TESTOGEL

testosterone

1 NAME OF MEDICINE

Testogel 16.2 mg/g transdermal 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: This medicine contains 0.9 g alcohol (ethanol) in each dose of 1.25 g gel.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Transdermal gel

Transparent or slightly opalescent, colourless gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicine 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 Dose 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, up 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).

Number of actuations	**Amount of gel (g)**	**Quantity of testosterone applied to the skin (mg)**
1	1.25	20.25
2	2.5	40.5
3	3.75	60.75
4	5.00	81.0

Patient suffering from severe renal or hepatic insufficiency

In patients suffering from severe 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. 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.

Patients should be informed that other people (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 application should be administered by the patient himself, onto clean, dry, healthy skin over right and left upper arms and shoulders.

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.

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 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.

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. For more information regarding post dose washing see section 4.4.

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 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 is not a treatment for male infertility.

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. In addition, diuretic therapy may be required.

In middle-aged and older patients with hypogonadism and pre-existing or a high risk of cardiovascular disease, testosterone-replacement therapy has not been shown to influence the incidence of major adverse cardiac events. Similarly, in patients with hypogonadism and without a risk for myocardial infarction, stroke or venous thromboembolism, treatment with testosterone is not associated with an increased risk for composite cardiovascular events.

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. Physicians 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 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.

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 virilising effects.

Potential for inadvertent testosterone transfer
If no precautions are taken, testosterone gel can be transferred to other persons by 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 or 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 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" in the CMI or pack insert, to patients with a major risk of not being able to follow these instructions.

Skin to skin transfer - pregnant women and children
Additional caution should be taken when using this product and in close physical contact with children. Secondary transmission of testosterone is reduced by clothing, but it cannot be excluded. It is essential to adhere to the application technique (see section 4.2) when in physical contact with children, including covering the application site with clean clothing once the gel has dried.
Furthermore, please wash the application site with soap once the recommended time period (at least 1 hour) has passed and cover again with clean clothing before physical contact with children.

In case of contact, the child's skin should be washed with soap and water as soon as possible. Consult a physician in case of signs and symptoms (secondary sexual changes) in a child that may have been exposed accidentally to testosterone gel.

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 a partner, the patient must pay extra attention to the precautions for use described above (also see section 4.6).

Precautions:

Testosterone Gel (TESTOGEL) may cause a burning sensation on damaged skin.

Testosterone Gel (TESTOGEL) contains ethanol to aid transdermal delivery and is flammable. Care should be taken to avoid sources of heat / naked flames when first administering the product, until the gel has dried on the skin.

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 t-shirt) once the gel has dried
- Shower and wash the application area thoroughly with soap and water to remove any testosterone residue before any situation in which close contact is foreseen once the recommended time period (at least 1 hour) has passed.

To improve partner safety (see Section 4.2):

- the patient should be advised to thoroughly wash the area with soap during a shower before sexual intercourse or, if this is not possible, to wear clothing such as a sleeved shirt covering the application site during the contact period.
- in the event of a partner coming into adventitious contact with this medicine, the person affected should immediately wash the affected area with soap and water,
- in addition, if the partner develops any signs of excessive androgen exposure such as acne or changes in hair growth, this should be reported to the doctor.

Patients should wait at least 1 hour before showering or bathing after applying this medicine.

4.5 Interactions with other medicines and other forms of interaction

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).

Sunscreens

Application of sunscreen or lotion does not reduce efficacy of Testogel.

4.6 Fertility, pregnancy and lactation

Pregnancy
Testogel 16.2 mg/g is intended for use by men only.

Testogel 16.2 mg/g is not indicated in pregnant women, due to potential virilising effects of the foetus.

Pregnant women must avoid any contact with Testogel 16.2 mg/g application sites (see section 4.4) because this product may have adverse virilising effects on the foetus. In the event of contact, wash with soap and water as soon as possible.

Breast-feeding
Testogel 16.2 mg/g should not be used in women who are breast-feeding.

Fertility
Spermatogenesis may be reversibly suppressed with Testogel 16.2 mg/g.

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
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.

Tabulated list of adverse reactions

Clinical trial data
The table below shows adverse reactions reported in the 182-day, double-blind period of this medicine's Phase III clinical trial and more frequently in this medicine's treated group (n=234) than the placebo treated group (n=40).

Table 1 Frequency of Adverse Reactions from 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)	

MedDRA System Organ Class	Adverse Reactions - Preferred Terms	
	Common (≥1/100; <1/10)	**Uncommon (≥1/1,000, <1/100)**
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 colour changes, 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	**Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance**				
	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)**

Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Prostate cancer (Data on prostate cancer risk in association with testosterone therapy are inconclusive.)	Hepatic neoplasm		
Metabolism and nutrition disorders				Electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water)	
Psychiatric disorders	Anxiety	Decreased libido	Emotional lability		Nervousness, depression, hostility
Nervous system disorders		Paraesthesia generalised, Headache			
Vascular disorders		Hypertension, Hot flushes/flushing			
Gastrointestinal disorders		Nausea			
Hepatobiliary disorders			Liver function test abnormalities	Jaundice	
Skin and subcutaneous tissue disorders		Acne, Pruritus, Alopecia, Hirsutism	Seborrhoea		Because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin.
Musculoskeletal and connective		Muscle cramps			

tissue disorders					
Reproductive system and breast disorders		Gynaecomastia (may develop and persist in patients treated for hypogonadism with testosterone), Prostate abnormalities, Benign prostate hyperplasia, Prostatomegaly prostatic disorder, Spermatogenesis, and semen disorders, Oligospermia, Testicular atrophy	Priapism, increased frequency of erections, Azoospermia		
Respiratory, thoracic and mediastinal disorders					Sleep apnoea
Renal and urinary disorders					urinary tract obstruction
General disorders and administration site conditions	Application site reaction, hypersensitivity	Peripheral oedema			Asthenia, malaise
Investigations	Changes in laboratory tests (polycythaemia, lipids)	PSA increased, red blood cell count increased, weight gain, haematocrit increased, altered blood lipid levels.	Reduction in HDL cholesterol.		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows

continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Symptoms

Only one case of acute testosterone overdose following an injection has been reported in the literature. This was a case of a cerebrovascular accident in a patient with a high plasma testosterone concentration of 114 ng/ml (395 nmol/l). It would be most unlikely that such blood testosterone levels would be achieved using the transdermal route.

Treatment

Treatment of overdosage consists of washing the application site immediately, with appropriate symptomatic and supportive care and discontinuing treatment if advised by the treating physician.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 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 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 2.5 g of this medicine produces an average testosterone level increase of approximately 2.2 ng/ml (7.7 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. No correlation between these findings and the actual risk in human beings has been established.

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.

Testosterone has a masculinising effect on the female foetus when administered to pregnant animals during organogenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer
Isopropyl myristate
Ethanol 96%
Sodium hydroxide
Purified Water

Contains ethanol: It may cause burning sensation on damaged skin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

This product is flammable until dry.

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 pump actuations.

Pack sizes:

1 container per carton

6.6 Special precautions for disposal and other handling

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington

Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL

02 November 2023

10 DATE OF REVISION OF THE TEXT

14 Nov 2024

CCDS Version 5.0

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.2, 5.3, 6.1	Update to align with CCDS 5.0 and as per Medsafe request.
Section 4.8	Addition of adverse events in alignment with the latest CCDS and per Medsafe request.