

## Approved Professional Information for TESTOGEL

### SCHEDULING STATUS

S5

#### 1. NAME OF THE MEDICINE

TESTOGEL, 50 mg/5 g, transdermal gel

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of 5 g contains 50 mg of testosterone.

Excipients with known effect: Ethanol 96 % v/v.

For the full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Transdermal gel.

A transparent or slightly opalescent, colourless gel in a sachet.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Testosterone replacement therapy for male hypogonadism in adult men when testosterone deficiency has been confirmed by clinical features and biochemical tests (see section 4.4).

TESTOGEL is not for use in children.

##### 4.2 Posology and method of administration

###### ***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 adjustment of posology should be achieved in steps of 2,5 g of gel.

Steady state plasma testosterone concentrations are reached approximately on the 2<sup>nd</sup> day of

treatment with TESTOGEL.

In order to adjust the TESTOGEL dose, serum testosterone concentrations must be measured in the morning before application, from the 3<sup>rd</sup> day after starting treatment (one week is 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, but not exceeding 10 g of gel per day.

### *Children*

TESTOGEL is not indicated for use in children.

### **Method of administration**

Transdermal use.

The application should be administered by the patient himself, onto clean, dry, healthy skin over both shoulders, both arms or abdomen.

After opening the sachets, the total contents must be extracted from the sachet and applied immediately onto the skin. TESTOGEL should be gently spread on the skin, 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**

TESTOGEL is contraindicated:

- In cases of known hypersensitivity to testosterone or to any other ingredients of TESTOGEL (see section 6.1).
- In cases of known or suspected prostatic cancer or breast carcinoma.

### **4.4 Special warnings and precautions for use**

- **TESTOGEL is indicated for use only in men with primary or secondary hypogonadism resulting from certain medical conditions.**
- **TESTOGEL should not be used for age-related hypogonadism.**

- **Before initiating TESTOGEL, ensure that the diagnosis of hypogonadism has been confirmed with laboratory testing. Verify that serum testosterone concentrations have been measured on at least two separate mornings and are consistently below the normal range. Avoid measuring testosterone concentrations later in the day, when measurements can be low even in men who do not have hypogonadism.**
- **Inform patients of the potential increased cardiovascular risk associated with TESTOGEL. Increases in myocardial infarction and stroke have been reported.**
- **Encourage patients to read the patient information leaflet they receive with TESTOGEL.**

TESTOGEL should be used only if hypogonadism (hyper- and hypogonadotropic) has been demonstrated and if other aetiology responsible for the symptoms has been excluded before treatment is initiated. 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 2 separate blood testosterone measurements.

Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

Prior to TESTOGEL initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breasts must be performed in accordance with recommended methods (digital rectal examination and estimation of serum PSA) in patients receiving TESTOGEL therapy at least once yearly and twice yearly in elderly patients and at-risk patients (those with clinical or familial factors).

TESTOGEL may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.

TESTOGEL should not be used 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 who have experienced myocardial infarction, suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with TESTOGEL may cause severe complications characterised by oedema with or without congestive cardiac failure. In this case, treatment must be stopped immediately.

TESTOGEL may cause a rise in blood pressure and should be used with caution in men with hypertension.

TESTOGEL 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.

The testosterone level should be monitored at baseline and at regular intervals during treatment. Health care providers should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.

In patients receiving long-term TESTOGEL therapy, the following laboratory parameters should also be monitored regularly: haemoglobin, haematocrit (to detect polycythaemia), liver function tests, and lipid profile.

There is limited experience on the safety and efficacy of the use of TESTOGEL 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.

TESTOGEL should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated.

There is an increased risk of sleep apnoea in hypogonadal patients treated with testosterone esters, such as TESTOGEL, especially in those with risk factors such as obesity and chronic respiratory disease.

Improved insulin sensitivity may occur in patients treated with TESTOGEL and may require a decrease in the dose of antidiabetic medicine (see section 4.5). Monitoring of the glucose level and HbA1c is advised for patients treated with TESTOGEL.

