SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TESTIM 50 mg Transdermal Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One single dose container of 5g contains 50 mg testosterone.

Excipient with known effect: 5 g contains 0.25 g propylene glycol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal Gel.
A clear to translucent gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults and the Elderly
The recommended starting dose of TESTIM is testosterone 50mg (1 tube)/per day.

Dose titration should be based on serum testosterone levels or the persistence of clinical signs and symptoms related to testosterone deficiency. To ensure proper serum testosterone levels are achieved, early morning serum testosterone should be measured before applying the next dose, approximately 7-14 days after initiation of therapy. Currently there is no consensus about age specific testosterone levels. The normal serum testosterone level for young eugonadal men is generally accepted to be approximately 300 – 1000 ng/dL (10.4 – 34.6 nmol/L). However, it should be taken into account that physiologically testosterone levels are lower with increasing age. If serum testosterone concentrations are below the normal range, the daily testosterone dose may be increased from 50mg (one tube) to 100mg (two tubes) once a day. The duration of treatment and frequency of subsequent testosterone measurements should be determined by the physician. Non-virilised patients may require treatment with one tube for a longer period of time before the dose is increased, as needed. At any time during treatment, after initial titration, the dose may need to be reduced if serum testosterone levels are raised above the upper limit of the normal range. If morning serum testosterone levels are above the normal range while applying 50mg (1 tube) of TESTIM, the use of TESTIM should be discontinued. If serum testosterone levels are below the normal limit, the dose may be increased, not exceeding 100mg per day.

Because of the variability in analytical values amongst diagnostic laboratories, all testosterone measurements should be performed at the same laboratory.

Female population
TESTIM is not indicated for use in women.

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

Method of administration

The gel should be applied once a day, at about the same time each day, to clean, dry, intact, skin of the shoulders and/or upper arms. It is preferable that the gel is applied in the morning. For patients who wash in the morning, TESTIM should be applied after washing, bathing or showering.

To apply the gel, patients should open one tube and squeeze the entire contents into the palm of one hand. They should then apply the gel immediately to their shoulders and/or upper arms. The gel should be spread on the skin gently as a thin layer. The gel should then be rubbed until no gel is left on the skin. This process should then be repeated with a second tube of TESTIM by patients who have been prescribed a daily dose of testosterone 100mg. It is suggested that patients who require two tubes of gel each day use both shoulders (one tube per shoulder) and/or upper arms as application sites. Patients should thoroughly wash their hands immediately with soap and water after TESTIM has been applied. After application of the gel, patients should allow the application sites to dry for a few minutes and then dress with clothing that covers the application sites.

Patients should be advised not to apply TESTIM to the genitals.

4.3 Contraindications

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.

Hypersensitivity to the active substance, which is chemically synthesized from soy, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude the risk of pre-existing prostate cancer. Careful and regular monitoring of the breast and prostate gland 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 prostate cancer and benign prostatic hyperplasia.

Care should be taken in patients with skeletal metastases due to the risk of hypercalcaemia/hypercalciuria developing from androgen therapy. In these patients, serum calcium levels should be determined regularly.

Testosterone may cause a rise in blood pressure and TESTIM 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.

Clotting disorders
Testosterone should be used with caution in patients with thrombophilia, as there have been post-marketing studies and reports of thrombotic events in these patients during testosterone therapy.

Testosterone 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 or 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.

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. 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. TESTIM should not be used to treat non-specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other aetiologies responsible for the symptoms have not been excluded. 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 TESTIM treatment.

TESTIM is not a treatment for male infertility or sexual dysfunction/impotence in patients without demonstrated testosterone deficiency. For the restoration of fertility in patients with hypogonadotrophic hypogonadism, therapeutic measures in addition to treatment with TESTIM are required.

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.

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

As washing after TESTIM administration reduces testosterone levels, patients are advised not to wash or shower for at least 6 hours after applying TESTIM. When washing occurs up to six hours after the gel application, the absorption of testosterone may be reduced.

TESTIM contains propylene glycol, which may cause skin irritation.

The contents of each tube are flammable.

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 and possibly adverse effects (e.g. growth of facial and/or body hair, acne, deepening of the voice, irregularities of the menstrual cycle) in case of repeat contact (inadvertent androgenisation).

The physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). TESTIM 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 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 this type of contact is foreseen.

For people not being treated with TESTIM:
- 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 guarantee partner safety, the patient should be advised for example to observe a long interval between TESTIM 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 TESTIM application sites. In case of pregnancy of the partner, the patient must reinforce his attention to the precautions for use (see section 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

When androgens are used simultaneously with anti-coagulants, the anti-coagulant effects may be increased. Patients receiving oral anticoagulants require close monitoring, especially when androgen therapy is started or stopped.

The concurrent administration of testosterone with ACTH or corticosteroids may enhance oedema formation; thus these drugs should be administered cautiously, particularly in patients with cardiac or hepatic disease.

Laboratory Test Interactions: 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.

4.6 Fertility, pregnancy and lactation

TESTIM is not indicated for women and must not be used in pregnant or breastfeeding women.

Testosterone may induce virilising effects on the female foetus.

Pregnant women should avoid skin contact with TESTIM application sites.

In the event that unwashed or unclothed skin to which TESTIM 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.

