NAME OF THE MEDICINE

Testosterone is an androgen. Chemically testosterone is 17β-hydroxyandrost-4-en-3-one and has the following structural formula:

![Chemical Structure of Testosterone](image)

Chemical Formula: \(\text{C}_{19}\text{H}_{28}\text{O}_{2}\)
Molecular Weight: 288.4
CAS No: 58-22-0

DESCRIPTION

Testosterone is a white, crystalline powder, odourless or almost odourless produced semisynthetically from plant origin. It is practically insoluble in water, freely soluble in ethanol (96%); slightly soluble in ethyl oleate.

Testogel is a clear, colourless, hydroalcoholic gel containing 1% testosterone (25 mg in 2.5 g or 50 mg in 5 g) and the excipients: isopropyl myristate, ethanol, carbomer 980, sodium hydroxide and purified water.

PHARMACOLOGY

Pharmacodynamic Properties

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

Endogenous androgens, principally testosterone, secreted by the testes and its major metabolite dihydrotestosterone (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 oestradiol, which binds to oestrogen receptors in the target cell nucleus e.g. the pituitary, fat, brain, bone and testicular Leydig cells.

**Pharmacokinetics**

Approximately 10% of the testosterone dose applied on the skin surface from Testogel is absorbed into the systemic circulation. The surface area of skin contact does not greatly affect the level of testosterone absorption.

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 the end of 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 avoids blood peaks or the first pass effect of oral androgen therapy.

Administration of 5 g of Testogel produces an average testosterone concentration increase in hypogonadic men of approximately 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 DHT and oestradiol.

Testosterone is excreted, mostly in urine, and in faeces as conjugated testosterone metabolites.

**CLINICAL TRIALS**

The pivotal study was a Phase III, randomised, positive-controlled, parallel-group study of Testogel and a commercially available non-scrotal transdermal testosterone patch. Hypogonadal men (N = 227) were assigned to receive 5g Testogel (50mg testosterone) per day, 10g Testogel (100mg testosterone) per day or 5mg testosterone patch (2 x 2.5mg) per day for 90 days. The primary efficacy analysis was designed to demonstrate the comparability of Testogel with the testosterone patch on the basis of $C_{\text{min}}$ and $C_{\text{avg}}$ serum testosterone levels being within the eugonadal range. Other efficacy variables that were examined included: testosterone concentrations at day 90, dihydrotestosterone, oestradiol, luteinising hormone, follicle stimulating hormone and steroid hormone binding globulin trough concentrations, sexual questionnaire, muscle strength, body composition and bone markers. Testogel was demonstrated to be non-inferior to the testosterone patch for the outcomes investigated.
The Table below demonstrates the C_{avg} serum testosterone levels (ng/dL) achieved from baseline up to 90 days of treatment in hypogonadal men (number of patients in parenthesis).

<table>
<thead>
<tr>
<th></th>
<th>TESTOGEL 5g/day</th>
<th>TESTOGEL 10g/day</th>
<th>TESTOSTERONE PATCH 5mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>237 ± 130 (73)</td>
<td>248 ± 140 (78)</td>
<td>237 ± 139 (76)</td>
</tr>
<tr>
<td>Day 1</td>
<td>398 ± 156 (73)</td>
<td>514 ± 227 (76)</td>
<td>482 ± 204 (74)</td>
</tr>
<tr>
<td>Day 30</td>
<td>565 ± 262 (66)</td>
<td>792 ± 294 (74)</td>
<td>419 ± 163 (70)</td>
</tr>
<tr>
<td>Day 90</td>
<td>553 ± 247 (65)</td>
<td>792 ± 276 (73)</td>
<td>417 ± 157 (64)</td>
</tr>
</tbody>
</table>

INDICATIONS

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

CONTRAINDICATIONS

Testogel is contraindicated:
- in cases of known or suspected prostatic cancer or breast carcinoma
- in cases of known hypersensitivity to testosterone or to any other constituent of the gel.

Testogel must not be used in women or children.

PRECAUTIONS

Testogel should be used only if hypogonadism (hyper- and hypogonadotrophic) has been demonstrated and if other aetiologies responsible for the symptoms have 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 biochemical tests (2 separate blood testosterone measurements). Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels fall with increasing age.

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

Testogel is not a treatment for male sterility or impotence.

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

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

Testogel should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of serum calcium concentrations is recommended in these patients.

In patients suffering from severe cardiac, hepatic or renal insufficiency, treatment with Testogel may cause severe complications characterised by oedema with or without congestive cardiac failure. In this case, treatment must be stopped immediately. In addition, diuretic therapy may be required.

Testogel should be used with caution in patients with ischaemic heart disease.

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

Testogel 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 occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.

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

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

The attention of athletes is drawn to the fact that this proprietary medicinal product contains an active substance (testosterone) which may produce a positive reaction in anti-doping tests.

Testogel must not be used in women, due to possible virilising effects.

Beside laboratory tests of the testosterone concentrations in patients on long-term androgen therapy the following laboratory parameters should be checked periodically: haemoglobin, haematocrit (to detect polycythaemia), liver function tests, and determination of lipids profile.

**Carcinogenicity and Mutagenicity**

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.

The genotoxic potential of testosterone has not been fully investigated, although limited data available to date suggest that it is not genotoxic.

**Potential Testosterone 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 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 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).

This transfer is avoided by wearing clothes covering the application area or showering prior to contact.

As a result, 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,
- shower before any situation in which this type of contact is foreseen.

*For people not being treated with Testogel:*
- 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 as soon as possible, using soap and water,
- report the development of signs of excessive androgen exposure such as acne or hair modification.

