SCHEDULING STATUS

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1 NAME OF THE MEDICINE

TestaForte (5 % *w/v* cream)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TestaForte contains 5 % *w/v* testosterone (50 mg in 1 ml or 100 mg in 2 ml).

Contains tree nut products (almond oil) and hydroxybenzoates.

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

3 PHARMACEUTICAL FORM

Cream.

TestaForte is a white, opaque, oil-in-water cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adult men (18 years old and above)

Application to the upper body

The recommended starting dose of TestaForte when applied to the upper body is 2 ml of cream (i.e., 100 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 and/or laboratory response in individual patients, not exceeding a maximum of 4 ml of cream per day. The adjustment of dosage should be achieved by 1 ml increments.
The application should be administered by the patient himself, onto clean, dry, healthy skin to the torso. The torso includes the abdomen and the sides of the body from the waist to just below the armpits. It is preferable to apply to areas with minimal hair and body fat.

Application to the scrotum

The recommended starting dose of TestaForte when applied to the entire scrotum is 0,5 ml of cream (i.e., 25 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 and/or laboratory response in individual patients, not exceeding 1 ml of cream per day. The adjustment of dosage should be achieved by 0,25 ml increments.
The application should be administered by the patient himself, onto clean, dry, healthy skin on the scrotum. The scrotum is not required to be shaved prior to application.

Method of administration

After opening the tube, the total contents must be extracted using the supplied dose measuring syringe and applied immediately onto the skin. The cream should be spread on the skin gently and massaged in until vanished. Typically, this takes 30 seconds or so. Wash hands with soap and water after applications. To clean the applicator after use, rinse in hot water.

Monitoring

Hypogonadal symptom control is the primary aim of testosterone therapy via achieving a serum testosterone concentration sufficient to restore physiological androgen status to that comparable with eugonadal men. Biochemistry is an adjunct indicator of treatment response together with the

identification and monitoring of the man's leading symptom. Trough testosterone levels should be within the lower limit of the reference interval for eugonadal men. Follow-up testosterone measurements should be made at intervals not exceeding one year.

Application to the upper body

Eugonadal serum testosterone concentrations are generally reached within 24 hours of a single dose of TestaForte. Absorption is variable between individuals. In order to adjust the testosterone dose, serum testosterone concentrations must be measured in the morning before application after the 15th day of starting treatment. Results of clinical and/or biochemical monitoring may prompt dose titration.

Application to the scrotum

Eugonadal serum testosterone concentrations are generally reached within 24 hours of a single dose of TestaForte applied scrotally. Absorption is variable between individuals and will have a different pharmacokinetic profile for men changing from non-scrotal testosterone medicines. In order to adjust the testosterone dose for scrotal application it is recommended that two (2) serum testosterone concentrations be measured at 3 hours (peak) and 24 hours (trough) from prior application after the 15th day of starting treatment. Results of clinical and/or biochemical monitoring may prompt dose titration.

Paediatric use

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

4.3 Contraindications

- TestaForte is contraindicated in patients with known sensitivity to testosterone, tree nuts (almond oil) or any of the excipients of TestaForte (see section 6.1).

- TestaForte is contraindicated in men with known or suspected carcinoma of the breast or prostate.

4.4 Special warnings and precautions for use

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

TestaForte should not be used by women or children due to possible virilising effects.

Prior to testosterone initiation, all patients must undergo a detailed examination in order to assess for pre-existing prostate cancer. Careful and regular monitoring of the prostate gland (digital rectal examination and estimation of serum Prostate Specific Antigen (PSA) and breast must be performed in accordance with recommended practice in patients receiving testosterone therapy at least once yearly and twice yearly in elderly and at risk patients (those with clinical or familial risk-factors). There is limited experience on the safety and efficacy of the use of the medicine in patients over 65 years of age. Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia. 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 such case, treatment must be stopped immediately.

Testosterone should be used only if hypogonadism (hyper- and hypogonadotrop~~hic~~) 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. Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

Testosterone concentrations should be monitored when switching the patient from another testosterone medicine to TestaForte or when switching from TestaForte upper body application to scrotal application and vice versa.

Modest elevations of serum dihydrotestosterone (DHT) concentrations are commonly observed after scrotal and non-scrotal administration of testosterone, however there is no evidence to suggest that high circulating DHT concentrations have a deleterious effect on the prostate and cardiovascular safety profile.

