AUSTRALIAN PRODUCT INFORMATION – TESTAVAN® (TESTOSTERONE) GEL

1. NAME OF THE MEDICINE

Testosterone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TESTAVAN contains 20 mg (2 % w/w) testosterone in one gram of gel. It is presented in a metered-dose pump. One pump actuation delivers 1.15 g (in 1.25 mL) of gel, equivalent to 23 mg of testosterone. Each pump contains 85.5 g of gel capable of dispensing 56 metered individual doses.

Excipient with known effect: propylene glycol.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Gel

TESTAVAN is a translucent to slightly opalescent, hydroalcoholic transdermal gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TESTAVAN is indicated for use as testosterone replacement therapy for adult male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

4.2 Dose and method of administration dosage

Dosage

Adult Men

The recommended starting dose is 23 mg testosterone (one pump actuation) applied once daily, preferably in the morning. To ensure proper dosing, serum testosterone levels should be periodically measured and dose titrated to maintain serum testosterone levels.

The serum testosterone level should be measured 2 to 4 hours after dosing approximately 14 days and 35 days after starting treatment or after a dose adjustment. If the serum testosterone concentration is below 17.3 nmol/L (500 ng/dL), the daily TESTAVAN dose may be increased by 1 pump actuation. If the serum testosterone concentration exceeds 36.4 nmol/L (1050 ng/dL), the daily dose may be decreased by 1 pump actuation.

Dose titration should be based on both serum testosterone levels and the existence of clinical signs and symptoms related to testosterone deficiency.

Patients switching from another testosterone product to TESTAVAN should have their dosage titrated according to serum testosterone levels and clinical signs and symptoms following the instructions in the dosage and administration section.

Maximum recommended dose

The maximum recommended dose is 69 mg testosterone per day, which is equivalent to 3 pump actuations of TESTAVAN.

Dosage adjustment in special populations

Elderly

Use the same dosage in the elderly as recommended under Adult Men. However, it should be taken into account that physiological testosterone levels are lower with increasing age (see **section 4.4 – Special warnings and precautions for use**).

Renal impairment

There are no studies undertaken to demonstrate the efficacy and safety of this medicinal product in patients with renal impairment. Therefore, testosterone replacement therapy should be used with caution in these patients (see **section 4.4 – Special warnings and precautions for use**).

Hepatic impairment

There are no studies undertaken to demonstrate the efficacy and safety of this medicinal product in patients with hepatic impairment. Therefore, testosterone replacement therapy should be used with caution in these patients (see **section 4.4 – Special warnings and precautions for use**).

Female population

TESTAVAN is not indicated for use in women.

Paediatric use

TESTAVAN is not indicated for use in children and has not been evaluated clinically in males under 18 years of age.

Method of administration

For transdermal use.

TESTAVAN should be administered by the patient using the applicator, onto clean, dry, healthy skin over the upper arm and shoulder. Patients should be instructed not to apply TESTAVAN with fingers or hands.

Priming of new pump

To ensure correct dosing, patients should be instructed to prime each new pump before using it for the first time by pressing the pump head all the way down over a tissue paper until gel appears. Discard the initial gel that appears and the gel from 4 subsequent pump actuations and safely discard the used tissue paper.

To apply the gel to the applicator head first remove the applicator lid and place the applicator head under the pump head. The pump head should be pressed all the way down once over the applicator head.

Patients should be instructed that the content of only one pump actuation should be applied onto the applicator at a time. The applicator should be used to spread the gel evenly across the maximum surface area of one upper arm and shoulder, making sure not to get any gel on the hands. When more than one pump actuation is needed to achieve the required daily dose, the procedure is repeated to the other upper arm and shoulder.

Table 1: Dosing Information for TESTAVAN 2 % Gel from the metered-dose pump.

Dose	**Application method**
23 mg (1 pump actuation)	**Apply one** pump actuation to an upper arm and shoulder.
46 mg (2 pump actuation)	**Apply one** pump actuation to an upper arm and shoulder. **Repeat** to apply one pump actuation to the opposite upper arm and shoulder.
69 mg (3 pump actuation)	**Apply one** pump actuation to an upper arm and shoulder. **Repeat** to apply one pump actuation to the opposite upper arm and shoulder. **Repeat again** to apply the third pump actuation to the original upper arm and shoulder.

