Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Testarzon 20 mg/g Transdermal gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of gel contains 20 mg testosterone. One pump actuation delivers 1.15 g (1.25 mL) of gel equivalent to 23 mg of testosterone.

Excipient with known effect: One gram of gel contains 0.2 g of propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal gel.
Homogenous, translucent to slightly opalescent gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Testosterone replacement therapy for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests.

4.2 Posology and method of administration

Posology

Adult men
The recommended starting dose of Testarzon is 23 mg testosterone (one pump actuation) applied once daily. To ensure proper dosing, serum testosterone levels should be periodically measured and dose titrated to maintain eugonadal serum testosterone levels (see section 4.4.).

The serum testosterone level should be measured 2-4 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 Testarzon dose may be increased by 1 pump actuation. If the serum testosterone concentration exceeds 36.4 nmol/L (1050 ng/dL), the daily Testarzon 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.

Elderly
Same dose as for adults. However, it should be taken into account that physiologically testosterone levels are lower with increasing age (see section 4.4).

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

Renal and hepatic impairment
There are no dedicated 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 (see section 4.4). After treatment with Testarzon, testosterone levels are similar in subjects with mild or moderate renal impairment compared to subjects with normal renal function (see section 5.2).

Female population
Testarzon is not indicated for use in women.

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

Method of administration
Transdermal use.

Testarzon is a gel, which should be applied to the upper arm and shoulder, using the applicator. Patients should be instructed not to apply Testarzon 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 and safely throw away the used tissue paper.

Administration
Testarzon should be applied once daily at about the same time, preferably in the morning to clean, dry, intact skin of the upper arm and shoulder using the applicator. A lower amount of testosterone will be delivered if Testarzon is applied to the abdomen or thigh and changing application site is therefore not recommended (see section 5.2).

To apply the gel after removal of the applicator lid, the pump head should be pressed all the way down once over the applicator head. Patients should be instructed to only make one pump actuation 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 required to achieve daily dose, the procedure is repeated to the other upper arm and shoulder.

Dose	**Application method**
23 mg (1 pump depression)	**Apply one** pump actuation to an upper arm and shoulder.
46 mg (2 pump depressions)	**Apply one** pump actuation to an upper arm and shoulder. **Repeat** to apply one pump depression to the opposite upper arm and shoulder.
69 mg (3 pump depressions)	**Apply one** pump actuation to an upper arm and shoulder. **Repeat** to apply one pump depression to the opposite upper arm and shoulder. **Repeat again** to apply the third pump depression to the initial 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 Testarzon.
Patients should be advised to let the application site dry completely before getting dressed.
Patients should be advised to wait at least 2 hours before showering, swimming or bathing to prevent reduced testosterone absorption (see section 4.4).
Wear clothing that covers the application side at all times to prevent accidental transfer to others.

4.3 Contraindications

· Hypersensitivity to the active substance, propylene glycol 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

Testarzon should be used only if male hypogonadism has been demonstrated and if other etiology, responsible for the symptoms, has been excluded before treatment is started. Testosterone deficiency 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 before initiating therapy with any testosterone replacement, including Testarzon treatment.

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).

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.

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

Testarzon 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.

Testarzon is not a treatment for male sterility or impotence.

There is limited experience on the safety and efficacy of the use of Testarzon 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 the physiologically testosterone serum levels are lower with increasing age.

Testosterone may cause a rise in blood pressure and Testarzon 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, 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.
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 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.

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

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

Testarzon contains propylene glycol, which may cause skin irritation.

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

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). Testarzon 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:
· 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 Testarzon:
· 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 for example 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 Testarzon application sites. In case of pregnancy of the partner, the patient must reinforce his attention to the precautions for use (see section 4.6).

Patients must be cautioned to minimise use of body lotion and sunscreen products at the area of application, at and just after application of Testarzon gel.

Laboratory test interactions: Androgens may decrease concentrations of thyroxin-binding globulins, resulting in decreased total thyroxine (T4) serum 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 Interaction with other medicinal products and other forms of interaction

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 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.
Interaction studies with body lotion and sunscreen products have not been performed.

4.6 Fertility, pregnancy and lactation

Testarzon is intended for use by men only.

