*].

8.4 Pediatric Use

The safety and effectiveness of TLANDO in pediatric patients less than 18 years old have not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients in controlled clinical studies with TLANDO to determine whether efficacy or safety in those over 65 years of age differs from younger subjects. Of the 95 patients enrolled in Study 16-002, the 24-day major safety and effectiveness study utilizing TLANDO, 16 (16.8%) were over 65 years of age. Additionally, there is insufficient long-term safety data in geriatric patients utilizing TLANDO to assess the potentially increased risk of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH and hypertension [see *Warnings and Precautions (5.1 and 5.4)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TLANDO contains testosterone undecanoate, a schedule III controlled substance.

9.2 Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9.3 Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

10 OVERDOSAGE

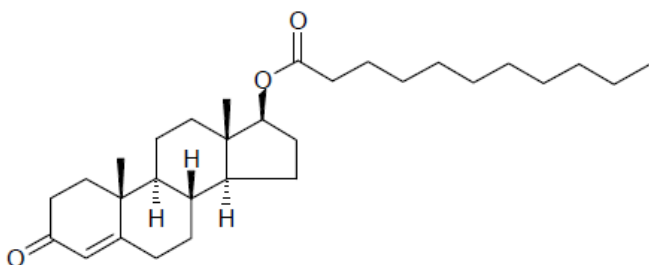
There is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident.

Treatment of overdosage consists of discontinuation of TLANDO and appropriate symptomatic and supportive care.

11 DESCRIPTION

TLANDO (testosterone undecanoate) capsules contain 112.5 mg testosterone undecanoate, an ester of testosterone, for oral administration. Testosterone, an androgen, is formed by cleavage of the ester side chain of testosterone undecanoate.

The chemical name of testosterone undecanoate is 17 β -undecanoyloxy-4-androsten-3-one. It has an empirical formula of C₃₀H₄₈O₃ and a molecular weight of 456.7. The structural formula is:



Testosterone undecanoate is a white to off-white crystalline substance.

The inactive ingredients in TLANDO capsules are ascorbyl palmitate, glyceryl monolinoleate, polyethylene glycol 8000, and polyoxyl 40 hydrogenated castor oil. The capsule shell contains black iron oxide, gelatin, and titanium dioxide. The capsule is imprinted with black ink that contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

There is insufficient data to characterize an exposure-response relationship or time course of pharmacodynamic response.

12.3 Pharmacokinetics

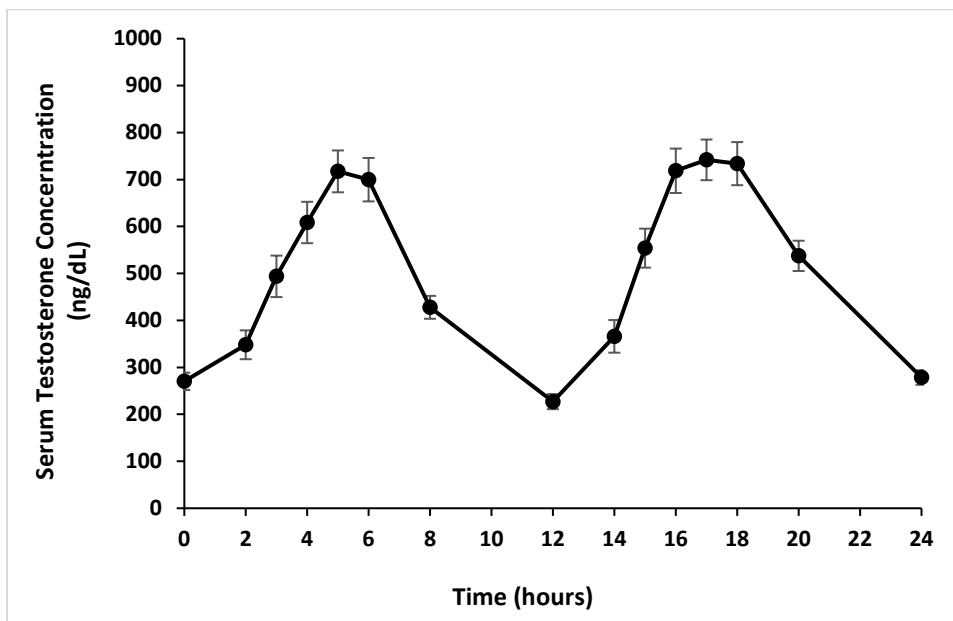
Absorption

Testosterone undecanoate is a lipophilic molecule that is primarily absorbed into the lymph system after oral administration and then released into the general blood circulation by the thoracic duct, avoiding absorption into the portal vein thereby circumventing first-pass metabolism in the liver. Testosterone undecanoate is converted to testosterone following absorption.