Cleaning of the applicator

After use the applicator should be cleaned with a tissue and the protective lid restored on top of the applicator. The used tissue paper should be safely thrown away and the product stored safely out of reach of children.

Following administration

If the gel was touched with the hands during the application procedure, patients should be instructed to wash their hands with water and soap immediately after applying TESTAVAN.

Patients should be advised to let the application site dry completely before getting dressed. Patients should be advised to wait 1-2 hours before showering, swimming or bathing to prevent reduced testosterone absorption (see **section 4.4 – Special warnings and precautions for use**).

Patients should be advised to wear clothing that covers the application site at all times to prevent accidental transfer to others.

4.3 Contraindications

TESTAVAN is contraindicated in cases of known hypersensitivity to the active substance, propylene glycol or to any of the excipients.

TESTAVAN is contraindicated in men with known or suspected carcinoma of the breast or the prostate (see **section 4.4 – Special warnings and precautions for use**).

TESTAVAN is contraindicated in all women, including women who are or may become pregnant or who are breastfeeding (see **section 4.4 – Special warnings and precautions for use**).

4.4 Special warnings and precautions for use

TESTAVAN should only be used if hypogonadism has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded before treatment is started. Testosterone deficiency should be clearly demonstrated by clinical features and confirmed by 2 separate blood testosterone measurements before initiating therapy with any testosterone replacement, including TESTAVAN treatment.

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

Prior to initiation of testosterone replacement therapy, 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 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 annually and twice yearly in elderly patients and at risk patients (those with clinical or familial factors).

TESTAVAN 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.

TESTAVAN is not a treatment for male sterility or impotence. TESTAVAN should not be used in men desiring fertility.

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. Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment.

There is limited experience on the safety and efficacy of the use of TESTAVAN in patients over 65 years of age. Currently, there is no consensus concerning age specific reference values for testosterone. However it should be taken into consideration that physiological testosterone serum levels are lower with increasing age.

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

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 this case, treatment must be stopped immediately.

Testosterone should be used with caution in patients with ischemic heart disease, epilepsy and migraine, as these conditions may be aggravated.

There are published reports of an increased risk of sleep apnoea in hypogonadal men treated with testosterone esters, especially in those with risk factors, such as obesity or chronic respiratory disease.

If the patient develops a severe application site reaction, treatment should be reviewed and discontinued if necessary.

In patients receiving long-term androgen therapy, the following laboratory parameters should also be monitored regularly: haemoglobin, and haematocrit, liver function tests and lipid profile.

Athletes treated for testosterone replacement in primary and secondary male hypogonadism should be advised that the product contains an active substance which may produce a positive reaction in anti-doping tests. Androgens are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.

TESTAVAN should not be used in women due to possible virilising effects.

As washing after TESTAVAN administration reduces testosterone levels, patients are advised not to wash or shower for at least 1 to 2 hours after applying TESTAVAN. When washing occurs up to 1 to 2 hours after the gel application, the absorption of testosterone may be reduced.

TESTAVAN contains propylene glycol, which may cause skin irritation.

Alcohol-based products including TESTAVAN are flammable; therefore avoid fire, flame or smoking until the gel has dried.

Clotting disorders

Testosterone should be used with caution in patients with thrombophilia, or risk factors for venous thromboembolism (VTE) as there have been post-marketing studies and reports of thrombotic events (e.g. deep-vein thrombosis, pulmonary embolism, ocular thrombosis) in these patients during testosterone therapy. In thrombophilic patients, VTE cases have been reported even under anticoagulation treatment, therefore continuing testosterone treatment after first thrombotic event should be carefully evaluated. In case of treatment continuation, further measures should be taken to minimise the individual VTE risk.

Potential for transfer

If no precaution is taken, testosterone gel can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels in the recipient 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 repeat contact (inadvertent androgenisation).

The doctor should inform the patient carefully about the risk of testosterone transfer and about the safety instructions below. TESTAVAN should not be prescribed for patients who are unlikely to comply with the safety instructions (e.g. severe alcoholism, drug abuse, severe psychiatric disorders).

