Package Insert
ANDROGEL , GEL IN SACHET

1. NAME OF THE MEDICINAL PRODUCT

ANDROGEL 25 mg, gel in sachet
ANDROGEL 50 mg, gel in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Testosterone ....0.025 g
Testosterone ....0.050 g
For excipients, see 6.1.
For one 2.5 g sachet
For one 5 g sachet

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4 . 2 Posology and method of administration

Cutaneous use.

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 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 both shoulders, and both arms and 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 application.

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 2^{nd} day of treatment by ANDROGEL. In order to adjust the testosterone dose, serum testosterone concentrations must be measured in the morning before application from the 3^{rd} day on after

starting treatment (and up to one week). 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

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

4.3 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 the gel.

4.4 Special warnings and precautions for use

ANDROGEL should be used only if hypogonadism (hyper- and hypogonadotrophic) has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded before treatment is started. Testosterone insufficiency should be clearly demonstrated by clinical signs (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.

ANDROGEL is not a treatment for male sterility or impotence.

Prior to testosterone initiation, all patients must mandatorily 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 - prostate-specific antigen) 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.

ANDROGEL 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 cardiac, hepatic or renal insufficiency-treatment with ANDROGEL may cause severe complications characterized by oedema with or without congestive cardiac failure. In this case, treatment must be stopped immediately. In addition, diuretic therapy may be required. Patients who experienced myocardial infarction, cardiac, hepatic or renal insufficiency, hypertension, should be monitored due to the risk of deterioration of or reoccurrence of disease. In such cases treatment must be stopped immediately.

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

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

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 be checked periodically: haemoglobin, haematocrit (to detect polycythemia), liver function tests and lipid profile. ANDROGEL 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 occur in patients treated with androgens who achieve normal testosterone plasma concentrations following therapy.

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.

Clotting Disorders

Testosterone should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism (VTE), as there have been post-marketing studies and 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.

ANDROGEL should not be used by women, due to possibly virilising 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 repeat contact (inadvertent androgenisation).
The physician 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).

This transfer is avoided by wearing clothes covering the application site 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 site 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 ANDROGEL:
- in the event of contact with an application site 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 on testosterone conducted with ANDROGEL, 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 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 ANDROGEL application and sexual Intercourse, to wear a cloth covering the application site, during contact period or to shower before sexual intercourse. Furthermore, it is recommended to wear a cloth, covering the application site, during contact period with children, in order to avoid a contamination risk.

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

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 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.

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.

+ Oxyphenbutazone

Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

In diabetic patients, the metabolic effect of androgens may decrease blood glucose and, therefore, insulin requirements.

4.6 Pregnancy and lactation

ANDROGEL is intended for use by men only.

ANDROGEL is not indicated in pregnant or breast- feeding 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_Special warnings and precautions for use). This product may have adverse virilising effects on the fetus. In the event of contact, wash with soap and water as soon as possible.

4.7 Effects on ability to drive and use machines

ANDROGEL has no influence on the ability to drive or use machines.

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 site, erythema, acne, dry skin.

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

Organ system class	Adverse reactions
Body as a whole- general	Changes in laboratory tests (polycythaemia, lipids), headache
Urogenital system	Prostatic disorders, gynecomastia, mastodynia
Central and peripheral nervous system	Dizziness, paresthesia, amnesia, hyperesthesia, mood disorders
Cardiovascular system	Hypertension
Gastro-intestinal system	Diarrhoea
Skin and appendages	Alopecia
Other known adverse reactions	Pruritus, arterial vasodilation, nausea

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

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 (dihydrosterone), 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 oestradiol, which than 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-physio logical hepatic concentrations of the steroid in contrast to oral androgen therapy.

Administration of 5 g of ANDROGEL produces an average testosterone concentration increase of approximately 2.5 ng/ml (8.7 nmol/1) 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 oestradiol.
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, 96% Ethanol, Sodium hydroxide, Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

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

6.6 Instructions for use.

Handling and disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. IMPORTER

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