

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

AndroGel 50 mg, transdermal gel in sachet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet of 5 g contains 50 mg of testosterone.

Excipients with known effect: Ethanol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal gel.

Transparent or slightly opalescent, colourless gel in sachet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests (see 4.4 Special warnings and precautions for use).

4.2 Posology and method of administration

Posology

Adult and Elderly men

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 physician 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.

Steady state plasma testosterone concentrations are reached approximately on the 2nd day of treatment by this medicine. 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.

Paediatric population

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

Use in women

This medicine is not indicated for use in women.

Method of administration

Transdermal use.

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

After opening the sachets, the total contents 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.

4.3 Contraindications

This medicine is contraindicated:

- in cases of known or suspected prostatic cancer or breast carcinoma,
- in cases of known hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

This medicine 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.

Prior to testosterone initiation, all patients should undergo a detailed examination in order to exclude a 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.

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

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately.

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

Testosterone should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism (VTE), as there have been post-marketing reports of thrombotic events (e.g. deep-vein thrombosis, pulmonary embolism, ocular thrombosis) in these patients during testosterone therapy. In thrombophilic patients, VTE cases have been reported even under anticoagulation treatment, therefore continuing testosterone treatment after first thrombotic event should be carefully evaluated. In case of treatment continuation, further measures should be taken to minimise the individual VTE risk.

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.

In patients receiving long-term androgen therapy, the following laboratory parameters should also be monitored regularly: haemoglobin, and haematocrit (to detect polycythaemia), liver function tests, and lipid profile.

There is limited experience on the safety and efficacy of the use of this medicine 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.

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

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

Improved insulin sensitivity may be observed in patients treated with androgens and may require a decrease in the dose of antidiabetic medications (see section 4.5). Monitoring of the glucose level and HbA1c is advised for patients treated with androgens.

Certain clinical signs: 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 proprietary medicinal product contains an active substance (testosterone) which may produce a positive reaction in anti-doping tests.

This medicine should not be used by women, due to possibly virilizing effects.

Potential testosterone transfer

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, for instance during close bodily contact between individuals including children and about safety instructions (see below).

When prescribing, the treating physician should give extra attention to the section in SmPC "Potential testosterone transfer" to patients with a major risk of not being able to follow these instructions.

The following precautions are recommended:

For the patient:

- wash hands with soap and water after applying the gel
- cover the application area with clothing once the gel has dried
- wash the application area before any situation in which close contact is foreseen

For people not being treated with this medicine:

- in the event of adventitious contact with this medicine, the person affected should wash the affected area with soap and water immediately
- report the development of signs of excessive androgen exposure such as acne or hair modification.

Patients should wait at least 1 hour before showering or bathing after applying this medicine.

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

This medicine contains 3.6 g alcohol (ethanol) in each sachet.

It may cause burning sensation on damaged skin.

This product is flammable until dry.

4.5 Interaction with other medicinal products and other forms of interactions

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.

Corticosteroids

Concomitant administration of testosterone and 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.

Laboratory tests

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.

Diabetic medication

Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin levels have been reported with androgens. In diabetic patients, the dose of antidiabetic medications may need reduction (see section 4.4).

4.6 Fertility, pregnancy and lactation

Fertility

Spermatogenesis may be reversibly suppressed with this medicine.

Pregnancy

This medicine is intended for use by men only.

This medicine is not indicated in pregnant women. No clinical trials have been conducted with this treatment in women.

Pregnant women must avoid any contact with Androgel application sites (see section 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.

Breast-feeding

This medicine is not indicated in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently observed adverse drug reactions at the recommended dosage per day were skin reactions: reaction at the application site, erythema, acne, dry skin.

b. Tabulated list of adverse reactions

Clinical trial data

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

Adverse effects have been ranked under headings of frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$; $< 1/10$); uncommon ($\geq 1/1,000$; $< 1/100$); rare ($\geq 1/10,000$; $< 1/1,000$); very rare ($< 1/10,000$); frequency not known (cannot be estimated from the available data).

| MedDRA System Organ Class | Adverse reactions – preferred term Common adverse reactions ($\geq 1/100$; $< 1/10$) |
|--|---|
| Psychiatric disorders | Mood disorders |
| Nervous system disorders | Dizziness, paraesthesia, amnesia, hyperaesthesia |
| Vascular disorders | Hypertension |
| Gastrointestinal disorders | Diarrhoea |
| Skin and subcutaneous tissue disorders | Alopecia, urticaria |
| Reproductive system and breast disorders | Gynaecomastia (which may be persistent, is a common finding in patients treated for hypogonadism.), mastodynia, Prostatic disorders |
| General disorders and administration site conditions | Headache |
| Investigations | Changes in laboratory tests (polycythaemia, lipids), Haematocrit increased, Red blood cell count increased, Haemoglobin increased |

Post marketing experience

The following table includes adverse reactions identified during post-approval use of this medicine in addition to other known undesirable effects reported in the literature following testosterone oral, injectable or transdermal treatment:

Adverse effects have been ranked under headings of frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$; $< 1/10$); uncommon ($\geq 1/1,000$; $< 1/100$); rare ($\geq 1/10,000$; $< 1/1,000$); very rare ($< 1/10,000$); frequency not known (cannot be estimated from the available data).

| MedDRA System Organ Class | Adverse reactions – preferred terms | | | |
|----------------------------------|--|---|---|---|
| | Frequency not known (cannot be estimated from the available data) | Common ($\geq 1/100$; $< 1/10$) | Rare ($\geq 1/10,000$; $< 1/1,000$) | Very rare ($< 1/10,000$) |
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|---|--|--|------------------|----------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Prostate cancer (Data on prostate cancer risk in association with testosterone therapy are inconclusive.) | | Hepatic neoplasm | |
| 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 | | | |
| psychiatric disorders | Nervousness, depression, hostility | | | |
| Respiratory thoracic and mediastinal disorders | Sleep apnoea | | | |
| Hepatobiliary disorders | | | | Jaundice |
| Skin and subcutaneous tissue disorders | acne, seborrhoea, balding | | | |
| Musculoskeletal and connective tissue disorders | Muscle cramps | | | |
| Renal and urinary disorders | Urinary obstruction | | | |
| 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; prostate abnormalities | | Priapism | |
| General disorders and administration | High dose or long-term administration of | | | |

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|-----------------|--|--|--|-----------------------------------|
| site conditions | testosterone occasionally increases the occurrences of water retention and oedema; hypersensitivity reactions may occur. Because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin. | | | |
| Investigations | | Haematocrit increased, haemoglobin increased, red blood cell count increased | | Liver function test abnormalities |

Reporting of 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

Serum testosterone levels should be measured if clinical signs and symptoms indicative of overexposure to androgen are observed.

Application site rash has also been reported in case reports of overdose with this medicine.

Treatment

Treatment of overdosage consists of washing the application site immediately and discontinuing treatment if advised by the treating physician.

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 this medicine 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 tumours 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

Carbomer 980
Isopropyl myristate
Ethanol 96%
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 g in sachet (PET/Aluminium/LDPE).
Boxes of 1, 2, 7, 10, 14, 28, 30, 50, 60, 90 or 100 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoires Besins International
3, rue du Bourg l'Abbe
75003 Paris
France

8 MARKETING AUTHORISATION NUMBER

PA1054/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 June 2003
Date of last renewal: 21 September 2006

10 DATE OF REVISION OF THE TEXT

October 2020