Testosterone transfer can be prevented by wearing clothes covering the application area or showering prior to contact.

As a result, the following Safety Instructions are recommended.

For the patient:

- Use the cap applicator for hands-free administration to reduce the risk of secondary exposure to testosterone
- If the gel was touched with the hands during the application procedure, wash hands thoroughly with soap and water after applying the gel,
- Cover the application area with clothing once the gel has dried,
- Shower before any situation in which skin to skin contact with another person is foreseen.

For people not being treated with TESTAVAN:

- In the event of contact with an application area which has not been washed or is not covered with clothing, wash the area of skin onto which testosterone may have been transferred to as soon as possible, using soap and water,
- Report the development of signs of excessive androgen exposure such as acne or hair modification.

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

Furthermore, it is recommended to wear a T-shirt covering the application site during contact periods with children in order to avoid a contamination risk of children's skin.

Pregnant women must avoid any contact with TESTAVAN application sites. In case of pregnancy of the partner, the precautions for use must be reinforced to the patient (see **section 4.6 – Fertility, pregnancy and lactation: Use in Pregnancy**).

Use in hepatic impairment

There are no studies undertaken to demonstrate the efficacy and safety of this medicinal product in patients with hepatic impairment. Therefore, testosterone replacement therapy should be used with caution in these patients (see **section 4.4 – Special warnings and precautions for use**).

Use in renal impairment

There are no studies undertaken to demonstrate the efficacy and safety of this medicinal product in patients with renal impairment. Therefore, testosterone replacement therapy should be used with caution in these patients (see **section 4.4 – Special warnings and precautions for use**).

Use in the elderly

There is limited experience on the safety and efficacy of the use of TESTAVAN in patients over 65 years of age.

Paediatric use

TESTAVAN is not indicated in children and has not been clinically evaluated in males under 18 years of age.

Effects on laboratory tests

Androgens may decrease concentrations of thyroxin-binding globulins, resulting in decreased total serum thyroxine (T4) concentration and increased resin uptake of triiodothyronine (T3) and T4. Free thyroid hormone concentration remains unchanged and there is no clinical evidence of thyroid dysfunction.

4.5 Interactions with other medicines and other forms of interactions

When androgens are given simultaneously with anticoagulants, the anticoagulant effects can increase. Patients receiving oral anticoagulants require close monitoring of their international normalized ratio (INR), especially when androgen treatment is started or stopped.

The concurrent administration of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may increase the likelihood of oedema; thus these drugs should be administered with caution, particularly in patients with cardiac, renal or hepatic disease.

Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Fertility studies in rodents and primates have shown that treatment with testosterone can impair fertility by suppressing spermatogenesis in a dose dependent manner.

TESTAVAN should not be used in men desiring fertility (see **section 4.4 – Special warnings and precautions for use**).

Use in pregnancy

(Category D)

TESTAVAN must not be used in women who are or may become pregnant (see **section 4.3 - Contraindications**).

Pregnant women should avoid skin contact with TESTAVAN application sites (see **Section 4.4 – Special warnings and precautions for use – Potential for Transfer**).

In the event that unwashed or unclothed skin to which TESTAVAN has been applied does come into direct contact with the skin of a pregnant woman, the general area of contact on the woman should be washed with soap and water immediately.

Testosterone may induce virilising effects on the fetus.

Use in lactation

TESTAVAN is contraindicated during breastfeeding. In the event of accidental contact, women are advised to immediately wash with soap and water.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

The most commonly reported adverse reactions in phase 2 and phase 3 clinical trials lasting up to 9 months were application site reactions (4 %), including rash, erythema, pruritus, dermatitis, dryness, and skin irritation. The majority of these reactions were mild to moderate in severity.

Adverse drug reactions reported in 1 to <10 % of patients treated with TESTAVAN in the phase 2 and phase 3 clinical trials are listed in the Table 2. This safety data is based on 395 hypogonadal patients studied in clinical trials. All adverse reactions reported with a suspected relationship are listed by class and frequency in Table 2:

Table 2: Adverse reactions reported in clinical trials.