According to *in vitro* absorption studies on testosterone conducted with Testogel, it seems preferable for patients to observe at least 6 hours between gel application and bathing or showering. Occasional baths or showers taken between 1 and 6 hours after application of the gel should not significantly influence the treatment outcome.

To facilitate 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 contact period or to shower before sexual intercourse. In the
case of a pregnant partner, the patient must reinforce his attention to the precautions for use.

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

**Use in Pregnancy (Pregnancy Category D)**

Testogel must not be used in pregnant women under any circumstance. No clinical study has been conducted with this treatment in women, but testosterone is known to have potential adverse virilising effects on the fetus.

Pregnant women must avoid any contact with Testogel application sites (see PRECAUTIONS). In the event of contact, wash with soap and water as soon as possible.

**Use in Lactation**

Testogel should not be used in breast-feeding women. Care should be taken by breast-feeding women to avoid contact with Testogel application sites. In the event of contact, wash with soap and water as soon as possible.

**Interactions with Other Medicines**

- **Oral anticoagulants**
  Changes in anticoagulant activity (the increased effect of the oral anticoagulant by modification of coagulation factor hepatic synthesis and competitive inhibition of plasma protein binding):
  Increased monitoring of the prothrombin time, and INR determinations, are recommended. Patients receiving oral anticoagulants require close monitoring especially when androgens are started or stopped.

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.

Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

In diabetic patients, the metabolic effects of androgens may decrease blood glucose levels, and therefore, insulin requirements.

Concurrent administration of testosterone and buproprion may result in a lowered seizure threshold.

Concurrent administration with cyclosporin may result in increased cyclosporin toxicity and elevated cyclosporin blood levels.

Theoretically, in general, any substance which affects liver function should not be taken with testosterone, although this may not be as problematic with transdermal preparations.
such as Testogel. Examples of herbal products include: angelica dahurica, chapparal, comfrey, eucalyptus, germander tea, Jin Bu Huan, kava, penny royal oil, skullcap, and valerian.

**Effects on Laboratory Tests**

Androgens may decrease levels of thyroxine binding globulin, resulting in decreased T₄ serum concentrations and in increased resin uptake of T₃ and T₄. Free thyroid hormone levels, however, remain unchanged and there is no clinical evidence of thyroid insufficiency.

**Effects on Ability to Drive and Use Machines**

Testogel has no influence on the ability to drive and use machines.

**ADVERSE EFFECTS**

The most frequently observed adverse drug reactions at the recommended dosage of 5 g of gel per day were skin reactions (10%): reaction at the application site, erythema, acne, and dry skin.

Adverse drug reactions reported in 1 - <10% of patients treated with Testogel in the controlled clinical trials are listed in the following table:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Changes in laboratory tests (polycythaemia, increased lipids)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Headache</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Prostatic disorders</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Gynaecomastia, Mastodynia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, Paraesthesia, Amnesia, Hyperaesthesia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Mood disorders</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Alopecia, Urticaria</td>
</tr>
</tbody>
</table>

Gynaecomastia, which may be persistent, is a common finding in patients treated for hypogonadism.

The other known adverse effects of oral or injectable treatments containing testosterone are: prostatic changes and progression of sub-clinical prostatic cancer, urinary
obstruction, pruritus, arterial vasodilatation, nausea, cholestatic jaundice, changes in liver function tests, increased libido, depression, nervousness, myalgia and, during high dose prolonged treatment, electrolyte changes (sodium, potassium, calcium, inorganic phosphate and water retention), oligospermia and priapism (frequent or prolonged erections).

Other rare known adverse effects associated with excessive dosages of testosterone include hepatic neoplasms.

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

The pivotal clinical trial of Testogel versus a transdermal testosterone patch showed that some individuals would achieve suboptimal bioavailability.

**DOSAGE AND ADMINISTRATION**

**Adult Men**

The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 10 g of gel per day. The adjustment of dosage should be achieved by 2.5 g of gel steps.

Lower doses may be required in renal or hepatic impairment.

The application should be administered by the patient himself, onto clean, dry, healthy skin over either shoulder or either arm or abdomen.

After opening the sachets, the total contents must be extracted from the sachet and applied immediately onto the skin. The gel has to be simply spread on the skin gently as a thin layer. It is not necessary to rub it on the skin. Allow drying for at least 3-5 minutes before dressing. Wash hands with soap and water after applications.

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

Steady state plasma testosterone concentrations are reached by the end of the 2nd day of treatment with Testogel. In order to adjust the testosterone dose, serum testosterone concentrations must be measured in the morning before application from the 3rd day on after starting treatment (one week seems reasonable). The dose may be reduced if the plasma testosterone concentrations are raised above the desired level. If the concentrations are low, the dosage may be increased, not exceeding 10 g of gel per day.

**Paediatric Use**

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

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 plasma testosterone concentrations could be achieved using the transdermal route.

PRESENTATION AND STORAGE CONDITIONS

Testogel is presented as individual doses of 1% testosterone gel in a sachet. Each sachet contains either 25 mg testosterone in 2.5 g gel or 50 mg testosterone in 5 g gel.

Boxes contain 1, 2, 7, 10, 14, 28, 30, 50, 60, 90 or 100 sachets. Not all pack sizes may be marketed.

Each sachet should not be opened until immediately prior to application of the gel.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Limited
ABN 22 000 138 714
875 Pacific Highway
Pymble
NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF TGA APPROVAL

17 December 2004

Date of most recent amendment: 28 January 2011