NEW ZEALAND DATA SHEET

1 ANDROFORTE 5 (50 MG/ML TOPICAL CREAM)

AndroForte® 5 (testosterone) 50 mg/mL topical cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AndroForte® 5 contains 5% w/v testosterone (50 mg testosterone in 1 mL or 100 mg testosterone in 2 mL).

Excipients with known effect

Contains tree nut products (almond oil), phenoxyethanol, butylhydroxytoluene, cetostearyl alcohol and hydroxybenzoates.

Please see Section 4.4 Special warnings and precautions for use.

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

3 PHARMACEUTICAL FORM

Topical Cream.

AndroForte® 5 is a white, opaque, oil-in-water cream.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AndroForte® 5 is indicated for use as testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests (see Section 4.4 Special warnings and precautions for use).

4.2 DOSE AND METHOD OF ADMINISTRATION

Adult men (18 years old and above)

Application to the scrotum

The recommended starting dose of AndroForte® 5 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.

Application to the upper body

The recommended starting dose of AndroForte® 5 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 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.

Patient suffering from severe cardiac, renal or hepatic insufficiency

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 a case, treatment must be stopped immediately.

Please see Section 4.4 Special warnings and precautions for use.

Paediatric use

AndroForte® 5 is not indicated for use in children and has not been evaluated clinically in males under 18 years of age.

Method of administration

Transdermal use.

After opening the tube, the patient should be directed to measure the appropriate dose using the graduated applicator and immediately apply to clean dry 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.

Application to the scrotum

Eugonadal serum testosterone concentrations are generally reached within 2-4 hours of a single dose of AndroForte® 5 applied scrotally. Absorption is variable between individuals and will have a different pharmacokinetic profile for men changing from non-scrotal testosterone products. 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.

Application to the upper body

Eugonadal serum testosterone concentrations are generally reached within 24 hours of a single dose of AndroForte® 5. 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.

4.3 CONTRAINDICATIONS

AndroForte® 5 is contraindicated:

- in case of known or suspected prostate cancer or breast carcinoma
- in case of known hypersensitivity to testosterone), tree nuts (almond oil) or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

AndroForte® 5 should not be used by women or children due to possible virilising effects.

This medicine is not a treatment for male infertility.

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 PSA (Prostate Specific Antigen) 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).

Testosterone should be used only if hypogonadism (hyper- and hypogonadotrophic) 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 product to AndroForte® 5 or when switching from AndroForte® 5 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.

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.

With specific reference to AndroForte® 5, 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 reversibly 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 a case, treatment must be stopped immediately. In addition, diuretic therapy may be required.

Patients with pre-existing cardiac, hepatic or renal diseases need to be monitored closely when undergoing androgen treatment. Because AndroForte® 5 is not taken orally hepatotoxicity is not a risk factor.

In middle-aged and older patients with hypogonadism and pre-existing or a high risk of cardiovascular disease, testosterone-replacement therapy has not been shown to influence the

incidence of major adverse cardiac events. Similarly, in patients with hypogonadism and without a risk for myocardial infarction, stroke or venous thromboembolism, treatment with testosterone is not associated with an increased risk for composite cardiovascular events.

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 AndroForte® 5 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 inadvertent testosterone 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 physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). AndroForte® 5 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.

For people not being treated with AndroForte® 5:

- 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.

If scrotal application is used, the patient should shower and thoroughly wash the scrotum prior to intercourse.

AndroForte® 5 may affect the rubber used in condoms or other contraceptive devices.

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 AndroForte® 5 application site. In case of pregnancy of the partner, the patient must be particularly careful to avoid potential transfer (also see Section 4.6 Fertility, pregnancy and lactation).

The patient should be advised to wash their hands well with soap and water after AndroForte® 5 has been applied in case of contact with children.

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.

Excipients with known effect

Butylated hydroxytoluene may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Benzoates may cause local irritation.

Parahydroxybenzoates may cause allergic reactions (possibly delayed).

AndroForte® 5 contains almond oil. Caution should be taken in patients with tree nut (almond) allergies.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Oral anticoagulants

Due to changes in anticoagulant activity (increased effect of the oral anticoagulant by modification of hepatic synthesis of coagulation factor and competitive inhibition of plasma protein binding) increased monitoring of the prothrombin time and international normalized ratio (INR) are recommended. Patients receiving oral anticoagulants require close monitoring especially when androgens are started or stopped.

Corticosteroids

Concomitant administration of testosterone and ACTH or corticosteroids may increase the risk of developing oedema. As a result, these medicinal products should be administered cautiously, particularly in patients suffering from cardiac, renal or hepatic disease.

Laboratory tests

Interactions with laboratory tests: androgens may decrease levels of thyroxin binding globulin, resulting in decreased T4 serum concentrations and an increased resin uptake of T3 and T4. Free thyroid hormone levels, however, remain unchanged and there is no clinical evidence of thyroid insufficiency.

