Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tostran 2% Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of gel contains 20 mg testosterone. One press of the canister piston delivers 0.5 g of gel containing 10 mg testosterone.

Excipient(s) with known effect:
One gram of gel contains 1 mg butylhydroxytoluene.

One gram of gel contains 350 mg propylene glycol.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Gel.

Clear, colourless to slightly yellow 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 Elderly Men
The recommended starting dose of Tostran is 3 g gel (60 mg of testosterone) applied once daily at approximately the same time each morning. Dose titration should be based on both serum testosterone levels and the existence of clinical signs and symptoms related to androgen deficiency. It should be taken into account that physiological testosterone levels decline with increasing age.

The daily dose should not exceed 4 g of gel (80 mg testosterone).

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

Method of administration
For cutaneous use.

The dose can be applied to the abdomen (entire dose over an area of at least 10 by 30 cm), or to **both** inner thighs (one half of the dose over an area of at least 10 by 15 cm for each inner thigh). Daily rotation between the abdomen and inner thighs is recommended to minimise application site reactions.
The gel should be applied to clean, dry, intact skin. It should be rubbed in gently with one finger until dry, then the application site should be covered, preferably with loose clothing. Hands should then be washed with soap and water.

Each full depression of the canister piston delivers one half gram of gel (10 mg testosterone). To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator repeatedly until gel appears. Depress the actuator a further six times.. Discard the gel from the six depressions. It is only necessary to prime the pump before the first dose. The canister should be stored in an upright position between use.

In Table 1 below the amount of gel dispensed once the pump is primed, and the amount of testosterone which would be applied to the skin from a number of piston depressions are shown.

Table 1: Dose of Tostran dispensed after pump priming

No of Depressions	Amount of Gel (g)	Amount of Testosterone Applied to the Skin (mg)
1	0.5	10
2	1	20
4	2	40
6	3	60
8	4	80

Patients who wash in the morning should apply Tostran after washing, bathing or showering.

Tostran must not be applied to the genitals.

Treatment Control
Serum testosterone concentration should be measured approximately 14 days after initiation of therapy to ensure proper dosing. The blood sample for measurement of serum testosterone level should be obtained 2 hours after application of Tostran. If the serum testosterone concentration is between 5.0 and 15.0 µg/l, the dose should not be changed from 3 g/day. If the serum testosterone concentration is below 5.0 µg/l, the dose should be increased to 4 g/day (80 mg testosterone). If the testosterone concentration is above 15.0 µg/l, the dose should be reduced to 2 g/day (40 mg testosterone). Smaller 0.5 g gel (10 mg testosterone) dosage adjustment may be made if necessary.

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

There is limited experience of treating men older than 65 years of age with Tostran.

No formal studies have been conducted with the product in patients with renal or hepatic impairment (see also Section 4.4).

4.3 Contraindications

Tostran 2% Gel is contraindicated in patients with:

· hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
· known or suspected carcinoma of the breast or the prostate

4.4 Special warnings and precautions for use

Tostran 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 two separate blood testosterone measurements before initiating therapy with any testosterone replacement, including Tostran treatment.

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

Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.

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

There is limited experience on the safety and efficacy of the use of Tostran 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.

Tostran is not indicated for treatment of male sterility or sexual impotence.

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).

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

There are no studies undertaken to demonstrate the efficacy and safety of this medicinal product in patients with renal or hepatic impairment. Therefore, testosterone replacement therapy should be used with caution in these patients.

The treatment of hypogonadal men with testosterone may potentiate sleep apnoea in some patients, especially those with risk factors such as obesity or chronic lung disease.

Care should be taken in patients with skeletal metastases due to the risk of hypercalcaemia/hypercalciuria developing from androgen therapy. Regular monitoring of the serum levels of calcium in these patients is recommended.

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

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

General: certain clinical signs may indicate excessive androgen exposure requiring dosage adjustment. The physician should instruct patients to report any of the following:
- Irritability, nervousness, weight gain.
- Too frequent or persistent erections of the penis.
- Any nausea, vomiting, changes in skin colour or ankle swelling.
- Breathing disturbances, including those associated with sleep.