MedDRA System Organ Class (SOC)	**Common (≥ 1/100 and < 1/10)**
General disorders and administration site conditions	Application site reaction (including rash, erythema, pruritus, dermatitis, dryness, and skin irritation)
Investigations	Blood triglycerides increased/hypertriglyceridaemia, PSA increased, haematocrit increased, haemoglobin increased
Vascular disorders	Hypertension

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

A meta-analysis of clinical trials of testosterone replacement therapy have identified the following additional adverse effect: slight reduction in serum high-density lipoprotein (HDL) cholesterol.

Post Marketing Experience

- There have been reports of venous thromboembolism in patients using products containing testosterone
- Increased risk of weight gain

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

No case of overdose with TESTAVAN has been reported in clinical trials.

Symptoms

Clinical signs such as irritability, nervousness, weight gain, prolonged or frequent erection can indicate overexposure to androgen and serum testosterone levels should therefore be measured.

Treatment

Treatment of overdosage consists of discontinuation of TESTAVAN together with appropriate symptomatic and supportive care.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia). Do this even if there are no signs of discomfort or poisoning. Wash the skin with soap and water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens.

ATC code: G03B A03

Mechanism of action

TESTAVAN is an androgen replacement therapy containing the male hormone testosterone.

Testosterone and its major metabolite dihydrotestosterone (DHT), endogenous androgens, are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. These effects include the growth and maturation of the prostate, seminal vesicles, penis and scrotum; the development of male hair distribution on the face, chest, axillae and pubis; and laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution.

Insufficient secretion of testosterone, due to testicular failure, pituitary pathology or gonadotropin or luteinising hormone-releasing hormone deficiency, results in male hypogonadism and low serum testosterone concentration. Symptoms associated with low testosterone include decreased sexual desire with or without impotence, fatigue, loss of muscle mass, mood depression and regression of secondary sexual characteristics.

Restoring testosterone levels to within the normal range can result in improvements over time in muscle mass, mood, sexual desire, libido and sexual function, including sexual performance and number of spontaneous erections.

During exogenous administration of testosterone to normal males, endogenous testosterone release may be decreased through feedback inhibition of pituitary luteinising hormone (LH). With large doses of exogenous androgens, spermatogenesis may also be suppressed through inhibition of pituitary follicle stimulating hormone (FSH).

Androgen administration causes retention of sodium, nitrogen, potassium and phosphorus and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. The nitrogen balance is improved only with sufficient intake of calories and protein. Androgens have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietin.

Clinical trials

TESTAVAN was evaluated in a multi-centre, open-label, 120-day Phase 3 clinical study (Study 000127) in 159 hypogonadal men aged 18 to 75 years (mean age 54.1 years). Subjects were white (77 %), African American (20 %), Asian (2 %) or multiracial (1 %).

Subjects applied 23, 46 or 69 mg of testosterone (i.e. one, two or three pump actuations of TESTAVAN) each morning to the skin of the shoulders and upper arms. The starting dose of testosterone was 23 mg, and the dose was titrated based on the testosterone levels at 4 hours after gel application on Days 14, 35 and 56. For the rest of the 120-day study, subjects continued to administer the dose based on the Day 56 testosterone level.

The primary efficacy analysis was the percent of responders, defined as subjects with an average serum total testosterone concentration over 24 hours ($C_{avg(0-24)}$) between 10.4 and 36.4 nmol/L, on Day 90. The primary analysis included 155 subjects who had sufficient testosterone profile data to determine a $C_{avg(0-24)}$ at any time point or had discontinued study treatment early for safety reasons. Subjects who discontinued the study early for safety reasons were considered non-responders. If the Day 90 $C_{avg(0-24)}$ value was not available, the last available value was used.

Of the 153 subjects included in the analysis (Full Analysis Dataset (FAS) population), 77.8 % had a $C_{avg(0-24)}$ between 10.4 and 36.4 nmol/L at Day 90; the study therefore met the pre- determined efficacy criteria (responder rate ≥75 %) (Table 3, Figure 1). A total of 143 subjects had a full pharmacokinetic assessment at Day 90; the response rate for this group was 80.4 % (Table 3, Figure 1).

Table 3. Number (N) and percent of responders (n %) by time point, Study 000127 full analysis set, LOCF.