No clinical trials have been conducted with Testarzon for assessment of male fertility. Spermatogenesis may be reversibly suppressed with Testarzon (see section 5.3).

Pregnant women should avoid skin contact with Testarzon application sites (see section 4.4).
In the event that unwashed or unclothed skin to which Testarzon 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 foetus.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. *Summary of the safety profile*
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.

b. Tabulated summary of adverse events
Adverse drug reactions reported in phase 2 and phase 3 clinical trials with Testarzon are listed in the following table. All adverse reactions reported with a suspected relationship are listed by class and are listed according to the following frequency: common (≥ 1/100 to < 1/10); uncommon (≥ 1/1.000 to < 1/100);.

Testarzon drug-related adverse reactions reported during clinical trials with more than one case (N=379)

MedDRA System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1.000 to < 1/100)
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

Nervous System Disorder Headache

According to literature and spontaneous reporting from testosterone gels, other known undesirable effects are listed in the below table:

MedDRA System Organ Class	**Adverse Reactions – Preferred term**
Blood and lymphatic system disorders	Polycythaemia, anaemia
Psychiatric disorders	Insomnia, depression, anxiety, aggression, nervousness, hostility
Nervous system disorders	Headache, dizziness, paraesthesia
Vascular disorders	Hot flushes (vasodilation), deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Dyspnoea, sleep apnoea
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Various skin reactions may occur including acne, seborrhoea and balding (alopecia), sweating, hypertrichosis
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, muscle cramps
Renal and urinary disorders	Urination impaired, urinary tract obstruction
Reproductive system and breast disorders	Gynaecomastia, erection increased, testis disorder, oligospermia, benign prostatic hyperplasia, libido changes (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*)
General disorders and administration site conditions	Asthenia, malaise, application site reaction. High dose or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema; hypersensitivity reactions may occur.
Investigations	Weight increase, elevated PSA, elevated haematocrit, red blood cell count increased or elevated haemoglobin
Metabolism and nutrition disorders	Electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water) during high dose and/or prolonged treatment.
Hepatobiliary disorders	Jaundice and liver function test abnormalities.

* Data on prostate cancer risk in association with testosterone therapy are inconclusive.
Because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin.

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, Website: www.hpra.ie.

4.9 Overdose

No case of overdose with Testarzon 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 Testarzon together with appropriate symptomatic and supportive care.

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. The nitrogen balance is improved only with 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

Testarzon delivers physiologic amounts of testosterone, which provide a level of circulating testosterone similar to the normal level in healthy men (i.e., 300-1050 ng/dL). Testarzon was evaluated in a multi-center, open-label, 120 day Phase 3 clinical study (study 000127) in 159 hypogonadal men ages 18 to 75 years (mean age 54.1 years). Subjects were white (77%), black (20%), Asian (2%), and multiracial (1%). In the phase 3 study, at the end of a 90 day treatment period during which the dose of Testarzon could be titrated based on total testosterone concentrations, 76.1% of men had average testosterone concentrations over a 24 hour period (Cave) within the eugonadal range (300 – 1050 ng/dL).

The mean testosterone concentration profile on Day 90 is shown in Figure 1 while the pharmacokinetic parameters for total testosterone on Day 90 are summarised for each Testarzon dose in Table 11.