Certain clinical signs such as irritability, nervousness, weight gain, and prolonged or frequent erections may indicate excessive TESTOGEL 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 TESTOGEL contains an active substance (testosterone) which may produce a positive reaction in anti-doping tests.

TESTOGEL should not be used by women, due to its potential virilising effects.

***Potential testosterone transfer***

**TESTOGEL 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 health care practitioner 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).**

**TESTOGEL 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).**

**Transfer of TESTOGEL is avoided by wearing clothes covering the application area or showering prior to contact.**

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 TESTOGEL***

- In the event of adventitious contact with TESTOGEL, 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 TESTOGEL.

To guarantee partner safety the patient should be advised, for example, to observe a long interval between TESTOGEL application and sexual intercourse, to wear a T-shirt covering the application site during the contact period or to shower before sexual intercourse.

Furthermore, it is recommended to wear a T-shirt covering the application site during any contact period with children, to avoid the risk of contaminating children's skin.

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

TESTOGEL is not a treatment for male sterility or impotence.

TESTOGEL contains 96 % v/v ethanol (alcohol).

It may cause burning sensation on damaged skin.

TESTOGEL is flammable until dry.

#### **4.5 Interaction with other medicines and other forms of interaction**

##### ***Oral anticoagulants***

Changes in anticoagulant activity (the increased effect of the oral anticoagulant by modification of hepatic synthesis of the coagulation factor and competitive inhibition of plasma protein binding):

Increased monitoring of the prothrombin time and international normalised ratio (INR) determinations, are recommended. Patients receiving oral anticoagulants require close monitoring, especially when treatment with androgens are started or stopped.

##### ***Adrenocorticotrophic hormone (ACTH) or corticosteroids***

Concomitant administration of TESTOGEL and ACTH or corticosteroids may increase the risk of developing oedema. As a result, these medicines should be administered cautiously, particularly in patients suffering from cardiac, renal or hepatic disease.

##### ***Interaction with laboratory tests***

TESTOGEL may decrease levels of thyroxin binding globulin, resulting in decreased T<sub>4</sub> serum concentrations and increased resin uptake of T<sub>3</sub> and T<sub>4</sub>. Free thyroid hormone levels, however, remain unchanged and there is no clinical evidence of thyroid insufficiency.

##### ***Diabetic medicine***

Improved insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin levels have been reported with androgens. In diabetic patients, the dose of antidiabetic medicine may need reduction (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

### ***Fertility***

Spermatogenesis may be reversibly suppressed with TESTOGEL.

### ***Pregnancy***

TESTOGEL is intended for use by men only.

TESTOGEL is not indicated in pregnant women. No clinical trials have been conducted with the treatment of TESTOGEL in women.

**Pregnant women must avoid any contact with TESTOGEL application sites (see section 4.4).**

**TESTOGEL may cause virilising effects on the fetus. In the event of contact, wash with soap and water as soon as possible.**

### ***Breastfeeding***

TESTOGEL is not indicated in women who are breastfeeding.

## 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

### ***Summary of the safety profile***

The most frequently observed adverse reactions at the recommended dosage of gel per day were skin reactions: reaction at the application site, erythema, acne, dry skin.

### ***Tabulated list of adverse reactions***

#### *Clinical trial data*

Adverse reactions reported in 1 - < 10 % of patients treated with TESTOGEL 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 ( $\geq 1/10$ ); common ( $\geq 1/100$ ;  $< 1/10$ ); uncommon ( $\geq 1/1\ 000$ ;  $< 1/100$ ); rare ( $\geq 1/10\ 000$ );