In addition to monitoring the testosterone concentrations in patients on long-term androgen therapy the following laboratory parameters should be checked periodically: haemoglobin, haematocrit (to avoid the risk of polycythaemia), liver function tests, and lipid profile.

Increases in haematocrit may require reductions in dose or discontinuation of testosterone therapy. Increased haematocrit may increase the risk for a thromboembolic event. Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

With specific reference to TestaForte, erythrocytosis and skin reactions are at the lowest end of the risk scale when transdermal testosterone is the mode of delivery. If the patient develops a severe application site reaction, treatment should be assessed and discontinued if necessary.

Testosterone is not a treatment for male sterility or impotence in men with normal serum testosterone levels.

With large doses of exogenous androgens, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

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

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischemic 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. There are no studies undertaken to demonstrate the efficacy and safety of TestaForte in patients with renal or hepatic impairment.

Patients with pre-existing cardiac, hepatic or renal diseases need to be monitored closely when undergoing androgen treatment. Because TestaForte is not taken orally hepatotoxicity is not a risk factor.

Gynecomastia occasionally develops and occasionally persists in patients being treated with androgens for hypogonadism.

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

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

Testosterone 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.
Testosterone may cause an increase in blood pressure and should be used with caution in patients with hypertension.

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

Athletes should be informed that TestaForte contains an active substance (testosterone), which may give positive results in an anti-doping test.

Androgens are not indicated for enhancing muscular development in healthy individuals.

Potential for transfer

Transdermal testosterone cream can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and, with repeated contact, possibly adverse effects. In women, this may cause growth of facial and/or body hair, deepening of the voice, irregularities of the menstrual cycle; in children this may cause premature puberty and genital enlargement, in case of repeat contact (inadvertent androgenisation). If virilisation occurs, testosterone therapy should be promptly discontinued until the cause has been identified.
The doctor should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). TestaForte should not be prescribed to patients with a major risk of non-compliance with safety instructions (e.g., severe alcoholism, drug abuse and severe

psychiatric disorders). The risk of transfer is substantially reduced by wearing clothes covering the application area. The majority of residual testosterone is removed from the skin surface by washing with soap and water prior to contact.

As a result, the following precautions are recommended:

For the patient:

- Wash hands thoroughly with soap and water after applying the cream.
- Cover the application area with clothing once the cream has dried.
- Wash before any situation in which skin-to-skin contact is foreseen.
- Clothing or items in contact with the area of application should be washed separately.

For people not being treated with TestaForte:

- 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.

To improve partner safety the patient should be advised to wear a T-shirt covering the upper body application site during the contact period or to shower before sexual intercourse.

To improve partner safety using scrotal application wash the genital area with a damp warm flannel before sexual intercourse.

Furthermore, it is recommended to wear clothing covering the upper body application site during contact periods with children in order to avoid transference to children.

Pregnant women must avoid any contact with TestaForte application sites. In case of pregnancy of the partner, the patient must be particularly careful to avoid potential transfer.

Use in hepatic impairment

No formal studies were conducted with TestaForte involving patients with hepatic impairment. Lower doses may be required in hepatic impairment.

Use in renal impairment

No formal studies were conducted with TestaForte involving patients with renal impairment. Lower doses may be required in renal impairment.

Use in the elderly

There is limited experience of the use of testosterone in elderly 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 physiological testosterone serum levels are lower with increasing age.

Paediatric use

The safety and efficacy of TestaForte in children and adolescents aged under 18 years of age has not been established.

The patient should be advised to wash their hands well with soap and water after TestaForte has been applied, especially in case of contact with children. Cases of contact with children may cause premature puberty and genital enlargement, in case of repeat contact (inadvertent androgenisation) (see Potential for transfer). Keep all clothes/implements of the person treated out of sight and reach of children.

Effects on laboratory tests

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

4.5 Interactions with other medicines and other forms of interaction

Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin have been reported with androgens. In diabetic patients, medication requirements may change.

When androgens are used simultaneously with anti-coagulants, the anti-coagulant effects may be increased. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored, particularly in patients with cardiac, renal or hepatic disease.

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

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

Concurrent administration with ciclosporin may result in increased ciclosporin toxicity and elevated ciclosporin 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 TestaForte. Examples of herbal medicines include: ancreamica dahurica, chapparal, comfrey, eucalyptus, germander tea, Jin Bu Huan, kava, penny royal oil, skullcap, and valerian.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

Testosterone is contraindicated in women who are or who anticipate becoming pregnant. Pregnant women must avoid any contact with TestaForte application sites. Exposure of a foetus to androgens may result in varying degrees of virilisation. In the event of contact, women are advised to wash with soap and water as soon as possible.

