Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT:
ANDROGEL, 50 mg, gel in unit-dose sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Testosterone 0.05 g per 5 g sachet
Excipients with known effect: Ethanol.
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM: Gel

Transparent or slightly opalescent, colorless 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 special precautions for use)

4.2 Posology and administration route

Posology

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 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.

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 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.

4.3 Contraindications

This medicine 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

This medicine should be used only if hypogonadism (hyper- and hypogonadotrophic) 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.

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.

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 concentration is recommended in these patients.

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischemic heart disease, treatment with with testosterone may cause severe complications characterized 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 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 tominimise 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 hematocrit (to detect polycythaemia), liver function tests, and lipids 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 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 be observed in patients treated with androgens and may require a descrease in thedose of antidiabetic medications (see section 4.5). Monitoring of the glucose level and HbA1c is advised for patientstreated with androgens.

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.

This medicine should not be used by women, due to possible 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 the 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 Androgel:

- 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 application sites. In case of pregnancy of the partner, the patient must reinforce his attention to the precautions for use (see 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 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 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.

Laboratory tests
Interaction with laboratory tests: androgens may decrease levels of thyroxin binding globulin, resulting in decreased T_4 serum concentrations and in increased resin uptake of T_3 and T_4. Free thyroid hormone levels, however, remain unchanged, and there is no clinical evidence of thyroid insufficiency.

Diabetic medication
Improved insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin levelshave been reported with androgens. In diabetic patients, the dose of antidiabetic medications may need reduction (seesection 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 this medicine's 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.

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 or 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 of gel per day were skin reactions 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 this medicine 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).

MedDRA Organ system class	Adverse reactions - Preferred Term Common adverse reactions (>1/100;<1/10)
Psychiatric disorders	Mood disorders
Nervous system disorders	Dizziness, paraesthesia, amnesia, hyperaesthesia
vascular disorders	Hypertension
Gastro-intestinal disorders	Diarrhoea
Skin and subcutaneous disorders	Alopecia, urticaria
Reproductive and 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 (polycythemia, 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	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 obstructions			
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

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/

4.9 Overdose

Symptoms
Serum testosterone levels should be measured if clinical signs and symptoms indicative of over exposure to androgen are observed. Application site rash has also been reported in case reports of overdose with this medicine.

Treatment
Treatment of over dosage 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 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-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 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
Purified water, Ethanol 96%, Sodium hydroxide, Carbomer 980, Isopropyl myristate

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
5 g in unit-dose sachet (PET/Aluminium/LDPE).

7. MANUFACTURER:

Laboratories BESINS INTERNATIONAL
3,rue du Bourg l'Abbe
75003 Paris
FRANCE

8. MANUFACTURER'S AGENT:
CTS Ltd.
4 Haharash Street
Hod Hasharon
Israel

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