Testiva™ Gel
(Testosterone)

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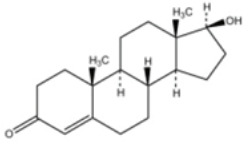
QUALITATIVE AND QUANTITATIVE COMPOSITION

Testiva Gel 1% (50mg/5g)
Each 5g sachet contains:
Testosterone (USP).....…… 50mg

DESCRIPTION

Testiva Gel (Testosterone) is a clear, colorless hydroalcoholic gel containing testosterone for topical use only. Testosterone is an androgen. Testosterone USP is a white to almost white crystalline powder chemically described as 17-beta hydroxyandrost - 4-en-3-one. The molecular formula is $C_{19}H_{28}O_2$ and the structural formula is:



WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- Virilization may occur in children who are secondarily exposed to testosterone gel
- Children should avoid contact with unwashed or unclothed application sites in men using Testosterone Gel
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use.

CLINICAL INFORMATION

Indications

Testiva Gel (Testosterone) 1% is indicated for 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.
- 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.

Limitations of use

- Safety and efficacy of Testiva Gel (Testosterone) 1% in males less than 18 years old have not been established.
- Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure.

Dosage and administration

Adult dosage

The recommended starting dose of Testiva Gel (Testosterone) 1% is 50 mg of testosterone (one 50 mg sachet), applied topically once daily in the morning to the shoulders and upper arms and/or abdomen area (preferably at the same time every day).

Dosage adjustment

To ensure proper dosing, serum testosterone concentrations should be measured at intervals. If the serum testosterone concentration is below the normal range, the daily Testiva Gel (Testosterone) 1% dose may be increased from 50 mg to 75 mg and from 75 mg to 100 mg for adult males as instructed by the physician. If the serum testosterone concentration exceeds the normal range, the daily Testiva Gel (Testosterone) 1% dose may be decreased. If the serum testosterone concentration consistently exceeds the normal range at a daily dose of 50 mg, Testiva Gel (Testosterone) 1% therapy should be discontinued. In addition, serum testosterone concentrations should be assessed periodically.

Steady state plasma testosterone concentrations are reached approximately on the 2nd day of treatment by Testiva Gel (Testosterone) 1%. In order to adjust the testosterone dose, serum testosterone concentrations must be measured in the morning before application from the 3rd day on after starting treatment (one week seems reasonable). The dose may be reduced if the plasma testosterone concentrations are raised above the desired level. If the concentrations are low, the dosage may be increased, not exceeding 10 g of gel per day. The application site and dose of Testiva Gel (Testosterone) 1% are not interchangeable with other topical testosterone products.

Pediatric Use

The safety and efficacy of Testiva Gel (Testosterone) 1% in pediatric patients less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

Geriatric Use

There is insufficient long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease and prostate cancer. Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of Benign prostrate Hyperplasia (BPH).

Renal Impairment

Data for use in patients with renal impairment is not available.

Hepatic Impairment

Data for use in patients with hepatic impairment is not available.

Administration requirements

Testiva Gel (Testosterone) 1% should be applied to clean, dry, healthy, intact skin of the right and left upper arms/shoulders and/or right and left abdomen. Area of application should be limited to the area that will be covered by the patient's short sleeve T-shirt. Do not apply Testiva Gel (Testosterone) 1% to any other part of the body including the genitals, chest or back. Testiva Gel (Testosterone) 1% should be evenly distributed between the right and left upper arms/shoulders or both sides of the abdomen.

After opening the sachet, the total contents must be extracted from the sachet and applied immediately onto the skin. The gel has to be simply spread on the skin gently as a thin layer. It is not necessary to rub it on the skin. Allow drying for at least 3-5 minutes before dressing.

Hands should be washed thoroughly with soap and water after application. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including Testiva Gel (Testosterone) 1%, are flammable.