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

Athletes should be informed that Tostran contains an active substance (testosterone), which may give positive results in a doping test. Androgens are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.

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

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 precautions are 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 physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). Tostran 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 bathing 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,
- bathe or shower before any situation in which this type of contact is foreseen.

For the health care professional or carer:

- disposable gloves should be used if a health care professional or carer needs to apply the testosterone gel to the patient,
- the disposable gloves should be resistant to alcohols as the gel contains both ethanol and isopropyl alcohol, which facilitate the penetration of testosterone.

For people not being treated with Tostran:

- 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 minimum of four hours between Tostran application and sexual intercourse, to wear clothing covering the application site, during contact period or to bathe or shower before sexual intercourse.

Furthermore, it is recommended to wear clothing covering the application site during contact periods with children, in order to avoid a risk of contamination to children's skin.
Pregnant women must avoid contact with Tostran application sites. In case of pregnancy of a partner, the patient must take extra care with the precautions for use described above (see also Section 4.6).

Absorption studies of testosterone conducted in patients treated with Tostran indicate that patients should wait at least two hours between gel application and bathing or showering.

Tostran contains butylhydroxytoluene (E321) which may cause local skin reactions (eg contact dermatitis) or irritation of the eyes and mucous membranes. Tostran contains propylene glycol which may cause skin irritation.

This medicine contains up to 1400 mg propylene glycol in each dosage unit which is equivalent to 350 mg/g.

4.5 Interaction with other medicinal products and other forms of interaction

When androgens are given simultaneously with anticoagulants, the anticoagulant effect can increase. Patients receiving oral anticoagulants require close monitoring of their INR especially when the androgen treatment is started, stopped or the dose of Tostran changed.

The concurrent administration of testosterone with 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.

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

4.6 Fertility, pregnancy and lactation

Tostran is only intended to be used by men.

Tostran is not indicated for pregnant or breastfeeding women. No studies on women have been carried out. Pregnant women should avoid all contact with skin treated with Tostran (see Section 4.4). Tostran can give rise to adverse, virilising effects on the foetus. In the event of contact with treated skin, the area should be washed with soap and water as soon as possible.

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

The most commonly reported adverse reactions in a controlled clinical study (up to 4 g Tostran) were application site reactions (ASR; 26%) including; paresthesia, xerosis, pruritus and rash or erythema. The majority of these reactions were mild to moderate in severity and diminished or cleared, despite continued application.

All adverse reactions reported with a suspected relationship are listed by class and frequency (very common (≤1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥ 1/10,000 to <1/1,000).

Organ System	**Very Common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**
Blood and lymphatic system disorders		Haematocrit increased Red blood cell count increased, Haemoglobin increase
Endocrine disorders		Increase in male pattern hair distribution
Vascular disorders		Hypertension
Reproductive system and breast disorders		Gynaecomastia
General disorders and administration site conditions	Administration site reactions	Peripheral oedema
Investigations		Increased PSA

Hyperglycaemia was reported as an adverse event in two patients with a history of diabetes mellitus.

Gynaecomastia develops in 1.5% of patients being treated with testosterone for hypogonadism and occasionally persists.

According to the literature, other known undesirable effects have been reported following testosterone treatment and are listed in the following table:

Organ System	**Adverse reactions**
Metabolism and nutrition disorders	Weight gain, electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water) during high dose and/or prolonged treatment.
Nervous system disorders	Nervousness, hostility, depression.
Respiratory, thoracic and mediastinal disorders	Sleep apnoea
Gastrointestinal Disorders	Nausea
Hepatobiliary disorders	In very rare cases jaundice and liver function test abnormalities.
Skin and subcutaneous tissue disorders	Various skin reactions may occur including acne, seborrhoea and balding (alopecia).
Musculoskeletal and connective tissue disorders	Muscle cramps, muscle pain
Reproductive system and breast disorders	Libido changes, increased frequency of erections; therapy with high

	doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism), prostate abnormalities, prostate cancer*, urinary obstruction.
General disorders and administration site conditions	High dose or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema; hypersensitivity reactions may occur.

