NEW DRUG APPROVAL

Brand Name	Kyzatrex™
Generic Name	testosterone undecanoate
Drug Manufacturer	Marius Pharmaceuticals LLC

New Drug Approval

FDA approval date: July 27, 2022

Review designation: Standard

Type of review: Type 5 – New Formulation or New Manufacturer; New Drug Approval (NDA): 213953

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Testosterone deficiency syndrome, or hypogonadism, is a condition in which a man's body does not produce sufficient testosterone, the primary male hormone. This condition generally affects older men, but younger patients can also be affected for a variety of reasons.

While the term "andropause" is sometimes used for this condition, it is inaccurate. Unlike menopause, testosterone deficiency syndrome is not an inevitable result of aging.

Testosterone plays a key role in a man's sex drive, muscle mass, as well as mental and physical energy.

Hypogonadism affects an estimated 4 to 5 million men in the United States, and although it may occur in men at any age, low testosterone levels are especially common in older males. More than 60% of men over age 65 have free testosterone levels below the normal values of men aged 30 to 35.

Symptoms

There are several symptoms that are associated with a deficiency in testosterone in men:

- Reduced libido
- Difficulty obtaining or maintaining an erection
- Difficulty concentrating or making decisions
- Poor results from exercise programs
- Increase in body fat
- Loss of lean body (muscle) mass
- Loss of bone density
- Depression
- Poor work performance
- Unfavorable changes in cholesterol profile.

Effects

Beyond the symptoms that many men experience, testosterone deficiency syndrome can also contribute to the onset or worsening of various diseases.

- Increased risk of cardiovascular disease.
- Increased risk of death from a cardiovascular event.
- Increased risk of metabolic syndrome: high blood pressure, elevated insulin levels, excess belly fat and abnormal cholesterol levels.

- Strong association with diabetes.
- Strong association with atherosclerotic disease of the aorta.
- Higher incidence of prostate cancer.
- Association with more aggressive variants of cancer.

Efficacy

The efficacy and safety of Kyzatrex™ were evaluated in Study MRS-TU-2019EXT (NCT04467697) a multi-center, open-label study of approximately 6 months of duration in 155 hypogonadal males.

Patients received Kyzatrex™ at a starting dose of 200 mg twice daily with meals. The dosage was adjusted on Days 28 and 56 between a minimum dose of 100 mg (single morning dose) and a maximum dose of 800 mg (400 mg twice daily) based on plasma testosterone concentration from a single blood draw between 3 to 5 hours after the morning dose.

The primary efficacy endpoint was the percentage of Kyzatrex™-treated patients with mean plasma total testosterone concentration (C_{avg}) over 24-hours within the normal range of 222-800 ng/dL on the final PK visit of the study at Day 90.

The efficacy population consisted of 139 hypogonadal, males with a median age of 50 years (range 22 to 66 years), 79% were White, 16% were Black, 3% were Asian, and 2% were American Indian, Alaskan Native or Other.

Table 1. Proportion of Patients in Study MRS-TU-2019EXT with Average Plasma Total Testosterone in the Normal Range (222-800 ng/dL) on Day 90

Parameter	N=139
Patients (%) with Testosterone, C_{avg} (ng/dL), 222-800 ng/dL	122 (88%)
95% Confidence Interval	(82%, 93%)
C_{avg} = 24-hour average concentration	

Secondary endpoints were the percentage of patients with a maximum total testosterone concentration (C_{max}) meeting three predetermined limits: less than or equal to 1.5 times the upper limit of normal range (ULN) (1200 ng/dL), between 1.8 and 2.5 times ULN (1440-2000 ng/dL), and greater than 2.5 times ULN (2000 ng/dL).

The percentage of patients who received Kyzatrex™ and had testosterone C_{max} threshold less than or equal to 1200 ng/dL, between 1440 and 2000 ng/dL, and greater than 2000 ng/dL at the final PK visit were 88%, 4%, and 0%, respectively.

Safety

ADVERSE EVENTS

Common Adverse Reactions

Table 2. Adverse Reactions in ≥ 2% of Patients Receiving Kyzatrex™ in STUDY MRS-TU-2019EXT

Adverse Reaction	N = 155 n (%)
Hypertension [a]	4 (2.6)
[a] Based upon blood pressure cuff measurements	

One (0.8%) patient who received Kyzatrex™ experienced an adverse reaction (acne) that lead to premature discontinuation from the study.

In a 12-month, open-label study in hypogonadal adult males (N=212) who received Kyzatrex™ 200 mg once daily to 400 mg twice daily (n=202) the following additional adverse reactions were reported: headache, arthralgia, diarrhea, hemoglobin increased, anxiety, constipation, peripheral edema, and PSA increased.

Blood Pressure Increases
No significant difference was observed between the 4-month and 6-month Changes from Baseline for study MRSTU-2019EXT.
A total of 5 of 155 patients (3.2%) in Study MRS-TU-2019EXT began taking new antihypertensive medications after study start. No patient had a dose increase in their antihypertensive medication by the end of treatment.
A history of antihypertensive treatment and diabetes mellitus at baseline were significant factors related to ambulatory SBP increases.