The patient should be advised to avoid swimming or showering for at least 5 hours after the application of Testiva Gel (Testosterone) 1%.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone

from Testiva Gel (Testosterone) 1%-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using Testiva Gel (Testosterone) 1%.
- Patients should wash hands with soap and water immediately after application of Testiva Gel (Testosterone) 1%.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the gel has dried.
- Prior to situation in which direct skin-to-skin contact is anticipated, patients should wash the application site thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which Testiva Gel (Testosterone) 1% has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

Contraindications

Testosterone Gel 1% is contraindicated in

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate.
- Women who are or may become pregnant, or who are breast feeding. Testosterone Gel 1% may cause fetal harm when administered to a pregnant woman. Testosterone Gel 1% may cause serious adverse reactions in nursing infants. Exposure of a female fetus or nursing infant to androgens may result in varying degrees of virilization. Pregnant women or those who may become pregnant need to be aware of the potential for transfer of testosterone from men treated with Testosterone Gel 1%. If a pregnant woman is exposed to Testosterone Gel 1%, she should be apprised of the potential hazard to the fetus.
- Patients with known hypersensitivity to the active substance.

Warning and Precautions

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 prior to initiating and during treatment with androgens.

Potential for Secondary Exposure to Testosterone

Secondary exposure may occur resulting in virilization of children. Signs and symptoms include enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behaviour, and advanced bone age. Mostly, these signs and symptoms regressed with removal of the exposure to testosterone gel. Sometimes, however, enlarged genitalia may not fully return to age-appropriate normal size, and bone age may remain modestly greater than chronological age. The risk of transfer may be increased sometimes by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using Testosterone Gel 1%.

Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to Testosterone Gel should also be brought to the attention of a physician. Testosterone Gel should be promptly discontinued until the cause of virilization has been identified.

Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating treatment. It would also be appropriate to re-evaluate the hematocrit 3 to 6 months after starting treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable concentration. An increase in red blood cell mass may increase the risk of thromboembolic events.

Use in Women

Due to lack of data in women and potential virilizing effects, Testosterone Gel is not indicated for use in women.

Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including Testosterone Gel 1%, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) may be 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 may produce multiple hepatic adenomas. Testosterone Gel 1% is not known to cause these adverse effects.

Edema

Androgens, including Testosterone Gel 1%, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease.

Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including Testosterone Gel 1%, for hypogonadism.

Sleep Apnea

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

Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

Hypercalcemia

Androgens, including Testosterone Gel 1%, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

Decreased Thyroxine-binding Globulin

Androgens, including Testosterone Gel 1%, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Clotting disorders

Testosterone should be used with caution in patients with thrombophilia, as it may cause thrombotic events in these patients.

Patients above 65 years of age

Data regarding the safety and efficacy of the use of Testosterone Gel 1% in patients over 65 years of age is limited.

Migraine & Epilepsy

Testosterone Gel 1% should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated.

Replacement therapy

Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.

Other Precautions

Testosterone Gel 1% should be used only if hypogonadism (hyper and hypogonadotrophic) has been demonstrated and if other etiology, responsible for the symptoms, has been excluded before treatment is started. Testosterone insufficiency should be clearly demonstrated by clinical features (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction etc.) and confirmed by 2 separate blood testosterone measurements. Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels are lower with increasing age. Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory. Testosterone Gel 1% is not a treatment for male sterility or impotence.

Interactions

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, may decrease insulin requirements.

Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

Corticosteroids

The concurrent use of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

Interaction with laboratory tests

Androgens may decrease levels of thyroxin binding globulin, resulting in decreased T_4 serum concentrations and in increased resin uptake of T_3 and T_4. Free thyroid hormone levels, however, remain unchanged and there is no clinical evidence of thyroid insufficiency.

Pregnancy and Breast Feeding

Pregnancy Category X

Testosterone Gel 1% is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Although it is not known how much testosterone transfers into human milk, Testosterone Gel 1% is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation.

Effects on ability to drive and use machines

Data regarding the effects on the ability to drive and use machines is not available.