Diabetic medication

Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin levels have been reported with androgens. In diabetic patients, the dose of antidiabetic medications might need reduction (see Section 4.4 Special warnings and precautions for use).

Sunscreens or lotions

Application of sunscreen or lotions should be avoided on areas where AndroForte® 5 is applied.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

AndroForte® 5 is intended for use in men only.

AndroForte® 5 should not be used in pregnant women, due to potential virilising effects of the foetus.

Pregnant women must avoid any contact with AndroForte® 5 application sites (see Section 4.4 Special warnings and precautions for use). In the event of contact, wash with soap and water as soon as possible.

Use in lactation

AndroForte® 5 should not be used in women who are breast-feeding.

Fertility

Spermatogenesis may be reversibly suppressed with testosterone.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

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

Table 1

System Organ Class	Adverse Events
Blood and lymphatic system disorders	Changes in laboratory tests (polycythaemia, lipids), Blood creatinine increased
Endocrine disorders	Increase in male pattern hair distribution, Hirsutism
Metabolism and nutrition disorders	Weight increased, Electrolyte changes (retention of sodium, potassium, chloride, calcium, inorganic phosphate, water) during high dose or prolonged treatment, Appetite increased, Oedema
Psychiatric disorders	Mood disorders, Nervousness, Hostility
Nervous system disorders	Amnesia, Hyperesthesia, Smell disorder, Taste disorder
Vascular disorders	Venous thromboembolism, Blood pressure diastolic decreased, Flushing, Vasodilation
Respiratory, thoracic and mediastinal disorders	Worsening of sleep apnoea, Dyspnoea
Hepatobiliary disorders	Abnormal liver enzyme/liver function tests (including bilirubin)[1],
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 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

System Organ Class	Adverse Events
General disorders and administration site conditions	Hypersensitivity reactions, Asthenia, Malaise
Investigations	Decreased high-density lipoprotein (HDL)

(1) Other rare known undesirable effects associated with testosterone include hepatic neoplasms.

Post-marketing experience

The following table includes adverse reactions and other known undesirable effects reported in the literature following testosterone oral, injectable or transdermal testosterone treatment:

Adverse effects have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000;<1/100); rare (≥1/10,000;<1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Table 2

MedDRA System Organ Class	**Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance**				
	Common (≥1/100; <1/10)	**Uncommon (≥1/1,000; <1/100)**	**Rare (≥1/10,000; <1/1,000)**	**Very rare (<1/10,000)**	**Frequency not known (cannot be estimated from the available data)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Prostate cancer (Data on prostate cancer risk in association with testosterone therapy are inconclusive.)	Hepatic neoplasm		
Metabolism and nutrition disorders				Electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water)	
Psychiatric disorders	Anxiety	Decreased libido	Emotional lability		Nervousness, depression, hostility

Nervous system disorders		Paraesthesia generalised, Headache			
Vascular disorders		Hypertension, Hot flushes/flushing			
Gastrointestinal disorders		Nausea			
Hepatobiliary disorders			Liver function test abnormalities	Jaundice	
Skin and subcutaneous tissue disorders		Acne, Pruritus, Alopecia, Hirsutism	Seborrhoea		Because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin.
Musculoskeletal and connective tissue disorders		Muscle cramps			
Reproductive system and breast disorders		Gynaecomastia (may develop and persist in patients treated for hypogonadism with testosterone), Prostate abnormalities, Benign prostate hyperplasia, Prostatomegaly prostatic disorder, Spermatogenesis, and semen disorders, Oligospermia, Testicular atrophy	Priapism, increased frequency of erections, Azoospermia		

Respiratory, thoracic and mediastinal disorders					Sleep apnoea
Renal and urinary disorders					Urinary tract obstruction
General disorders and administration site conditions	Application site reaction, hypersensitivity	Peripheral oedema			Asthenia, malaise
Investigations	Changes in laboratory tests (polycythaemia, lipids)	PSA increased, red blood cell count increased, weight gain, haematocrit increased, altered blood lipid levels.	Reduction in HDL cholesterol.		

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. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

Symptoms

Only one case of acute testosterone overdose following an injection has been reported in the literature. This was a case of a cerebrovascular accident in a patient with a high plasma testosterone concentration of 114 ng/ml (395 nmol/l). It would be most unlikely that such blood testosterone levels would be achieved using the transdermal route.

Treatment

Treatment of overdosage consists of washing the application site immediately, with appropriate symptomatic and supportive care and discontinuing treatment if advised by the treating physician.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Androgens. ATC code: G03B A03.

Endogenous androgens, 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). Androgens have also an effect on protein anabolism, on development of skeletal muscle and body fat distribution and also reduce urinary nitrogen, sodium, potassium, chloride, phosphate and water excretion.

Testosterone reduces the pituitary secretion of gonadotropins.