Following administration of 225 mg of TLANDO in ninety-five hypogonadal males, maximum serum testosterone concentrations were observed at a median (T_{max}) of about 5 hours. The mean maximum (C_{max}) serum testosterone concentrations observed were 979 ng/dL and 989 ng/dL following the morning and evening TLANDO doses, respectively. The average serum testosterone concentrations over 24 hours ($C_{avg0-24h}$) observed following TLANDO administration was 476 ng/dL.

Figure 1 shows the mean serum total testosterone concentration-time profile for hypogonadal men (N=90) administered TLANDO.

Figure 1: Mean (\pm SEM) Serum Total Testosterone Concentrations (ng/dL)



Following TLANDO administration, the mean serum dihydrotestosterone (DHT) $C_{avg0-24h}$ was 108 ng/dL, the mean serum testosterone undecanoate $C_{avg0-24h}$ was 11,100 ng/dL and the mean serum dihydrotestosterone undecanoate $C_{avg0-24h}$ was 4,700 ng/dL.

Effect of Food

Administration of TLANDO with moderate fat containing food did not significantly impact the pharmacokinetic parameters of testosterone compared to high or low fat. However, there is decrease in exposure when administered without food compared to fed conditions.

In studies with 13 to 14 hypogonadal males, mean testosterone C_{max} and AUC were comparable when TLANDO was administered with food containing low, moderate or high fat amounts. Administration in fasting conditions resulted in approximately 65 % and 38% lower C_{max} and AUC, respectively, compared to administration with food (high fat).

Distribution

Circulating testosterone is primarily bound in serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

Elimination

The elimination half-life of testosterone undecanoate is approximately 2 hours. Once testosterone is formed from testosterone undecanoate, there is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes.

Metabolism

Testosterone undecanoate is metabolized to testosterone via ester cleavage of the undecanoate group and reduced to DHTU by 5α -reductase. Testosterone is metabolized to various 17-keto steroids. The major active metabolites of testosterone are DHT and estradiol.

Excretion

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis

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

Mutagenesis

Mutagenic effects of testosterone undecanoate were not detected in a battery of in vitro tests including bacterial mutation assays (Ames test) and chromosomal aberration tests in human lymphocytes. Testosterone undecanoate was also negative in an in vivo bone marrow micronucleus assay in rats. Testosterone was negative in the in vitro Ames and in the in vivo mouse micronucleus assays.

Impairment of Fertility

The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

The efficacy and safety of TLANDO was evaluated in Study 16-002 a multicenter, open-label, single-arm study in adult hypogonadal male patients (NCT03242590). Patients received TLANDO 225 mg, orally twice daily with food for approximately 24 days; no titration was performed to adjust the dosage.

A total of 95 hypogonadal men received a dose of TLANDO and were included in the efficacy evaluation. Patients had a median age of 56 years (range 29-74 years), 81% were White, 16% were Black, 2% were mixed race, and 1% were Asian; 26% were Hispanic.

The primary endpoint was the percentage of patients who achieved a 24-hour average serum testosterone concentration (Cavg0-24h) within the normal range of 300-1080 ng/dL on the final visit of the study.

Table 3 shows the proportion of subjects, Study 16-002, with an average serum total testosterone concentration in the normal range (300-1080 ng/dL).

Table 3: Proportion of Subjects in Study 16-002 With Average Serum Total Testosterone in the Normal Range (300-1080 ng/dL) at Day 24

Parameter	N=95
% subjects with testosterone, C _{avg0-24h} 300 to 1080 ng/dL	80%
95 % Confidence Interval	(72%, 88%)

Secondary endpoints were the percentage of patients with maximum total testosterone concentration (C_{max}) meeting three predetermined limits: less than or equal to 1.5 times the upper limit of the normal range (ULN) (1620 ng/dL), between 1.8 and 2.5 times ULN (1944 - 2700 ng/dL), and greater than 2.5 times ULN (2700 ng/dL).