Adverse Reactions

Blood and lymphatic system disorders	Elevated Hgb, Hct (polycythemia)
Endocrine disorders	Hirsutism
Gastrointestinal disorders	Nausea
General disorders an d administration site reactions	Asthenia, edema, malaise
Genitourinary disorders	Impaired urination
Hepatobiliary disorders	Abnormal liver function tests (e.g. transaminases, elevated GGTP, bilirubin)
Investigations	Elevated PSA, electrolyte changes (nitrogen, calcium, potassium, phosphorus, sodium), changes in serum lipids (hyperlipidemia, elevated triglycerides, decreased HDL), impaired glucose tolerance, fluctuating testosterone concentrations, weight increase
Neoplasms benign, malignant and unspecified (cysts and polyps)	Prostate cancer
Nervous system	He adache, dizziness, sleep apnea, insomnia
Psychiatric disorders	Depression, emotional lability, decreased libido, nervousness, hostility, amnesia, anxiety
Reproductive system and breast disorders	Gynecomastia, mastodynia , prostatic enlargement, testicular atrophy, oligospermia, priapism (frequent or prolonged erections)
Respiratory disorders	Dyspnea
Skin an d subcutaneous tissue disorders	Acne, alopecia, application site reaction (pruritus, dry skin, erythema, rash, discolored hair, paresthesia), sweating
Vascular disorders	Hypertension, vasodilation (hot flushes)

Overdose

Treatment of overdosage would consist of discontinuation of Testosterone Gel 1%, washing the application site with soap and water, and appropriate symptomatic and supportive care.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Androgens. ATC code: G03B A03

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 chord thickening, alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression,

regression of secondary sexual characteristics and osteoporosis.
Male hypogonadism can present as primary hypogonadism caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia while secondary hypogonadism is the failure of the hypothalamus or pituitary to produce sufficient gonadotropins.

Pharmacokinetic properties

Absorption

Testosterone Gel 1% delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal concentrations (298 - 1043 ng/dL) seen in healthy men. Testosterone Gel 1% provides continuous transdermal delivery of testosterone for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

Testosterone Gel 1% is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone dose applied on the skin surface from Testosterone Gel is absorbed into systemic circulation. Absorption of testosterone into the blood continues for the entire 24-hour dosing interval. Serum concentrations approximate the steady-state concentration by the end of the first 24 hours and are at steady state by the second or third day of dosing.

With single daily applications of Testosterone Gel 1%, serum testosterone concentrations are generally maintained within the eugonadal range.

Distribution

Circulating testosterone is primarily bound in the 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.

Metabolism

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT). DHT concentrations increase in parallel with testosterone concentrations during Testosterone Gel 1% treatment. The mean steady-state DHT/T ratio during 180 days of Testosterone Gel treatment range from 0.23 to 0.29 (50 mg of Testosterone Gel 1%/day) and from 0.27 to 0.33 (100 mg of Testosterone Gel 1%/day).

Elimination

When Testosterone Gel 1% treatment is discontinued after achieving steady state, serum testosterone concentrations remain in the normal range for 24 to 48 hours but return to their pretreatment concentrations by the fifth day after the last application.

PHARMACEUTICAL INFORMATION

Shelf life

2 years

Special Precautions for Storage

- Store at 25°C. (excursions permitted between 15°C to 30°C).
- Keep out of the reach of children.
- Protect from light, moisture and flame.

ہدایات:

دوا کو ۲۵ ڈگری سینٹی گریڈ پر رکھیں۔
(درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)
بچوں کی پہنچ سے دور رکھیں۔
دوا کو روشنی، نمی اور آگ سے بچائیں۔

Nature and contents of container

Testiva (Testosterone) 1% (50mg/5g) Gel is available in a pack of 30 sachets .

MANUFACTURED BY

OBS Pakistan (Pvt.) Ltd.
C-14, Manghopir Road, S.I.T.E.,
Karachi-75700, Pakistan.

MARKETED BY

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An OBS Group Company

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