Time Point	N	n (%)
Day 14	151	44 (29.1 %)
Day 35	153	89 (58.2 %)
Day 56	153	109 (71.2 %)
Day 90	153	119 (77.8 %)
Day 90 (per protocol population)	143	115 (80.4 %)

2 subjects were excluded from day 14 because there was not sufficient PK data at Day 14.
2 Subjects were excluded because there was not sufficient PK data at any visit.
Response is defined as serum total testosterone 10.4-36.4 nmol/L.
LOCF = last observation carried forward; PK = pharmacokinetics

The mean serum concentration of testosterone on Day 90 after titration by dose in Study 000127 is shown in Figure 1.

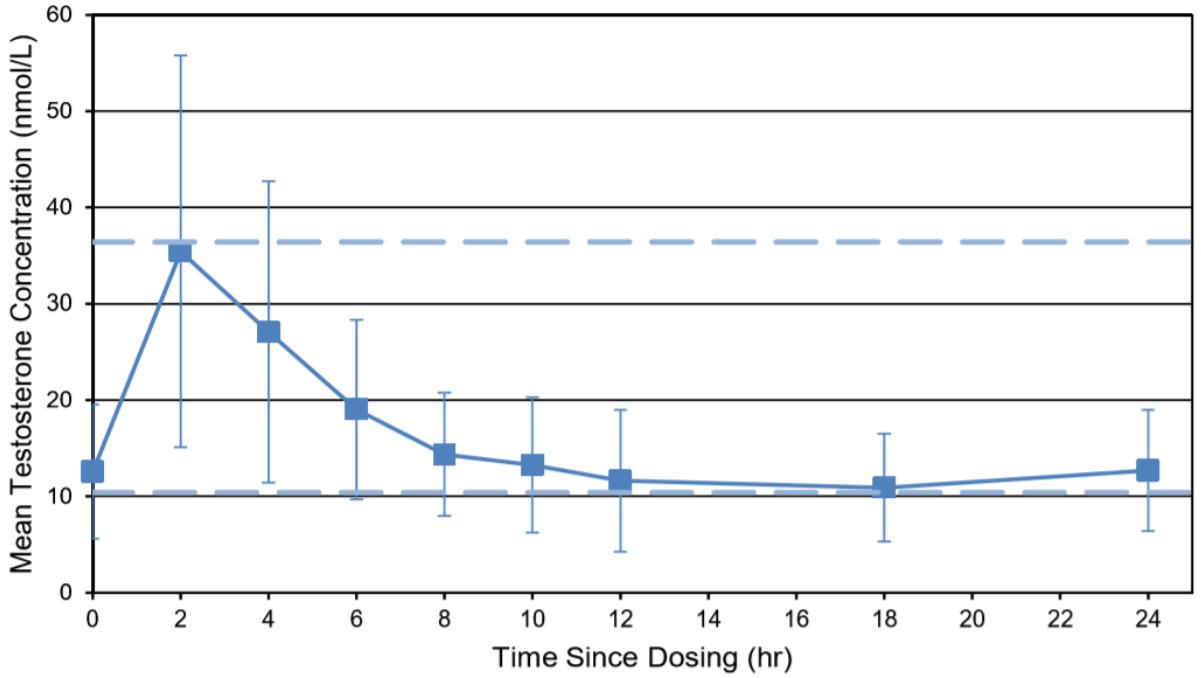


Figure 1. Mean±SD serum concentrations of testosterone on day 90 after titration, Study 000127 full analysis set.

In the 139 subjects who completed the Day 90 assessment, total testosterone and DHT mean concentrations were in the normal range for all TESTAVAN doses. On Day 90, the median T_{max} for testosterone occurred approximately 2 hours after the 46 mg and 69 mg doses and 4 hours after the 23 mg dose.

Table 4 summarises the pharmacokinetic parameters for total testosterone at Day 90 by TESTAVAN Day 90 dose.

Table 4. Pharmacokinetic parameters for total testosterone on day 90 after titration, study 000127 full analysis set (completers).