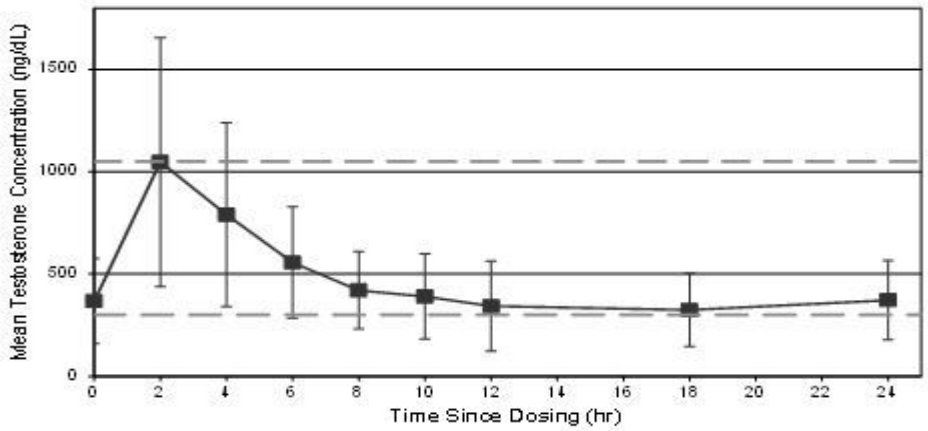

Figure 1 Mean ±SD serum concentrations of testosterone on day 90 after dose titration of Testarzon
Table 1 Pharmacokinetic parameters for total testosterone on day 90 after titration, study 000127 full analysis set

Testarzon Dose on Day 90	**N**	**C_{min} (ng/dL)** Mean ±SD	**C_{ave} (ng/dL)** Mean ±SD	**C_{max} (ng/dL) Mean ±SD**	**T_{max} (hr) Median**
23 mg	5	191 ± 49	368 ± 121	721 ± 254	4.02
46 mg	45	277 ± 140	506 ± 207	1,228 ± 640	2.02
69 mg	89	229 ± 82	438 ± 164	1,099 ± 595	2.08

C_{min}: minimum concentration; C_{ave}: average concentration over a 24 hour period; C_{max}: maximum concentration; T_{max}: time of maximum concentration; SD: standard deviation

Absorption
Testarzon provides transdermal delivery of testosterone, with a median Tmax of approximately 2-4 hours after dosing. Total testosterone concentrations return to pre-dose values approximately 12 hours after application and no accumulation occurs after daily application for 10 days. Application on the upper arm and shoulder results in higher serum testosterone concentrations compared to application on the abdomen or the inner side of the thigh. The mean Cmax was 926, 451 and 519 ng/dL, respectively, and the mean Cave 557, 372 and 395 ng/dL, respectively.

Phase 2 study results show that total testosterone concentrations increased with increasing dose after daily application of 23, 46 and 69 mg Testarzon.

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 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).

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.

Effect of Showering
Showering 1 hour and 2 hours following Testarzon administration decreased Cave by 19.2% and 14.3%, respectively, compared with subjects who did not shower after Testarzon administration. Showering 6 hours following Testarzon administration did not result in a decrease in Cave.

Renal function

Testosterone Cave and Cmax was similar in subjects with normal renal function and subjects with mild and moderate renal impairment. No data is available in subjects with severe renal impairment.

5.3 Preclinical safety data

Toxicological studies have not revealed other effects than those which can be explained on the base of the hormone profile of Testarzon.
Fertility studies in rodents and primates have shown that treatment with testosterone can impair male fertility by suppressing spermatogenesis in a dose dependent manner.
Testosterone has been found to be non-mutagenic in vitro using the reverse mutation model (Ames test) or Chinese hamster ovary cell line. A relationship between androgen treatment and certain cancer forms has been found in laboratory animals. Data in rats have shown increased incidences of prostate cancer after treatment with testosterone.

Sex hormones are known to facilitate the development of certain types of tumour induced by known carcinogenic agents. No correlation between these findings and the actual risk in human beings has been established.

Environmental risk assessment (ERA)
Environmental risk assessment studies have shown that Testarzon may pose a risk to the aquatic environment. (See section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol (96%)
Water, purified
Propylene glycol (E 1520)
Diethylene glycol monoethyl ether
Carbomer 980
Trolamine
Disodium edetate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Testarzon is supplied in a multidose container consisting of a metering pump with a laminate foil pouch in a bottle, and is provided with a cap applicator with or without a hygienic lid. Metering pumps without cap applicators will be fitted with an extra lid on top of the pump head. 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 a rigid polypropylene bottle.

The product is available in packs of one or three (3x1) multidose containers. Each pump contains 85.5 g Testarzon gel and is capable of dispensing 56 metered doses. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment. (See section 5.3)

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

7 MARKETING AUTHORISATION HOLDER

The Simple Pharma Company Limited
Ground Floor
71 Lower Baggot Street
Dublin 2
D02 P593
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8 MARKETING AUTHORISATION NUMBER

PA23202/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th April 2018
Date of last renewal: 15th February 2023

10 DATE OF REVISION OF THE TEXT

September 2023