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

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
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 (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.
Paediatric population
ANDROGEL 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 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 applications.
Do not apply to the genital areas as the high alcohol content may cause local irritation.
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.
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 - 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 severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause severe complications characterized by oedema with or without congestive cardiac failure. In this case, treatment must be stopped immediately.
Testosterone may cause a rise in blood pressure and this medication should be used with caution in patients with hypertension.
Testosterone should be used with caution in patients with thrombophilia, as there have been post-marketing reports of thrombotic events 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 virilising 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 androgenisation).
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 "Potential testosterone transfer" to patients with major risk of not being able to follow these instructions.
For the patient:
The following precautions are recommended:
- wash hands with soap and water after applying the gel,
- cover the application site 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 ANDROGEL:
- in the event of adventitious contact with this medication, 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.

Patient should wait at least 1 hour before showering or bathing after applying this medicine. Pregnant women must avoid any contact with this medicine 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).
Drug Abuse and Dependence
Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids (AAS). Abuse of testosterone and other AAS are seen in adults and adolescents, including athletes and body builders. Testosterone and AAS abuse can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Section Adverse Effects/Undesirable Effects).
If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and AAS. Conversely, consider the possibility of testosterone and AAS abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.
Continued abuse of testosterone and other AAS may result in dependence and withdrawal symptoms. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism. Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.
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.
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 virilising effects on the fetus. 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 Undesirableeffects
a. Summary of 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 adversereactions: 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 (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000;<1/100); rare (≥1/10,000;<1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

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MedDRA System Organ Class	Adverse Reactions- preferred term Common adverse reactions (>1/100; <1/10)
Psychiatric disorders	Mood disorders
Nervous system disorders	Dizziness, paresthesia, amnesia, hyperaesthesia
Vascular disorders	Hypertension
Gastro-intestinal disorders	Diarrhoea
Skin and subcutaneous tissue disorders	Alopecia, urticaria
Reproductive system and breast disorders	Gynecomastia (which may be persistent, is a common finding in patients treated for hypogonadism) mastodynia, prostatic disorders
General disorders and administrative 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 (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000;<1/100); rare (≥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			
	Frequency not known (cannot be estimated from the available data)	**common (≥1/100; <1/10)**	**rare (≥1/10,000; <1/1,000)**	**very rare (<1/10,000)**
Neoplasms benign, malignant and unspecified (including 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 site conditions	High dose or long- term administration of 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

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse testosterone and anabolic androgenic steroids (AAS) and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidaemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilisation, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty. Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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 the national reporting system.

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.

Chronic Overdose Caused by Abuse

Chronic overdose caused by abuse of testosterone and other anabolic androgenic steroids (AAS) can lead to serious adverse outcomes particularly cardiovascular and psychiatric dverse events (See Sections Warnings and Precautions and Adverse Effects/ Undesirable Effects).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmaco dynamic 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 Pharmacokineticproperties

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 this medicine 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 safetydata

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. PHARMACEUTICALPARTICULARS

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 30°C.

6.5 Nature and contents of container

2.5 g in sachet (PET/Aluminium/PE)

5.0 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.

6 .6 Instructions foruse.

No special requirements.

7. PRODUCT OWNER

Laboratoires Besins International
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8. IMPORTER

Product registration holder
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9. MANUFACTURER

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