TESTAVAN Dose on Day 90	N	$C_{avg(0-24)}$ (nmol/L) Mean±SD	C_{max} (nmol/L) Mean±SD	T_{max} (hour) Median
23 mg	5	12.8±4.2	25±8.8	4.02
46 mg	45	17.5±7.2	43±22.2	2.02
69 mg	89	15.2±5.7	38.1±20.6	2.08

$C_{avg(0-24)}$: average serum total testosterone concentration over 24 hours; C_{max}: maximum concentration observed; T_{max}: time of maximum observed concentration (C_{max}); SD: standard deviation

The long-term efficacy of TESTAVAN was evaluated over 9 months in the 90-day Study 000023 and the 6-month extension Study 000077. In Study 000023, 180 hypogonadal men with a mean age of 18 to 75 years (mean age 56.8 years) were treated. Subjects were white (87.7 %), African American (10.6 %), Asian (1.1 %), or American Indian or Alaskan Native (0.6 %). Subjects applied 23, 46 or 69 mg of testosterone each morning to the skin of the shoulders and upper arms.

In Study 000023, the starting dose of testosterone was 46 mg; the dose was titrated up or down on Days 21 and 56. Subjects continued to administer the Day 56 dose for the rest of the 90-day study.

In the 6-month extension Study 000077, doses of 23, 46 or 69 mg testosterone were administered based on the final titrated dose and the pharmacokinetic assessment on Day 90 in Study 000023.

In the 110 subjects who completed 9 months of treatment with TESTAVAN, the responder rate was 83 %.

Effect of Showering

In a randomised, open-label, four-way crossover study, the effects of showering on the pharmacokinetics of total testosterone following application of TESTAVAN 69 mg were assessed in 16 hypogonadal men. Subjects showered 1, 2 or 6 hours following application of TESTAVAN, or did not shower. Each subject was randomly assigned to one of four showering condition sequences.

Showering 1 hour and 2 hours following TESTAVAN administration decreased $C_{avg\ (0-24)}$ by 19.2% and 14.3% respectively compared with subjects who did not shower after TESTAVAN administration. Showering 6 hours following TESTAVAN administration did not result in a decrease in $C_{avg(0-24)}$.

In this study, residual testosterone on the skin at the application site was also determined. The concentration of residual testosterone ranged between 21.3 and 211 micrograms/mL in subjects who did not shower, and was between 0.885 (below the limit of detection) and 14.7 micrograms/mL in subjects who showered one hour after TESTAVAN application.

5.2 Pharmacokinetic properties

Absorption

TESTAVAN provides transdermal delivery of testosterone, mimicking the natural circadian rhythm in terms of temporal changes in testosterone levels, with a median T_{max} of approximately 2-4 hours after dosing.

TESTAVAN delivers physiological amounts of testosterone, by providing a level of circulating testosterone similar to the normal level in healthy men (i.e. 10.4-36.4 nmol/L).

In a Phase 1 randomised open-label crossover bioavailability trial in 11 men in whom endogenous testosterone had been down-regulated, the bioavailability of TESTAVAN when administered as a 50 mg dose on Days 1 and 7 of the study was 1.6-fold (p<0.001) and 1.4- fold (p=0.050) higher, respectively, than observed with the same dose of another proprietary testosterone gel (Testogel 1 %; Figure 2).

