Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Testogel 16.2 mg/g, gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of gel contains 16.2 mg testosterone. One pump actuation delivers 1.25 g of gel containing 20.25 mg of testosterone.
Excipients with known effect: Ethanol.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel

Transparent or slightly opalescent, colourless gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Testogel 16.2 mg/g is indicated in adults as 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 two pump actuations of gel (*i.e.* 40.5 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 four pump actuations or 81 mg testosterone per day. The adjustment of posology should be achieved by increments of one pump actuation of gel.

The dose should be titrated based on the pre-dose morning testosterone blood levels. Steady state blood testosterone levels are reached usually by the second day of treatment with this medicine. In order to evaluate the need to adjust the testosterone dosage, blood testosterone levels should be measured in the morning before application of the product, after the steady state is reached. Testosterone blood levels should be assessed periodically. The dose may be reduced if the testosterone blood levels are raised above the desired level. If the levels are low, the dosage may be increased stepwise, to a daily administration of 81 mg of testosterone (four actuations of gel) per day.

Therapy should be discontinued if the blood testosterone levels consistently exceeds the normal range at the lowest daily dose of 20.25 mg (1.25 g gel, equivalent to one pump actuation) or if blood testosterone levels in the normal range cannot be achieved with the highest dose of 81 mg (5 g gel, equivalent to four pump actuations).

Patient suffering from severe renal or hepatic insufficiency
Please see section 4.4 Special warnings and precautions for use.

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

Method of administration

Transdermal use

The application should be administered by the patient himself, onto clean, dry, healthy skin over right and left upper arms and shoulders.

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 to dry for at least 3-5 minutes before dressing. Wash hands with soap and water after application, and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. For more information regarding post dose washing see section 4.4 (subsection Potential for testosterone transfer).

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

To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose.

After the priming procedure, fully depress the actuator once for delivering 1.25 g of this medicine into the palm of the hand and then apply to the upper arms and shoulders.

4.3 Contraindications

This medicine is contraindicated:
- in case of known or suspected prostate cancer or breast carcinoma
- in case of known hypersensitivity to testosterone or to any of the excipients listed in section 6.1.

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 aetiology, responsible for the symptoms, has 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 levels. However, it should be taken into account that physiologically testosterone blood levels decrease with age.

Due to interlaboratory variability, all measurements of testosterone should be carried out by the same laboratory.

Prior to testosterone initiation, all patients should undergo a detailed examination in order to exclude a risk of pre-existing prostate 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 prostate specific antigen (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 risk factors).

Androgens may accelerate the progression of sub-clinical prostate cancer and benign prostate 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 blood calcium levels is recommended in these patients.

In patients suffering from severe cardiac, hepatic or renal insufficiency, or ischaemic 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.

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 levels 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 haemotocrit (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 levels. However, it should be taken into account that physiologically testosterone blood levels are decreasing with 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 re-evaluated and discontinued if necessary.

With large doses of exogenous androgens, spermatogenesis may be 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 virilising effects.

The attention of athletes should be drawn to the fact that this proprietary medicinal product contains an active substance (testosterone) that may produce a positive result in doping control tests.

Potential for inadvertent testosterone transfer

Testosterone gel can be transferred to other persons by close skin to skin 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 the event of repeated contact (inadvertent androgenisation). If virilisation occurs, testosterone therapy should be promptly discontinued until the cause has been identified.

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 (such as a sleeved shirt) once the gel has dried
- shower and wash the application area before any situation in which close contact is foreseen

For people not being treated with this medicine:
- 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's application sites. In case of pregnancy of a partner, the patient must pay extra attention to the precautions for use described above (also see section 4.6).

This medicine contains 0.9 g alcohol (ethanol) in each dose of 1.25 g gel.
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 interactions

Oral anticoagulants

Due to changes in anticoagulant activity (increased effect of the oral anticoagulant by modification of hepatic synthesis of coagulation factor and competitive inhibition of plasma protein binding) increased monitoring of the prothrombin time and international normalized ratio (INR) 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

Interactions 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 might need reduction (see section 4.4).

Application of sunscreen or lotion don’t reduce efficacy.

Washing 2 hours after application doesn’t have significant effect on blood testosterone levels.

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 or breast-feeding women, due to potential virilising effects of the foetus.

Pregnant women must avoid any contact with this medicine's application sites (see section 4.4). 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

This medicine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently observed clinical adverse drug reactions observed with this medicine used at the recommended dosage were psychiatric disorders and skin reactions at the application site.

b. Tabulated list of adverse reactions
Clinical trial data

The table below shows adverse reactions reported in the 182-day, double-blind period of the TESTOGEL 16.2 mg/g Phase III clinical trial and more frequently in the TESTOGEL 16.2 mg/g treated group (n=234) than the placebo treated group (n=40).

