

PACKAGE INSERT FOR ANDROGEL

SCHEDULING STATUS:

S5

PROPRIETARY NAME AND DOSAGE FORM:

ANDROGEL gel in sachet

COMPOSITION:

One sachet of 5 g contains 50 mg of testosterone.

Inactive ingredients:

Carbopol 980, ethanol 96 % v/v, isopropyl myristate, sodium hydroxide and purified water.

PHARMACOLOGICAL CLASSIFICATION:

A 21.7 Male sex hormones

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Testosterone is an androgen hormone.

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.

Application of 5 g of ANDROGEL 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.

INDICATIONS:

Testosterone replacement therapy for male hypogonadism in adult men when testosterone deficiency has been confirmed by clinical features and biochemical tests (see **WARNINGS AND SPECIAL PRECAUTIONS**).

ANDROGEL is not for use in children.

CONTRAINDICATIONS:

ANDROGEL is contraindicated:

- In cases of known or suspected prostatic cancer or breast carcinoma.
- In cases of known hypersensitivity to testosterone or to any other constituent of ANDROGEL (see **COMPOSITION**).

WARNINGS AND SPECIAL PRECAUTIONS:

- **ANDROGEL is indicated for use only in men with primary or secondary hypogonadism resulting from certain medical conditions.**
- **ANDROGEL should not be used for age-related hypogonadism.**
- **Before initiating ANDROGEL, ensure that the diagnosis of hypogonadism has been confirmed with laboratory testing. Verify that serum testosterone concentrations have been measured on at least two separate mornings and are consistently below**

the normal range. Avoid measuring testosterone concentrations later in the day, when measurements can be low even in men who do not have hypogonadism.

- **Inform patients of the potential increased cardiovascular risk associated with ANDROGEL. Increases in myocardial infarction and stroke have been reported.**
- **Encourage patients to read the patient information leaflet they receive with ANDROGEL.**

ANDROGEL should be used only if hypogonadism (hyper- and hypogonadotropic) has been demonstrated and if other aetiology responsible for the symptoms has been excluded before treatment is initiated. 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.

Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

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

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

ANDROGEL should not be used 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.

Patients who have experienced myocardial infarction, cardiac, hepatic or renal insufficiency, hypertension, epilepsy, or migraine should be monitored due to the risk of deterioration of or reoccurrence of disease. In this case, treatment must be stopped immediately.

ANDROGEL should not be used in patients with ischaemic heart disease.

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

The testosterone level should be monitored at baseline and at regular intervals during treatment.

Healthcare practitioners should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.

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

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.

There is an increased risk of sleep apnoea in hypogonadal patients treated with testosterone esters, such as ANDROGEL, especially in those with risk factors such as obesity and chronic respiratory disease.

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

Certain clinical signs such as irritability, nervousness, weight gain, and prolonged or frequent erections may indicate excessive ANDROGEL 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 ANDROGEL contains an active substance (testosterone) which may produce a positive reaction in anti-doping tests.

ANDROGEL should not be used by women, due to its potential virilising effects.

Potential testosterone transfer:

ANDROGEL 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 androgenisation).

The healthcare practitioner should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below).

ANDROGEL 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).

Transfer of ANDROGEL 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 the gel.
- Cover the application area with clothing once the gel has dried.
- Shower before any situation in which this type of skin contact is foreseen.

For people not being treated with ANDROGEL:

- 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 ANDROGEL, it seems preferable for patients to observe at least 6 hours between gel application and bathing or showering.

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

Furthermore, it is recommended to wear a T-shirt covering the application site during any contact period with children, in order to avoid the risk of contaminating children's skin.

Pregnant women must avoid any contact with ANDROGEL application sites. In case of pregnancy of the partner, the patient must reinforce his adherence to the precautions for use (see **PREGNANCY AND LACTATION**).

ANDROGEL is not a treatment for male sterility or impotence.