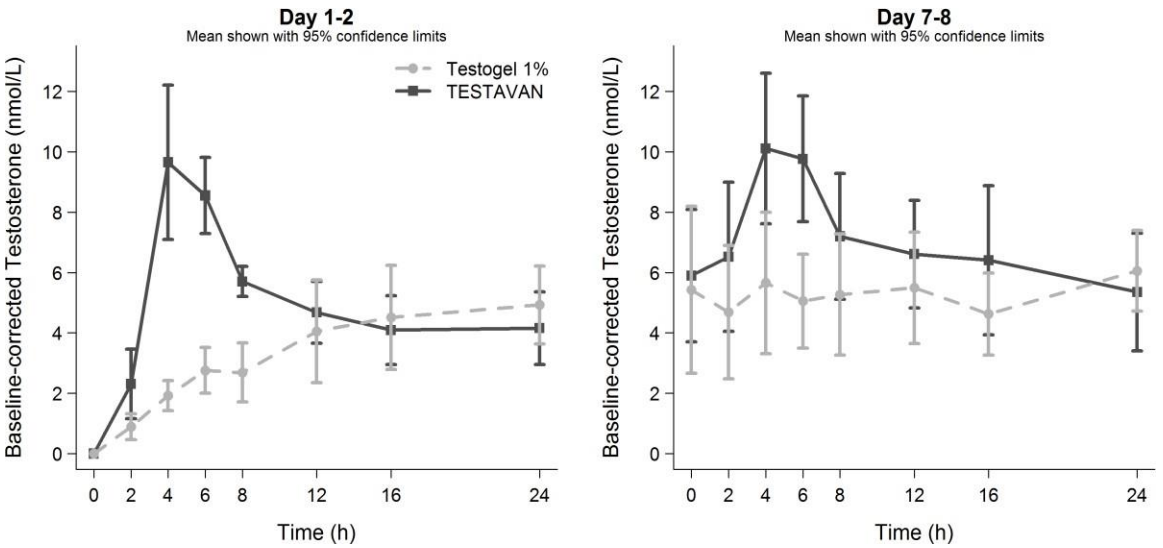


Figure 2. Time-course of baseline-corrected serum testosterone concentrations on days 1-2 (left) and days 7-8 (right) shown as mean (95 % CI) values.

In a Phase 2 open-label, sequential, dose-escalation trial in 20 hypogonadal men, greater absorption of testosterone occurred following application to the shoulder and upper arm than following application to the thigh or abdomen, based on difference in C_{avg} (p<0.05). In this study, serum testosterone concentration, with repeat dosing, generally decreased to their lowest levels approximately 8-9 hours after each dose. No accumulation in serum testosterone was observed after 10 days of daily applications.

In another Phase 2 open-label, sequential, dose- escalation study in 20 hypogonadal men, the administration of 23, 46 and 69 mg TESTAVAN with the applicator resulted in total serum testosterone and DHT concentrations that increased with increasing dose. Average serum total testosterone concentration profiles after 7 days of treatment are shown in Figure 3.

The dose effects of testosterone gel on C_{max}, C_{min} and C_{avg} were statistically significant (p<0.05).

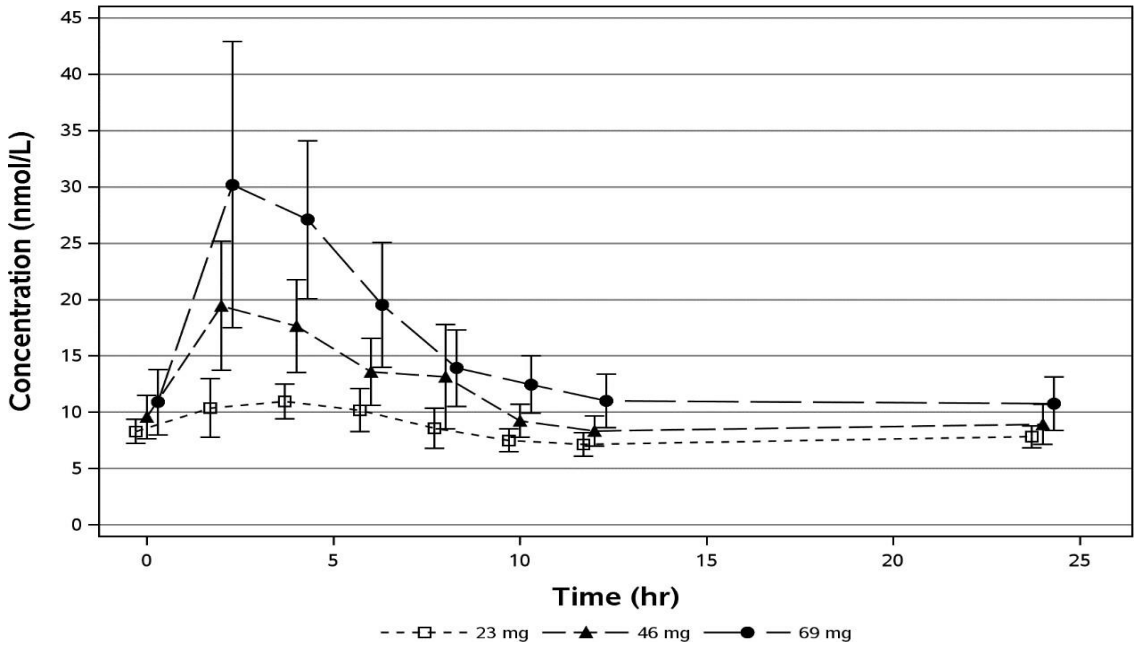


Figure 3. Average serum total testosterone concentration by dose (95 % CI).