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).

Table 1 Frequency of Adverse Reactions from TESTOGEL 16.2 mg/g Phase III Study

MedDRA System Organ Class	**Adverse Reactions - Preferred Terms**	
	Common (≥1/100; <1/10)	**Uncommon (>1/1,000, <1/100)**
Psychiatric disorders	Emotional symptoms* (mood swings, affective disorder, anger, aggression, impatience, insomnia, abnormal dreams, increased libido)	
Vascular disorders		Malignant hypertension, flushing, phlebitis
Gastrointestinal disorders		Diarrhoea,abdominal distension, oral pain
Skin and subcutaneous tissue disorders	Skin reactions* (acne, alopecia, dry skin, skin lesions, contact dermatitis, hair colourchanges, rash, application site hypersensitivity, application site pruritus)	
Reproductive system and breast disorders		Gynaecomastia, nipple disorder, testicular pain, increased erection
General disorders and administration site conditions		Pitting oedema
Investigations	PSA increased, increased haematocrit or haemoglobin	

* Events grouped

Because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin.

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 (incl cysts and polyps)	Prostate cancer (Data on prostate cancer riskin 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			
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,red blood cell count increased, haemoglobin increased		Liver function test abnormalities

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:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens. ATC code: G03B A03.

Endogenous androgens, 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). Androgens have also an effect on protein anabolism, on development of skeletal muscle and body fat distribution and also reduce urinary nitrogen, sodium, potassium, chloride, phosphate and water excretion.

Testosterone 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 after administration of this medicine lies between 1% and 8.5%.

Following percutaneous absorption, testosterone diffuses into the systemic circulation and provides relatively constant concentrations during the 24 hour cycle.

Blood testosterone levels increase from the first hour after an application, reaching steady state from day two. Daily changes in testosterone levels 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 level increase of approximately 2.3 ng/ml (8.0 nmol/l) in plasma.

When treatment is stopped, testosterone levels start decreasing approximately 24 hours after the last administration. Testosterone levels return to baseline approximately 72 to 96 hours after the final administration.

The major active metabolites of testosterone are dihydrotestosterone and oestradiol.

Testosterone is excreted mostly in urine as conjugated testosterone metabolites and a small amount is excreted unchanged in the faeces.

In the phase III double blind study at the end of a 112 day treatment period, during which the dose of this medicine could be titrated based on total testosterone concentrations, 81.6% (CI 75.1-87.0%) of men had total testosterone levels within the normal range for eugonadal young men (300 -1000 ng/dl). In patients on a daily dose of this medicine the average (±SD) daily testosterone concentration on day 112 (C_{av}) was 561 (±259) ng/dl, mean C_{max} was 845 (±480) ng/dl and mean C_{min} was 334 (±155) ng/dl. The corresponding concentrations on Day 182 (double blind period) were C_{av} 536 (±236) ng/dl, mean C_{max} 810 (±497) ng/dl and mean C_{min} 330 (±147) ng/dl.

In the phase III open label study at the end of a 264 day treatment period, during which the dose of this medicine could be titrated based on total testosterone concentrations, 77 % (CI 69.8-83.2%) of men had total testosterone levels within the normal range for eugonadal young men (300 -1000 ng/dl).
In patients on a daily dose of this medicine the average (±SD) daily testosterone concentration on day 266 (C_{av}) was 459 (±218) ng/dl, mean C_{max} was 689 (±414) ng/dl and mean C_{min} was 305 (±121) ng/dl. The corresponding concentrations on Day 364 (extended open-label period) were C_{av} 454 (±193) ng/dl, mean C_{max} 698 (±382) ng/dl and mean C_{min} 302 (±126) ng/dl.

5.3 Preclinical safety data

Testosterone has been found to be non-mutagenic *in vitro* using the reverse mutation model (Ames test) or Chinese 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. The importance of these findings and the actual risk in human beings is unknown.

The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

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

Multi-dose container (comprised of a polypropylene canister with an LDPE lined pouch) with metering pump that contains 88 g gel and delivers a minimum of 60 doses.

Pack sizes:
1 container per carton
Supplied in packs of 1, 2, 3 or 6 containers

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoires Besins International
3, rue du Bourg l'Abbe
75003 Paris
France

8 MARKETING AUTHORISATION NUMBER

PA1054/002/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th December 2015
Date of last renewal: 31st December 2020

10 DATE OF REVISION OF THE TEXT

June 2021