Heart Rate Increases
Kyzatrex™ increased mean (95%CI) 24-hour ambulatory heart rate by an average of 0.7 (-0.5 to 1.9) beats per minute (bpm) at 4 months and 1.9 (0.6 to 3.1) bpm at 6 months in Study MRSTU-2019EXT. Changes in heart rate were similar between patients with or without hypertension or diabetes. Changes in heart rate with treatment were most prominent in the evening, 12 to 17 hours after the morning dose.

Increases in Hemoglobin
Increases in hemoglobin were reported in 7 out of 155 patients (4.5%) in Study MRS-TU2019EXT. None of these increases led to premature discontinuation of Kyzatrex™. Hematocrit was not assessed in this study.

Headaches
Headaches were reported in 3 of 155 patients (1.9%) receiving Kyzatrex™ in Study MRS-TU2019EXT.

Increases in Serum PSA
Four out of 155 patients (2.6%) receiving Kyzatrex™ in Study MRS-TU-2019EXT had an increase in PSA from baseline greater than 1.4 ng/mL and two out of 155 patients (1.3%) had a PSA of at least 4.0 ng/mL during Study MRS-TU-2019EXT. The mean (SE) increase in PSA from baseline was 0.15 (±0.04) ng/mL at 6 months (n=135).

Additional Adverse Reactions Identified Postmarketing
Cardiovascular Disorders: myocardial infarction, stroke
Vascular Disorders: Venous thromboembolism.

WARNINGS & PRECAUTIONS

- Polycythemia: Monitor hemoglobin or hematocrit approximately every 3 months to detect increased red blood cell mass and polycythemia. Discontinue Kyzatrex™ if necessary.
- Worsening of benign prostatic hyperplasia (bph) and potential risk of prostate cancer: Monitor patients 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.
- Venous thromboembolism (VTE): VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone. Discontinue Kyzatrex™ if VTE is suspected and initiate appropriate workup and management.
- 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.
- Potential for adverse effects on spermatogenesis: Kyzatrex™ may cause azoospermia.

- Edema: Edema, with or without congestive heart failure (CHF), may occur in patients with pre-existing cardiac, renal, or hepatic disease. Discontinue Kyzatrex™ and initiate appropriate workup.
- Sleep apnea: Kyzatrex™ may potentiate sleep apnea in those with risk factors.
- Lipid changes: Kyzatrex™ may affect serum lipid profile. Monitor patient lipid concentrations periodically; if necessary, adjust dosage of lipid lowering drug(s) or discontinue Kyzatrex™.

CONTRAINDICATIONS

Kyzatrex™ is contraindicated in:

- Patients with carcinoma of the breast or known or suspected carcinoma of the prostate.
- Women who are pregnant. Testosterone can cause virilization of the female fetus when administered to a pregnant woman.
- Patients with known hypersensitivity to Kyzatrex™ or any of its ingredients.
- Men with hypogonadal conditions, such as "age-related hypogonadism," that are not associated with structural or genetic etiologies. The efficacy of Kyzatrex™ has not been established for these conditions, and Kyzatrex™ can increase BP that can increase the risk of MACE.

Clinical Pharmacology

MECHANISMS 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 syndrome or Leydig cell aplasia, whereas secondary hypogonadism (also known as hypogonadotropic hypogonadism) is the failure of the hypothalamus (or pituitary gland) to produce sufficient gonadotropins (FSH, LH).

Dose & Administration

ADULTS

Recommended Dosage and Administration
Individualize the dosage of Kyzatrex™ based on the patient's serum testosterone concentration response to the drug.
The recommended starting dose is 200 mg orally twice daily, once in the morning and once in the evening. Take Kyzatrex™ with food.

Dosage Adjustment
Check serum testosterone concentrations 7 days after starting treatment or after dosage adjustment, 3 to 5 hours after the morning dose. Adjust the Kyzatrex™ dose as necessary as shown in Table 3. Thereafter, periodically monitor serum testosterone concentrations.
The minimum recommended dose is 100 mg once daily in the morning. The maximum recommended dose is 400 mg twice daily. For total daily doses greater than 100 mg, administer the same dose in the morning and evening.

Table 3. Kyzatrex™ Dosage Adjustment Scheme

Serum Testosterone Concentration	Current Kyzatrex™ Dosage	New Kyzatrex™ Dosage
Less than 460 ng/dL	100 mg with breakfast only	100 mg twice daily with meals
	100 mg twice daily with meals	200 mg twice daily with meals
	200 mg twice daily with meals	300 mg twice daily with meals
	300 mg twice daily with meals	400 mg twice daily with meals
460 to 971 ng/dL	No Dosage Change	
More than 971 ng/dL	400 mg twice daily with meals	300 mg twice daily with meals
	300 mg twice daily with meals	200 mg twice daily with meals
	200 mg twice daily with meals	100 mg twice daily with meals
	100 mg twice daily with meals	100 mg with breakfast only
	100 mg with breakfast only	Discontinue treatment

PEDIATRICS

Kyzatrex™ is not recommended for use in patients less than 18 years of age.

GERIATRICS

Clinical studies of Kyzatrex™ did not include any patients 65 years of age and older. Therefore, it cannot be determined whether these patients respond differently from younger adult patients.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 100 mg, 150 mg, 200 mg