Distribution

Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be biologically active. The portion of testosterone bound to SHBG is not considered biologically active. Approximately 45 % of testosterone in plasma is bound to SHBG, 2 % remains unbound (free) and the rest is bound to albumin and other proteins.

Metabolism

As reported in the literature, there is considerable variation in the half-life of testosterone, ranging from ten to 100 minutes. Testosterone is metabolised to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are oestradiol and DHT.

Excretion

About 90 % of testosterone given intramuscularly is excreted in the urine as glucuronic and sulphuric acid conjugates of testosterone and its metabolites; about 6 % of a dose is excreted in the faeces, mostly in the unconjugated form.

5.3 Preclinical safety data

Genotoxicity

Testosterone has been found to be non-mutagenic *in vitro* in bacteria using the reverse mutation model (Ames test), and non-clastogenic *in vitro* in assays with hamster lung fibroblasts and mouse hamster embryo fibroblasts, and negative *in vivo* in the mouse bone marrow micronucleus test. Testosterone was also negative in assays for unscheduled DNA synthesis in rat and human hepatocytes.

Carcinogenicity

Sex hormones are known to promote the growth of certain hormone-dependent tissues and tumours. Subcutaneous implantation of testosterone produced cervical-uterine tumours in female mice, which metastasised in some cases. Metastasising prostatic adenocarcinomas occurred in male rats after chemical induction and subcutaneous implantation of testosterone. Testosterone promotes hepatocarcinogenesis in mice and rats. Hepatocellular carcinoma has been reported in patients receiving long-term therapy with androgens.

Chronic androgen deficiency is a protective factor for prostatic disease, and hypogonadal men receiving androgen replacement therapy require surveillance for prostatic disease similar to that recommended for eugonadal men of comparable age.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients are ethanol, purified water, propylene glycol, diethylene glycol monoethyl ether, carbomer 980, trolamine and disodium edetate.

Refer to **Section 2 – Qualitative and quantitative composition**

6.2 Incompatibilities

Incompatibilities were not assessed as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

Once opened, do not use this product for longer than 60 days.

6.5 Nature and contents of container

TESTAVAN is available for use in a metered-dose dispenser consisting of a pump with a laminate foil pouch in a bottle and is provided with a cap applicator with a hygienic lid.

The pump is composed of polypropylene, ethylene propylene diene monomer and stainless steel and the pouch is a polyethylene/polyethylene terephthalate/aluminium/polyethylene laminate encased in rigid polypropylene bottle.

The product is available in packs of one metered-dose dispenser and a cap applicator with a hygienic lid.

6.6 Special precautions for disposal

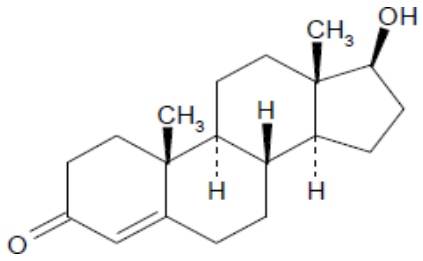
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical Structure

Structure of the active substance:

Testosterone is an androgen.



Chemical name:

17β-hydroxyandrost-4-en-3-one and has the following structural formula:

Chemical Formula: C19H28O2

Molecular Weight: 288.4

Physicochemical characteristics:

Testosterone is an odourless or almost odourless, white, crystalline powder, produced semi- synthetically from plant origin. It is practically insoluble in water, freely soluble in ethanol (96 %) and slightly soluble in ethyl oleate.

CAS Number

58-22-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8. SPONSOR

Clinect Pty Ltd

120-132 Atlantic Drive

Keysborough, VIC 3173

Australia

Telephone: 1800 899 005

9. DATE OF FIRST APPROVAL

26 May 2017

10. DATE OF REVISION

01 September 2021

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/

Summary table of changes

Section Changed	Summary of new information
All	Update to styles.
8	Address and contact details for the new sponsor