

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT:

TESTOMAX 50 mg

TESTOMAX 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

TESTOMAX 50 mg: Testosterone 0.05 g per 5 g sachet

TESTOMAX 25 mg: Testosterone 0.025 g per 2.5 g sachet

For excipients, see 6.1.

3. PHARMACEUTICAL FORM: Gel

Clear, transparent colorless gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Testosterone replacement therapy for males hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

4.2 Posology and administration route

Cutaneous use

Adults and elderly

The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily, at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 10 g of gel per day. The adjustment of posology should be achieved by 2.5 g of gel steps.

The application should be administered by the patient himself, onto clean, dry, healthy skin over the shoulders, or both arms or abdomen.

After opening the sachet, the total content must be extracted from the sachet and applied immediately onto the skin. The gel has just 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. Wash hands with soap and water after applications.

Do not apply to the genital areas as the high alcohol content may cause local irritation.

Steady state plasma testosterone concentrations are reached approximately on the 2nd day of treatment with Testomax. 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.

Children

Testomax is not indicated for use for children and has not been evaluated clinically in males under 18 years of age.

4.3 Contraindications

Testomax is contraindicated:

- In case of known or suspected breast carcinoma or prostatic cancer,
- In case of known hypersensitivity to testosterone or any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

Testomax should be used only if hypogonadism (hyper- and hypogonadotropic) has been demonstrated and if other etiology, responsible for the symptoms, has not 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 two 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.

Testomax is not a treatment for male sterility or impotence.

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude any risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breast must be performed in accordance with recommended methods (digital rectal examination and estimation of serum PSA) in patients receiving testosterone therapy at least once yearly and twice yearly in elderly patients and at risk patients (those with clinical or familial factors).

Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.

Testomax should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of serum calcium concentration is recommended in these patients.

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischemic heart disease, treatment with Testomax may cause severe complications characterized by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately. In addition, diuretic therapy may be required.

Testomax should be used with caution in patients with ischemic heart disease.

Testosterone may cause a rise in blood pressure and Testomax should be used with caution in men with hypertension.

Clotting disorders

Testosterone should be used with caution in patients with thrombophilia, as there have been post-marketing studies and reports of thrombotic events in these patients during testosterone therapy.

Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.

Beside laboratory tests of the testosterone concentrations in patients on long-term androgen therapy the following laboratory parameters should also be monitored regularly: haemoglobin, hematocrit (to detect polycythaemia), liver function tests, and lipids profile.

There is limited experience on the safety and efficacy of the use of Testomax in patients over 65 years of age. 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.

Testomax should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated.

There are published reports on increased risk of sleep apnoea in hypogonadal patients treated with testosterone esters, especially in those with risk factors such as obesity and chronic respiratory disease.

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

Certain clinical signs such as: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment.

If the patient develops a severe application site reaction, treatment should be reviewed and discontinued if necessary.

The attention of athletes is drawn to the fact that this medicinal product contains an active substance (testosterone) which may produce a positive reaction in anti-doping tests.

Testomax should not be used by women, due to possible virilizing effects.

Potential testosterone transfer

If no precaution is taken, testosterone gel can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and possibly adverse effects (e.g. growth of facial and/or body hair, deepening of the voice, irregularities of the menstrual cycle) in case of repeated contact (inadvertent androgenization).

The physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). Testomax should not be prescribed in patients with a major risk of non-compliance with safety instructions (e.g. severe alcoholism, drug abuse, severe psychiatric disorders).

This transfer is avoided by wearing clothes covering the application area or showering prior to contact.

As a result, the following precautions are recommended:

For the patient:

- Wash hands with soap and water after applying Testomax.
- Cover the application area with clothing once the gel has dried.
- Shower before any situation in which this type of contact is foreseen

For people not being treated with Testomax:

- In the event of contact with an application area which has not been washed or is not covered with clothing, wash the area of skin onto which testosterone may have been transferred as soon as possible, using soap and water.
- Report the development of signs of excessive androgen exposure such as acne or hair modification.

According to *in vitro* absorption studies of testosterone conducted with Testomax, it seems preferable for patients to observe at least 6 hours between gel application and bathing or showering. Occasional baths or showers taken between 1 and 6 hours after the application of the gel should not significantly influence the treatment outcome.

To guarantee partner safety the patient should be advised for example to observe a long interval between Testomax application and sexual intercourse, to wear a T-shirt covering the application site, during contact period or to shower before sexual intercourse.

Furthermore, it is recommended to wear a T-shirt, covering the application site, during contact period with children, in order to avoid a contamination risk of children skin.

Pregnant women must avoid any contact with Testomax application sites. In case of pregnancy of the partner, the patient must reinforce his attention to the precautions for use (see 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

+ Oral anticoagulants

Changes in anticoagulant activity (the increased effect of the oral anticoagulant by modification of coagulation factor hepatic synthesis and competitive inhibition of plasma protein binding):

Increased monitoring of the prothrombin time and INR determinations are recommended. Patients receiving oral anticoagulants require close monitoring especially when androgens are started or stopped.

Concomitant administration of testosterone with ACTH or corticosteroids may increase the risk of developing oedema. As a result, these medicinal products should be administered cautiously, particularly in patients suffering from cardiac, renal or hepatic disease.

Interaction with laboratory tests: androgens may decrease levels of thyroxin binding globulin, resulting in decreased T₄ serum concentrations and in increased resin uptake of T₃ and T₄. Free thyroid hormone levels, however, remain unchanged, and there is no clinical evidence of thyroid insufficiency.

4.6 Fertility, Pregnancy and Lactation

Testomax is intended for use by men only.