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

a. Summary of the safety profile
In double-blind clinical trials comparing TESTIM to placebo, the most frequently observed adverse drug reactions in TESTIM treated patients were application site erythema and increased PSA, both occurring in approximately 4% of patients.

b. Tabulated summary of adverse events
Adverse Drug Reactions terminology used for the classification of incidence: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000) and not known (can not be estimated from the available data).

The cumulative safety experience of TESTIM is derived from Phase I to Phase III clinical trials and post-marketing experience.

The adverse reactions listed in the table below have been observed in clinical studies with TESTIM and/or post-marketing experience.

MedDRA System Organ Class (SOC)	**Very common** (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to <1/1,000)	**Very rare** (<1/10,000)	**Not Known***
Gastrointestinal disorders						Nausea
General disorders and administration site conditions		Application site reaction (including erythema, rash and pruritus)	Peripheral oedema			
Hepatobiliary disorders						Jaundice and liver function test

						abnormalities
Investigations		PSA increased, haematocrit increased, haemoglobin increased, red blood cell count increased				Altered blood lipid levels, reduction in HDL cholesterol and weight gain
Metabolism and nutrition disorders						Electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water)
Musculoskeletal and connective tissue disorders						Muscle cramps
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						Prostate Cancer
Nervous system disorders		Headache				Paresthesia generalised
Psychiatric disorders						Decreased libido, anxiety, emotional lability
Reproductive system and breast disorders			Gynecomastia (may develop and persist in patients being treated for hypogonadism with testosterone)		Azoospermia	Increased frequency of erections; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism), and prostate abnormalities
Skin and subcutaneous tissue disorders		Acne	Pruritus			Various skin reactions may occur including hirsutism,

						alopecia and seborrhoea
Vascular disorders		Hypertension worsened	Hot flushes/flushing			Hypertension

*can not be estimated from the available data, majority from post-marketing reports and class effects of testosterone.

Patients should be instructed to report any of the following to a physician; too frequent or persistent erections of the penis; any changes in skin colour, ankle swelling or unexplained nausea or vomiting; any breathing disturbances including those associated with sleep.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal .

4.9 Overdose

Reports describing overdose have included doses up to TESTIM 150 mg. No dose limiting toxicity has been reported from these spontaneous cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens, ATC code: G03B A03

Testosterone and 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; laryngeal enlargement, vocal chord 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, phosphorus and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein. Androgens have been reported to stimulate production of red blood cells by enhancing the production of erythropoietin.

5.2 Pharmacokinetic properties

TESTIM dries very quickly when applied to the skin surface. The skin acts as a reservoir for the sustained release of testosterone into the systemic circulation.

With once daily application of TESTIM 50mg or 100mg to adult males with early morning serum testosterone levels ≤ 300 ng/dL, follow up measurements at 30, 60 and 90 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the normal range.

Absorption

Following 50 mg TESTIM daily in hypogonadal men, the Cavg was shown to be 365±187 ng/dL (12.7±6.5 nmol/L), Cmax was 538±371 ng/dL (18.7±12.9 nmol/L) and Cmin was 223±126 ng/dl (7.7± 4.4 nmol/L), measured at steady-state. The corresponding concentrations following 100 mg TESTIM daily were Cavg = 612±286 ng/dL (21.3±9.9 nmol/L), Cmax = 897±566 ng/dL (31.1±19.6 nmol/L) and Cmin = 394±189 ng/dL (13.7±6.6 nmol/L). Steady state is reached by day 7. Steady state may be reached at an earlier time-point although the timing for this was not determined from the clinical studies.

In the young eugonadal man, normal levels of serum testosterone are in the range of 300 – 1000 ng/dL (10.4 – 34.6 nmol/L).

The measurement of serum testosterone levels can be variable depending on the laboratory and method of assay used (see section 4.2).

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 bioactive. The portion of testosterone bound to SHBG is not considered biologically active. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

Biotransformation

There is considerable variation in the half-life of testosterone as reported in the literature, 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 dihydrotestosterone (DHT). Testosterone is metabolised to DHT by steroid 5α reductase located in the skin, liver and the urogenital tract of the male. DHT binds with greater affinity to SHBG than does testosterone. In many tissues, the activity of testosterone depends on its reduction to DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription and cellular changes related to androgen action. In reproductive tissues, DHT is further metabolised to 3- α and 3-β androstanediol.

Inactivation of testosterone occurs primarily in the liver.

DHT concentrations increased during TESTIM treatment. After 90 days of treatment, mean DHT concentrations remained within the normal range for TESTIM treated subjects.

Elimination

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.

Special Patient groups:
In patients treated with TESTIM no differences in the average daily serum testosterone concentration at steady state were observed based on age or cause of hypogonadism.

5.3 Preclinical safety data

Toxicological studies have not revealed effects other than those which can be explained based on the hormonal profile of TESTIM.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water
Pentadecalactone
Carbomer 980
Carbomer copolymer
Propylene glycol
Glycerol
Macrogol 1000
Ethanol
Trometamol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C
This medicinal product is flammable and should be protected from direct sunlight.

6.5 Nature and contents of container

TESTIM is supplied in unit dose aluminium tubes with epoxy phenolic liners and screw caps, each containing 5g gel. The tubes are packed in cartons containing 7, 14, 30 and 90 tubes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals Limited
Drayton Hall
Church Road West Drayton
UB7 7PS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

MA832/00901

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03rd January 2013

10. DATE OF REVISION OF THE TEXT

20th December 2016