Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Androgel 25 mg, transdermal gel in sachet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet of 2.5 g contains 25 mg of testosterone.
Excipients with known effect: this medicine contains 1.8 g alcohol (Ethanol) in each 2.5 g sachet.
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

This medicine is indicated in adults for 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 doctor depending on the clinical or laboratory response in individual patients, not exceeding 10 g of gel per day (100 mg testosterone). 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.

Patients suffering from severe renal or hepatic insufficiency.
See Section 4.4: Special warnings and precautions for use.

Paediatric population
The safety and efficacy of this medicine in males under 18 years of age has not been established. No data is available.

Use in women
This medicine is not indicated for use in women

Method of administration
Transdermal use.

Patients should be informed that other persons (including children and adults) should not come in contact with the area of the body where testosterone gel has been applied (see Section 4.4).The gel should be administered by the patient himself, onto clean, dry, healthy skin over both shoulders, or both arms or the abdomen.
After opening the sachets, the total contents must be extracted from the sachet and applied immediately onto the skin.

- The gel should 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 thoroughly with soap and water after applying the gel
- Once the gel has dried, cover the application site with clean clothing (such as a T-shirt)
- After applying this medicine patients should wait at least 1 hour before showering or bathing.

Do not apply to the genital areas as the high alcohol content may cause local irritation.

Skin to skin contact
Before close physical contact with another person (adult or child), wash the application site with soap and water once the recommended time period (at least 1 hour) has passed and cover again with clean clothing.

For more information regarding post dose washing see section 4.4 (subsection Skin to skin transfer).

4.3 Contraindications

This medicine is contraindicated:

- Hypersensitivity to the active substance or any excipients listed in Section 6.1.
- Known or suspected prostate cancer or breast carcinoma.

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 deficiency should be clearly demonstrated by clinical features (regression of secondary sexual characteristics, change in body composition, fatigue, 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 for any given individual 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. In addition, diuretic therapy may be required.
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.

Currently, there is no consensus about age specific testosterone reference values. 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.

With large doses of exogenous androgens, spermatogenesis may be reversibly suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

Gynecomastia occasionally develops and occasionally persists in patients being treated with androgens for hypogonadism.

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

Skin to Skin transfer
If no precautions are taken, testosterone gel can be transferred to other persons by close physical contact, at any time after dosing, 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 women and premature puberty and genital enlargement in children) in case of repeated contact (inadvertent androgenization). Additional caution should be taken when using this product and in close physical contact with children as secondary transmission of testosterone through clothing cannot be excluded. Consult a physician in case of signs and symptoms in another person that may have been exposed accidentally to testosterone gel. The physician should inform the patient carefully about the risk of testosterone transfer, for instance during contact with another person including children and about safety instructions. The treating physician should give extra attention to patients with a major risk of not being able to follow these instructions in Method of Administration (see Section 4.2). It is essential to adhere to the application technique when in physical contact with another person. Before close physical contact with another person (adult or child), wash the application site with soap and water once the recommended time period (at least 1 hour) has passed and cover the site again with clean clothing. In the event of a person coming into contact with this medicine, the person affected should immediately wash the affected area with soap and water.

This product contains ethanol: in neonates (pre-term and term newborn infants), high concentrations of ethanol may cause severe local reactions and systemic toxicity due to significant absorption through immature skin (especially under occlusion).

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 1.8 g alcohol (ethanol) in each sachet.
It may cause a burning sensation on damaged skin.
This medicine contains ethanol to aid transdermal delivery and is flammable. Care should be taken to avoid sources of heat / naked flames when administering the product, until the gel has dried on the skin.

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 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
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).

Sunscreens
Application of sunscreen or lotion does not reduce efficacy.

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 (see section 4.4) because this product may have adverse virilizing effects on the foetus. In the event of inadvertent skin-to-skin contact, wash thoroughly 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

The adverse reactions listed in the table are based on post-marketing data, clinical trials and class-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: reaction at the application site (erythema, acne, dry skin) and emotional symptoms.

b. Tabulated list of adverse reactions
Adverse reactions reported in clinical trials and derived from post-marketing experience via spontaneous reports or literature cases are listed below.
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). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.
Adverse Reaction Tabulation for Transdermal Testosterone.

MedDRA System Organ Class	**Adverse reactions – preferred term**				
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to ≥1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**	**Frequency not known** (cannot be estimated from the available data)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Hepatic Neoplasm		Prostate Cancer
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	Mood Disorders, Emotional symptoms (mood swings, affective disorder, anger, aggression, impatience, insomnia, abnormal dreams, increased libido)				Nervousness, Depression, Hostility
Nervous system disorders	Dizziness, Paraesthesia, Amnesia, Hyperaesthesia, Headache				
Vascular disorders	Hypertension	Malignant hypertension, Hot flushes/flushing, Phlebitis			
Respiratory, thoracic and mediastinal disorders					Sleep apnoea
Gastrointestinal disorders	Diarrhoea	Oral pain, Abdominal distension			
Hepatobiliary disorders				Jaundice, Liver function test abnormalities	
Skin and subcutaneous tissue disorders	Alopecia, Urticaria	Acne, Hirsutism, Rash, Dry Skin, Seborrhoea, Skin lesions, Contact			skin reactions[2]

		dermatitis, Hair colour changes, application site hypersensitivity, application site pruritus			
Renal and urinary disorders					Urinary tract obstruction
Musculoskeletal and connective tissue disorders					Muscle Cramps
Reproductive system and breast disorders	Gynaecomastia[1]	Nipple Disorder, Prostate-abnormalities, Testicular pain, Increased frequency of erections	Priapism		Libido changes, therapy with high dose of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles
General disorders and administration site conditions	Application site reaction	Pitting oedema			Asthenia, Malaise, oedema, hypersensitivity reactions, increases the occurrences of water retention and oedema[3]
Investigations	Changes in laboratory tests (polycythaemia, lipids), Haematocrit increased, Haemoglobin increased, Red blood cell count increased	PSA increased			

1. May develop and persist in patients treated for hypogonadism with testosterone.
2. Skin reactions, because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin
3. High dose or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema

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 HPRA Pharmacovigilance; Website: www.hpra.ie.

4.9 Overdose

Symptoms

Alterations to serum testosterone levels may occur with overexposure to testosterone. 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 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

Absorption
The percutaneous absorption of testosterone ranges from approximately 9% to 14% of the applied dose.

Distribution
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.

Biotransformation
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.

Elimination
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

2.5 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

PA1054/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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