< 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	
	Common adverse reactions (> 1/100; < 1/10)	Uncommon adverse reactions (≥ 1/1 000; < 1/100)
<b>Psychiatric disorders</b>	Mood disorders	
<b>Nervous system disorders</b>	Dizziness, paraesthesia, amnesia, hyperaesthesia	
<b>Vascular disorders</b>	Hypertension	Arterial vasodilation
<b>Respiratory, thoracic and mediastinal disorders</b>		Asthma
<b>Gastro-intestinal disorders</b>	Diarrhoea	Nausea
<b>Skin and subcutaneous tissue disorders</b>	Alopecia, urticaria	Pruritus
<b>Musculoskeletal and connective tissue disorders</b>		Myalgia
<b>Reproductive system and breast disorders</b>	Gynaecomastia (which may be persistent, is a common finding in patients treated for hypogonadism), mastodynia, prostatic disorders	Oligospermia
<b>General disorders and administration site conditions</b>	Headache	
<b>Investigations</b>	Changes in laboratory tests (polycythaemia, lipids), increased: haematocrit, red blood count and haemoglobin.	

### *Post-marketing experience*

The following table includes adverse reactions identified during post-approval use of TESTOGEL 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 ( $\geq 1/100$ ; $< 1/10$ )	Rare ( $\geq 1/10\ 000$ ; $< 1/1\ 000$ )	Very rare ( $< 1/10\ 000$ )
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>	Prostate cancer (data on prostate cancer risk in association with testosterone therapy are inconclusive)		Hepatic neoplasm	
<b>Metabolism and nutrition disorders</b>	Increase in body mass, electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water) during high dose and/or prolonged treatment			
<b>Psychiatric disorders</b>	Nervousness, depression, hostility			
<b>Respiratory, thoracic and mediastinal disorders</b>	Sleep apnoea			
<b>Hepatobiliary disorders</b>				Jaundice
<b>Skin and subcutaneous tissue disorders</b>	Acne, seborrhoea, balding			
<b>Musculoskeletal and connective tissue disorders</b>	Muscle cramps			
<b>Renal and urinary disorders</b>	Urinary obstructions			
<b>Reproductive system and breast disorders</b>	Libido changes, increased frequency of erections; therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby		Priapism	

	reducing the size of the testicles; prostate abnormalities			
<b>General disorders and administration site conditions</b>	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 TESTOGEL, frequent applications to the skin may cause irritation and dry skin.			
<b>Investigations</b>		Increased: haematocrit, haemoglobin, red blood cell count		Liver function test abnormalities

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TESTOGEL is important. It allows continued monitoring of the benefit/risk balance of TESTOGEL. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reaction Reporting Form**”, found online under SAHPRA’s publications: <https://www.sahpra.org.za/Publications/Index/8>

## 4.9 Overdose

### *Symptoms*

In overdose, side effects will be exacerbated and exaggerated (see section 4.8). 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 TESTOGEL.

### *Treatment*

Treatment is symptomatic and supportive. Treatment of overdosage consists of washing the application

site immediately and discontinuing treatment if advised by the treating health care practitioner.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Category and class: A 21.7 Male sex hormones

Pharmacotherapeutic group: Sex Hormones and Modulators of the Genital System, Androgens, ATC code: G03BA03.

Testosterone is an androgen hormone. 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 then 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.

Application of 5 g of TESTOGEL 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 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**

Carbopol 980

Ethanol 96 % v/v

Isopropyl myristate

Purified water

Sodium hydroxide (pH adjuster).

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf life**

36 months.

Store at or below 25 °C.

### **6.4 Special precautions for storage**

TESTOGEL does not require any special storage conditions.

### **6.5 Nature and contents of container**

5 g PET/aluminium/PE sachets.

Pack sizes: 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 and other handling**

See section 4.2 for handling of TESTOGEL.

## **7. HOLDER OF CERTIFICATE OF REGISTRATION**

Medi Challenge (Pty) Ltd

493 De Jonge Street

Elardus Park

Pretoria, 0181

## **8. REGISTRATION NUMBER**

A40/21.7/0726

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of registration: 28 April 2021

## **10. DATE OF REVISION OF THE TEXT**

27 October 2022