The percentage of patients who received TLANDO and had T C_{max} threshold less than or equal to 1620 ng/dL, between 1944 ng/dL and 2700 ng/dL, and greater than 2700 ng/dL at the PK visit were 82%, 5%, and 0%, respectively.

16 HOW SUPPLIED / STORAGE AND HANDLING

TLANDO capsules for oral administration are available containing 112.5 mg of testosterone undecanoate. The capsules have a white opaque body imprinted with “112” in black ink and a grey opaque cap, banded with a colorless band.

TLANDO capsules are supplied in HDPE bottles with a foil liner and a child resistant cap. Bottles of 120 capsules: NDC 54436-112-20.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

Dispose of unused TLANDO via a take-back option. If a take-back option is unavailable, follow FDA instructions at www.fda.gov/drugdisposal.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide).

Increase in Blood Pressure and Cardiovascular Risk

Advise patients that TLANDO can increase blood pressure (BP) which can result in an increase in the risk of major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and cardiovascular death. This risk is greater in patients with established cardiovascular disease or risk factors for cardiovascular disease. Advise patients about the importance of monitoring BP periodically while on TLANDO. Advise patients to report to their healthcare provider the use of concomitant prescription or nonprescription medication, including cough and cold medications which can also increase BP [see *Warnings and Precautions (5.1 and 5.3)*].

Polycythemia

Advise patients that TLANDO can cause an increase in hematocrit levels that may increase the risk of thromboembolic events. Advise patients about the importance of completing laboratory testing as instructed by their health care provider while on TLANDO [see *Warnings and Precautions (5.2)*].

Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

Advise patients that TLANDO can cause increased symptoms of BPH and can increase the risk for prostate cancer. Advise patients to contact their health care provider if they have any prostate-related symptoms [*see Warnings and Precautions (5.4)*].

Edema

Advise patients with preexisting cardiac, renal, or hepatic disease that TLANDO can cause edema. Advise patients to notify their health care provider if edema develops or worsens [*see Warnings and Precautions (5.10)*].

Sleep Apnea

Advise patients that TLANDO can worsen sleep apnea especially in patients with risk factors such as obesity or chronic lung diseases [*see Warnings and Precautions (5.11)*].

Gynecomastia

Advise patients that TLANDO can cause gynecomastia. [*see Warnings and Precautions (5.12)*].

Administration Instructions

- Advise patients to take TLANDO with food [*see Dosage and Administration (2.3)*].

Manufactured for:



Manufactured for Antares

Pharma, Inc.

Ewing, NJ 08628

Manufactured in the United Kingdom

LB-0190 V02

MEDICATION GUIDE
TLANDO® (Tee-lan-doh)
(testosterone undecanoate) capsules, for oral use CIII

What is the most important information I should know about TLANDO?

TLANDO can cause serious side effects, including:

- **Increase in blood pressure.**
 - TLANDO can increase your blood pressure, which can increase your risk of having a heart attack or stroke and can increase your risk of death due to a heart attack or stroke. Your risk may be greater if you have already had a heart attack or stroke or if you have other risk factors for heart attack or stroke.
 - If your blood pressure increases while on TLANDO, blood pressure medicines may need to be started. If you are taking blood pressure medicines, new blood pressure medicines may need to be added or your current blood pressure medicines may need to be changed to control your blood pressure.
 - If your blood pressure cannot be controlled, TLANDO may need to be stopped.
 - Your healthcare provider will monitor your blood pressure while you are being treated with TLANDO.

What is TLANDO?

TLANDO is a prescription medicine that contains testosterone. TLANDO is used to treat adult men who have low or no testosterone due to certain medical conditions.

It is not known if TLANDO is safe or effective in children younger than 18 years old. Improper use of TLANDO may affect bone growth in children.

TLANDO is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your TLANDO in a safe place to protect it. Never give your TLANDO to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and is against the law.

TLANDO is not meant for use by women.

Do not take TLANDO if you:

- have breast cancer.
- have or might have prostate cancer.
- are a woman who is pregnant. TLANDO may harm your unborn baby.
- are allergic to TLANDO or any ingredients in TLANDO. See the end of this Medication Guide for a complete list of ingredients in TLANDO.
- have low testosterone without certain medical conditions. For example, do not take TLANDO if you have low testosterone due to age.