* Data on prostate cancer risk in association with testosterone therapy are inconclusive.

Other rare known undesirable effects associated with excessive dosages of testosterone treatments include hepatic neoplasms. Because of the excipients (butylhydroxytoluene and propylene glycol) contained in the product, applications to the skin may cause irritation and dry skin which usually reduce over time.

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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

There is a single case of acute overdosage after parenteral administration of testosterone enanthate reported in the literature. This resulted in testosterone concentrations of up to 114.0 µg/l, which was implicated in a cerebrovascular accident. Oral ingestion of Tostran will not result in clinically significant testosterone concentrations due to extensive first-pass metabolism. It is unlikely that such serum testosterone levels could be achieved using the transdermal route of administration.

Treatment of transdermal overdosage is by washing the site of application with soap and water as soon as possible, discontinuing application of Tostran and treatment of any symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens; ATC-code G03BA03

Endogenous androgens, which are excreted by the testicles, mainly testosterone and its main metabolite dihydrotestosterone (DHT) are responsible for the development of the external and internal male sex organs and for maintaining secondary sex characteristics (stimulation of the hair growth, voice breaking and development of libido). They have a general effect on the protein anabolism, affect the development of the skeletal muscles and the distribution of body fat, reduce the excretion in the urine of nitrogen, sodium, potassium, chloride, phosphates and water.

Testosterone does not affect the development of the testicles but reduces the excretion of gonadotrophin from the pituitary gland.

The effect of testosterone on certain target organs occurs after a peripheral transformation of testosterone to oestradiol which then binds to the oestradiol receptors in the nuclei of the target cell, e.g., in the pituitary gland, fat tissue, brain, bone tissue and the Leydig cells in the testicle.

5.2 Pharmacokinetic properties

Absorption

Tostran is a hydroalcoholic formulation that dries quickly when rubbed into the skin. The skin acts as a reservoir for the sustained release of testosterone into the systemic circulation. Testosterone absorption into the blood continues throughout the entire 24 hour dosing interval, with concentrations significantly above the base level the whole time. Varying application areas between 200 and 800 cm^2 in size has not been shown to have any clinically relevant effect on serum testosterone concentrations.

Application on the inside of the thighs and the abdomen results in comparable serum testosterone concentrations.

The bioavailability of Tostran is estimated to be 12%. Administration of 3 g gel daily over 6 months results in time-averaged serum testosterone concentrations of 5.0 ± 2.0 µg/l and individual minimal concentrations of 3.0 ± 1.0 µg/l and maximum concentrations of 12.0 ± 7.0 µg/l.

Distribution

About 40% of the testosterone in plasma is bound to sex hormone binding globulin (SHBG), 2% remains unbound (free) and the rest is loosely bound to albumin and other proteins. Albumin bound testosterone easily dissociates and is considered to be biologically active. However the binding to SHBG is strong. Thus, the concentration of serum bioactive testosterone is the unbound fraction plus that bound to albumin.

Metabolism

The major active metabolites of testosterone are oestradiol and DHT. DHT binds with greater affinity to SHBG than does testosterone. DHT is further metabolised to 3-α and 2-β androstanediol.

Excretion

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic acid and sulphate 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

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

Testosterone has been found to be non-mutagenic *in vitro* using the reverse mutation model (Ames test) or hamster ovary cells. A relationship between androgen treatment and certain cancers has been found in laboratory animals. Experimental data in rats have shown increased incidences of prostate cancer after treatment with testosterone. Sex hormones are known to facilitate the development of certain tumours induced by known carcinogenic agents. The clinical relevance of this observation is not known.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Ethanol, anhydrous
Isopropyl alcohol
Oleic acid
Carbomer 1382

Trolamine
Butylhydroxytoluene (E321)
Water, purified
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25ºC.
Do not refrigerate or freeze.
Once opened store canister upright.

6.5 Nature and contents of container

60 g multi-dose container (comprised of a polypropylene canister with a piston) with a fixed volume metering pump.

Pack sizes: 60 g, 2 x 60 g or 3 x 60 g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
Netherlands

8 MARKETING AUTHORISATION NUMBER

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