Effects on ability to drive and use machines:

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

INTERACTIONS:

Oral anticoagulants:

Changes in anticoagulant activity (the increased effect of the oral anticoagulant by modification of hepatic synthesis of the coagulation factor and competitive inhibition of plasma protein binding): Increased monitoring of the prothrombin time and international normalised ratio (INR) determinations, are recommended. Patients receiving oral anticoagulants require close monitoring, especially when treatment with androgens are started or stopped.

Adrenocorticotrophic hormone (ACTH) or corticosteroids:

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

Interaction with laboratory tests:

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

PREGNANCY AND LACTATION:

ANDROGEL is intended for use by men only.

ANDROGEL is not indicated in pregnant or breastfeeding women.

Pregnant women must avoid any contact with ANDROGEL application sites (see WARNINGS AND SPECIAL PRECAUTIONS). ANDROGEL may cause virilising effects on the fetus. In the event of contact, wash with soap and water as soon as possible.

DOSAGE AND DIRECTIONS FOR USE:

Cutaneous use.

Adults 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 adjustment of posology should be achieved in steps of 2,5 g of gel.

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. ANDROGEL simply has to be gently spread on the skin, 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 ANDROGEL.

In order to adjust the ANDROGEL dose, serum testosterone concentrations must be measured in the morning before application, from the 3rd day after starting treatment (one week is 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, but not exceeding 10 g of gel per day.

Children:

ANDROGEL is not indicated for use in children.

SIDE EFFECTS:***Neoplasms benign and malignant (including cysts and polyps):***

Frequency unknown: Hepatic neoplasms.

Blood and the lymphatic system disorders:

Frequent: Changes in laboratory tests (polycythaemia, lipids), increased: haematocrit, red blood cell count and haemoglobin.

Immune system disorders:

Less frequent: Hypersensitivity reactions.

Metabolism and nutritional disorders:

Less frequent: Weight gain, electrolyte changes (sodium, chloride, potassium, calcium, inorganic phosphate and water retention) during high dose and/or prolonged treatment.

Psychiatric disorders:

Frequent: Mood disorders, amnesia.

Less frequent: Nervousness, depression, hostility, anxiety, irritability.

Nervous system disorders:

Frequent: Headache, dizziness, paraesthesia, hyperaesthesia.

Vascular disorders:

Frequent: Hypertension.

Less frequent: Arterial vasodilation.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Sleep apnoea, asthma.

Gastrointestinal disorders:

Frequent: Diarrhoea.

Less frequent: Nausea.

Hepatobiliary disorders:

Less frequent: Jaundice.

Skin and subcutaneous disorders:

Frequent: Alopecia, urticaria, skin reactions, erythema, acne, dry skin, skin irritation.

Less frequent: Seborrhoea, balding, pruritis.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle cramps, myalgia.

Renal and urinary disorders:

Frequent: Prostatic disorders.

Less frequent: Urinary obstruction.

Reproductive system and breast disorders:

Frequent: Gynaecomastia, mastodynia.

Less frequent: Libido changes; increased frequency of erections; therapy with ANDROGEL reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; persistent, painful erections (priapism); prostate abnormalities or prostate cancer; oligospermia.

General disorders and administration site conditions:

Frequent: Reaction at the application site.

Less frequent: Water retention and oedema during high dose and/or prolonged treatment.

Investigations:

Frequent: Changes in laboratory tests (polycythaemia, lipids).

Less frequent: Liver function test abnormalities, electrolyte changes (sodium, potassium, calcium, inorganic phosphate and water retention), during high dose prolonged treatment.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In overdose, side effects will be exacerbated and exaggerated (see **SIDE EFFECTS**).

Treatment is symptomatic and supportive.

IDENTIFICATION:

ANDROGEL is a transparent or slightly opalescent, colourless gel in a sachet.

PRESENTATION:

5 g in sachet (PET/aluminium/PE).

Boxes of 1, 2, 7, 10, 14, 28, 30, 50, 60, 90 or 100 sachets.

Not all the pack sizes may be marketed.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

STORE OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A40/21.7/0260

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF

REGISTRATION:

Medi Challenge (Pty) Ltd

Fancourt Office Park

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Response to Clinical recommendation dated: 20 September 2017

DATE AND PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 1 October 2010