Before you take TLANDO, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure or are treated for high blood pressure.
- have heart problems.
- have high red blood cell count (hematocrit) or high hemoglobin laboratory value.
- have urinary problems due to an enlarged prostate.
- have liver or kidney problems.
- have a history of mental health illness including suicidal thoughts or actions, depression, anxiety or mood disorder.
- have problems breathing while you sleep (sleep apnea).

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Using TLANDO with certain other medicines can affect each other. Especially, tell your healthcare provider if you take:

- insulin.
- medicines that decrease blood clotting (blood thinners).
- corticosteroids.
- medicines that increase blood pressure such as some cold medicine and pain medicines.

Know the medicines you take. Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take TLANDO?

- Take TLANDO exactly as your healthcare provider tells you take it.
- Take TLANDO by mouth two times daily. Take 2 capsules in the morning and take 2 capsules in the evening.
- Take TLANDO with food.

What are the possible side effects of TLANDO?

TLANDO may cause serious side effects including:

- See “What is the most important information I should know about TLANDO?”

- **Increase in red blood cell count (hematocrit) or hemoglobin.**
 - TLANDO increases red blood cell counts in some people. High red blood cell counts increase the risk of blood clots, strokes, and heart attacks.
 - You may need to stop TLANDO if your red blood cell count increases.
 - Your healthcare provider should check your red blood cell count and hemoglobin while you use TLANDO.
- **If you already have an enlarged prostate, your signs and symptoms may worsen while using TLANDO.** These may include:
 - increased urination at night
 - trouble starting your urine stream
 - urinating many times during the day
 - urge to go to the bathroom right away
 - a urine accident
 - inability to pass urine or weak urine flow
- **Increased risk of prostate cancer.** Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use TLANDO.
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- **Abuse.** Testosterone can be abused, when taken at higher than prescribed doses and when used with other anabolic androgenic steroids. Abuse can cause serious heart and psychological side effects. Your healthcare provider should check you for signs of abuse before and during treatment with TLANDO.
- **In large doses TLANDO may lower your sperm count.**
- **Liver problems.** Symptoms of liver problems may include:
 - nausea or vomiting
 - yellowing of your skin or whites of your eyes
 - dark urine
 - pain on the right side of your stomach area (abdominal pain)
- **Swelling of your ankles, feet, or body (edema), with or without heart failure.**
- **Enlarged or painful breasts.**
- **Breathing problems while you sleep (sleep apnea).**

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of TLANDO include:

- | | |
|-------------------------------------|-------------------------|
| • increased prolactin in your blood | • increased weight |
| • high blood pressure | • headache |
| • increased red blood cell count | • joint and muscle pain |
| • common cold | |

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TLANDO. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TLANDO?

- Store TLANDO at room temperature between 68°F to 77°F (20°C to 25°C).
- Store TLANDO in a dry place.

Keep TLANDO and all medicines out of the reach of children.

How should I throw away (dispose of) TLANDO?

- Throw away unused TLANDO via a take-back option.
- If a take-back option is unavailable, follow FDA instructions at www.fda.gov/drugdisposal for properly throwing away medicine.

General information about the safe and effective use of TLANDO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TLANDO for a condition for which it was not prescribed. Do not give TLANDO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TLANDO that is written for health professionals.

What are the ingredients in TLANDO?

Active ingredient: testosterone undecanoate

Inactive ingredients: ascorbyl palmitate, glyceryl monolinoleate, polyethylene glycol 8000, and polyoxyl 40 hydrogenated castor oil.

Capsule shell: contains black iron oxide, gelatin, and titanium dioxide and imprint ink (ammonium hydroxide, black iron oxide, propylene glycol, and shellac).

Manufactured for:
Antares Pharma, Inc.
Ewing, NJ 08628

Manufactured in the United Kingdom

For more information, go to www.TLANDO.com or call 1-844-996-7833.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: 03/2022

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+6.

NDC 54436-112-20

Rx only

Recommended Dosage: See prescribing information.

Active Ingredient: Testosterone Undecanoate 112.5 mg

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

Do NOT flush unused product.



TLANDOTM
(*testosterone undecanoate*)

Capsules 112.5 mg 

Dispense accompanying
Medication Guide to each patient



antares
pharma

120 capsules

Manufactured for:
Antares Pharma, Inc
Ewing, NJ 08628
Manufactured in the United Kingdom

LB-0189 V02



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S/N: 123456789012

LOT: 1234ABCD

EXP: YYYY MM



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/s/

CATHERINE A SEWELL
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