Lactation

Testosterone should not be used by breastfeeding women. 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

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

According to the literature, additional undesirable events that are possibly or probably related to testosterone use are shown in Table 1.

Table 1

System Organ Class	Adverse Events (Frequency unknown)
Blood and lymphatic system disorders	Changes in laboratory tests (polycythaemia, lipids), increased blood creatinine.
Endocrine disorders	Increase in male pattern hair distribution, hirsutism.
Metabolism and nutrition disorders	Electrolyte changes (retention of sodium, potassium, chloride, calcium, inorganic phosphate, water) during high dose or prolonged treatment, increased appetite, oedema.
Psychiatric disorders	Mood disorders, nervousness, hostility.
Nervous system disorders	Amnesia, hyperaesthesia, smell disorder, taste disorder.
Vascular disorders	Decreased blood pressure diastolic, flushing, vasodilation.
Respiratory, thoracic and mediastinal disorders	Worsening of sleep apnoea, dyspnoea.
Gastrointestinal disorders	Diarrhoea
Hepatobiliary disorders	Abnormal liver enzyme/liver function tests (including bilirubin)
Skin and subcutaneous tissue disorders	Alopecia, urticaria, discoloured hair, skin reactions including seborrhoea.
Musculoskeletal and connective tissue disorders	Muscle cramps, muscle pain.
Renal and urinary disorders	Prostatic disorders, worsening symptoms of

System Organ Class	Adverse Events (Frequency unknown)
	benign prostatic hyperplasia (BPH), Impaired urination, urinary tract infections, urinary tract obstruction.
Reproductive system and breast disorders	Virilisation of foetuses, infants, children and women, foetal harm, suppression of lactation, gynaecomastia/mastodynia, sensitive nipples, libido changes, increased frequency of erections, suppression of spermatogenesis, reduction in the size of the testicles/testicular atrophy, priapism.
General disorders and administration site conditions	Hypersensitivity reactions, asthenia, malaise.
Investigations	Decreased high-density lipoprotein (HDL).

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No cases of overdose with TestaForte have been reported in clinical trials.

Treatment of overdose would consist of discontinuation of TestaForte together with appropriate symptomatic and supportive care including determination of blood testosterone levels. Wash the skin with soap and water.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens. ATC code: G03B A03.

Mechanism of action

TestaForte 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.

Clinical trials

Application to upper body

The pivotal study was a Phase II, randomised, crossover bioequivalence study of TestaForte and a commercially available non-scrotal 1 % transdermal testosterone gel (TESTOGEL®).
Hypogonadal men (N = 15) were assigned to receive 2 ml TestaForte (100 mg testosterone) per

day, or 50 mg testosterone gel (5 ml of a 1 % gel) per day for 30 days. The primary efficacy analysis was designed to demonstrate the bioequivalence of TestaForte with the 1 % testosterone gel on the basis of AUC and C_{avg} serum testosterone levels being within the eugonadal range. Other efficacy variables that were examined included: testosterone concentrations at day 30, dihydrotestosterone, oestradiol, luteinising hormone, follicle stimulating hormone and steroid hormone binding globulin concentrations, sexual questionnaire, mood/energy questionnaire, general health survey and erectile function questionnaire. TestaForte was bioequivalent to TESTOGEL® for the key pharmacokinetic parameters of C_{max}, C_{avg} and AUC using adjusted and unadjusted for baseline values.

Table 2 demonstrates the C_{max} and C_{avg} serum testosterone levels (nmol/l) achieved from baseline up to 30 days of treatment in hypogonadal men from the pivotal Phase-II comparator trial in the same hypogonadal subjects.