Testomax is not indicated in pregnant or breast feeding women. No clinical trial has been conducted with this treatment in women.

Pregnant women must avoid any contact with Testomax application areas (see 4.4). This product may have adverse virilizing effects on the foetus. In the event of contact, wash with soap and water as soon as possible.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed.

4.8 Undesirable effects

The most frequently observed adverse drug reactions at the recommended dosage of 5 g of gel per day were skin reactions (10%); reaction at the application area, erythema, acne, dry skin.

Adverse drug reactions reported in 1 - <10% of patients treated with Testomax in the controlled clinical trials are listed in the following table:

Organ system class	Adverse reactions
Blood and lymphatic system disorders	Changes in laboratory tests (polycythemia, lipids), Haematocrit increased, Red blood cell count increased, Haemoglobin increased
General disorders and administration site conditions	Headache
Renal and Urinary disorders	Prostatic disorders
Reproductive and system and breast disorders	gynaecomastia, mastodynia
Nervous system disorders	Dizziness, paraesthesia, amnesia, hyperaesthesia
Psychiatric disorders	Mood disorders
vascular disorders	Hypertension
Gastro-intestinal disorders	Diarrhoea
Skin and subcutaneous disorders	Alopecia, urticaria

Gynaecomastia, which may be persistent, is a common finding in patients treated for hypogonadism.

According to the literature, other known undesirable effects have been reported following testosterone oral or injectable treatment and are listed in the following table:

Organ system	Adverse reactions
Metabolism and nutrition disorders	Weight gain, electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water) during high dose and/or prolonged treatment
Musculoskeletal system	Muscle cramps
Nervous system	Nervousness, depression, hostility
Respiratory system	Sleep apnoea
Hepatobiliary disorders	In very rare cases jaundice and liver function test abnormalities
Skin and appendages	Various skin reactions may occur including acne, seborrhoea, and balding
Reproductive system and breast disorders	Libido changes, increased frequency of erections; therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces

	spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism), prostate abnormalities, prostate cancer*, urinary obstruction
General disorders and administration site conditions	High dose or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema; hypersensitivity reactions may occur.

* Data on prostate cancer risk in association with testosterone therapy are inconclusive.

Other rare known undesirable effects associated with excessive dosages of testosterone include hepatic neoplasms.

Because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il>.

Additionally, you can also report to [Padagis.co.il](https://www.padagis.co.il).

4.9 Overdose

Only one case of acute testosterone overdose following an injection has been reported in the literature. This was a case of a cerebrovascular accident in a patient with a high plasma testosterone concentration of 114 ng/ml (395 nmol/l). It would be most unlikely that such plasma testosterone concentrations be achieved using the transdermal route.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANDROGENS, ATC Code: G03B A03

Endogenous androgens, principally testosterone, secreted by the testes and its major metabolite DHT, are responsible for the development of the external and internal genital organs and for maintaining the secondary sexual characteristics (stimulating

hair growth, deepening of the voice, development of the libido); for a general effect on protein anabolism; for development of skeletal muscle and body fat distribution; for a reduction in urinary nitrogen, sodium, potassium, chloride, phosphate and water excretion.

Testosterone does not produce testicular development: it reduces the pituitary secretion of gonadotropins. The effects of testosterone in some target organs arise after peripheral conversion of testosterone to estradiol, which then binds to oestrogen receptors in the target cell nucleus e.g. the pituitary, fat, brain, bone and testicular Leydig cells.

5.2 Pharmacokinetic properties

The percutaneous absorption of testosterone ranges from approximately 9% to 14% of the applied dose.

Following percutaneous absorption, testosterone diffuses into the systemic circulation at relatively constant concentrations during the 24 hour cycle.

Serum testosterone concentrations increase from the first hour after an application, reaching steady state from day two. Daily changes in testosterone concentrations are then of similar amplitude to those observed during the circadian rhythm of endogenous testosterone. The percutaneous route therefore avoids the blood distribution peaks produced by injections. It does not produce supra-physiological hepatic concentrations of the steroid in contrast to oral androgen therapy.

Administration of 5 g of Testomax produces an average testosterone concentration increase of approximately 2.5 ng/ml (8.7 nmol/l) in plasma.

When treatment is stopped, testosterone concentrations start decreasing approximately 24 hours after the last dose. Concentrations return to baseline approximately 72 to 96 hours after the final dose.

The major active metabolites of testosterone are dihydrotestosterone and estradiol.

Testosterone is excreted, mostly in urine, and in faeces as conjugated testosterone metabolites.

5.3 Preclinical safety data

Testosterone has been found to be non-mutagenic *in vitro* using the reverse mutation model (Ames test) or hamster ovary cells. A relationship between androgen treatment and certain cancers has been found in studies on laboratory animals. Experimental data in rats have shown increased incidences of prostate cancer after treatment with testosterone.

Sex hormones are known to facilitate the development of certain tumors induced by known carcinogenic agents.

No correlation between these findings and the actual risk in human beings has been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dehydrated alcohol, Purified water, Carbomer homopolymer type C, Isostearic acid, Sodium hydroxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Testomax 25 mg: aluminium sachet of 2.5 g

Testomax 50 mg: aluminium sachet of 5 g

Pack size: 30 sachets

7. Manufacturer and marketing authorization holder:

Padagis Israel Pharmaceuticals LTD., 1 Rakefet street, Shoham, Israel.

8. Marketing authorization number (s):

Testomax 25 mg: 136-20-31297

Testomax 50 mg: 136-21-31298

Revised in March 2022 according to MOH guidelines.