Table 2

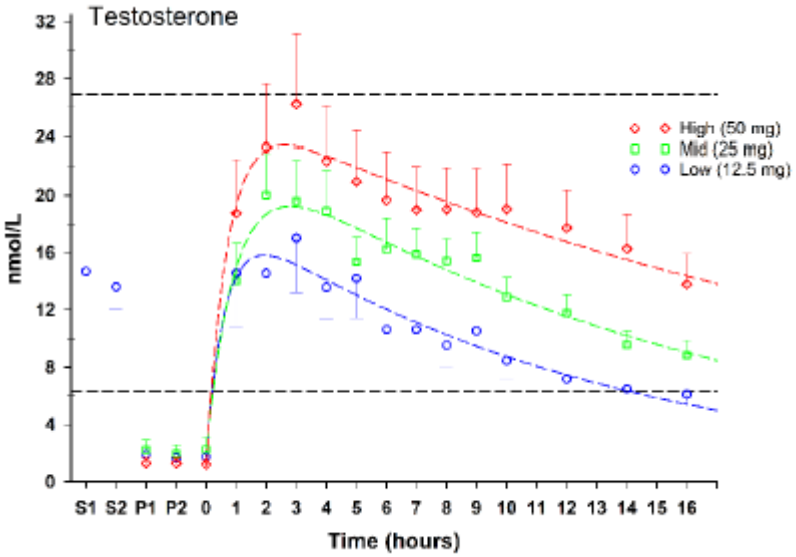
	TestaForte 100 mg/day	**TESTOSTERONE GEL 50 mg/day**
C_{max} Day 30	16,3 ± 6,5	19,4 ± 12,8
C_{avg} Day 30	11,4 ± 5,2	11,3 ± 3,7

Application to the scrotum

A three-phase single-dose cross-over pharmacokinetic study of TestaForte in endogenous testosterone suppressed healthy volunteers (n=11) described by Iyer 20171 demonstrated a nonlinear dose-dependent increase in serum testosterone C_{max} following scrotal administration of testosterone doses of 12,5 mg, 25 mg and 50 mg. Testosterone was rapidly absorbed from the scrotal skin with a mean T_{max} of 3,3 - 5,3 h. The mean C_{max} (± SEM) for the 12,5 mg, 25 mg and 50 mg testosterone doses was 19,8 ± 3,8; 21,9 ± 2,8 and 28,8 ± 3,8 nmol/L, respectively. Serum

testosterone concentrations were maintained within the physiological reference range of 1,8 – 7,8 ng/mL (6,2 – 26,9 nmol/L) for at least 12 h at the lowest 12,5 mg dose and for over 16 h for the 25 mg and 50 mg dose levels. Serum DHT concentrations after scrotal testosterone administration were higher than the physiological reference range of 0,07 – 0,64 ng/mL (0,24 – 2,21 nmol/L) and independent of dose with a mean C_{max} of 4,5 – 4,9 nmol/L. Serum oestradiol concentrations were independent of testosterone dose and remained within the physiological range of 15 - 68 pg/mL (55 - 250 pmol/L) for 16 h post-dose. TestaForte cream was well tolerated when applied to the scrotum with no complaints of skin irritation or discomfort after application.

Figure 1: Serum testosterone concentrations following application of three doses (12,5, 25, 50 mg) of TestaForte to the scrotal skin. Data are plotted as mean and standard error of the mean. Biexponential curves are fitted to all data for each dose. Y-axis units modified from Iyer 20171.



5.2 Pharmacokinetic properties

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 of TestaForte, reaching eugonadal levels within 24 hours. 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 2 ml of TestaForte (100 mg testosterone) to the torso produces an average testosterone concentration increase in hypogonadic men of approximately 7,7 nmol/L in serum with a T_{max} around 14,8 hours after application.

Administration of a single dose 0,5 ml of TestaForte (25 mg testosterone) to the scrotum of healthy eugonadal volunteers with endogenous testosterone suppressed by administration of nandrolone decanoate produced a C_{max} serum testosterone concentration of 19,1 nmol/L with a T_{max} around 2,8 hours after application.

The half-life of testosterone is controlled by skin permeation and not clearance/metabolism.

Metabolism

The major active metabolites of testosterone are DHT and oestradiol.

Excretion

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Almond oil

Butylated hydroxytoluene

Carbomer 940

Cetomacrogol 1000

Cetostearyl alcohol

Citric acid

Dl-alpha-tocopheryl acetate

Phenonip (PI 10352) which contains methyl-, ethyl-, propyl-, iso-butyl- and butylhydroxybenzoates

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

The tube should not be opened until immediately prior to application of the cream.

Store at or below 25 °C. Do not freeze.

In-use storage: TestaForte should be used within 12 weeks of opening.

6.5 Nature and contents of container

TestaForte is supplied in a 50 ml sealed tube with a graduated syringe-style measuring device in a carton.

6.6 Special precautions for disposal and other handling

No special precautions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACORP (PTY) LTD

29 Victoria Link

Route 21 Business Park

Irene, Pretoria

0178

RSA

8 REGISTRATION NUMBER: 55/21.7/0727

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 May 2023

10 DATE OF REVISION OF THE TEXT