The effects of testosterone in some target organs arise after peripheral conversion of testosterone to oestradiol, which then binds to oestrogen receptors in the target cell nucleus e.g. the pituitary, fat, brain, bone and testicular Leydig cells.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The percutaneous absorption of this medicine varies significantly by up to 8-fold depending upon the site of application, either torso or scrotem.

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 AndroForte® 5, 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 AndroForte® 5 (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 AndroForte® 5 (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.

When treatment is stopped, testosterone levels start decreasing approximately 24 hours after the last administration. Testosterone levels return to baseline approximately 72 to 96 hours after the final administration.

Metabolism

The major active metabolites of testosterone are DHT and oestradiol.

Excretion

Testosterone is excreted mostly in urine as conjugated testosterone metabolites and a small amount is excreted unchanged in the faeces.

Clinical trials

Application to upper body

The pivotal study was a Phase II, randomised, crossover bioequivalence study of AndroForte® 5 and a commercially available non-scrotal 1% transdermal testosterone gel. Hypogonadal men (N = 15) were assigned to receive 2 mL AndroForte® 5 (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 AndroForte® 5 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. AndroForte® 5 was bioequivalent to the 1% transdermal testosterone gel for the key pharmacokinetic parameters of C_{max}, C_{avg} and AUC using adjusted and unadjusted for baseline values.

Table 3 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 3

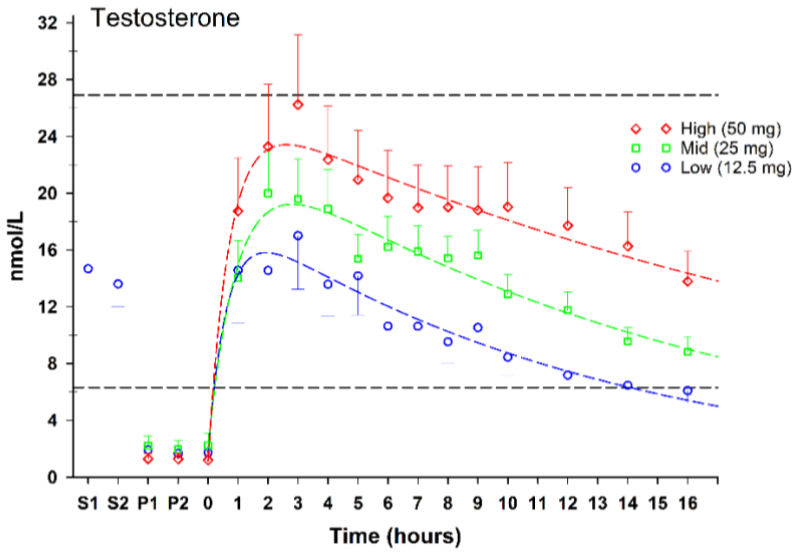
	ANDROFORTE 5 100 mg/day	**TESTOSTERONE 1% GEL 50 mg/day**
C_{max} Day 30	16.3 ± 6.5	19.4 ± 12.8
C_{avg} Day 30	11.4 ± 5.2	11.3 ± 3.7

Application to the scrotum

A three-phase single-dose cross-over pharmacokinetic study of AndroForte® 5 in healthy volunteers with suppressed endogenous testosterone (n=11) demonstrated a 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 quoted physiological reference range of 6.2-26.9 nmol/L (1.8-7.8 ng/mL) 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 0.24-2.21

nmol/L (0.07-0.64 ng/mL) 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 55-250 pmol/L (15-68 pg/mL) for 16 h post-dose. AndroForte® 5 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 AndroForte® 5 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 study.



5.3 PRECLINICAL SAFETY DATA

Testosterone has been found to be non-mutagenic *in vitro* using the reverse mutation model (Ames test) or Chinese hamster ovary cells. A relationship between androgen treatment and certain cancers has been found in studies on 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 importance of these findings and the actual risk in human beings is unknown. No correlation between these findings and the actual risk in human beings has been established.

The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

Testosterone has a masculinising effect on the female foetus when administered to pregnant animals during organogenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

almond oil

butylhydroxytoluene

carbomer 940

macrogol cetostearyl ether

cetostearyl alcohol

citric acid

DL-alpha tocopheryl acetate

phenoxyethanol

ethyl parahydroxybenzoate

iso-butyl parahydroxybenzoate

methyl parahydroxybenzoate

propyl parahydroxybenzoate

butyl parahydroxybenzoate

purified water

trolamine

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

3 years.

After first opening, use within 125 days.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Store below 25°C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

AndroForte® 5 is supplied in a 50 mL aluminium laminated tube closed with a foil tamper evident seal and polypropylene cap. The tube is packed in a carton with a dose applicator marked with 0.25mL graduations and patient information leaflet.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Alchemy Health Limited
120 Ngapuhi Road
Remuera
Auckland 1050
NEW ZEALAND

Medical enquires: 0508 ALCHEMY (0508 252436)

9 DATE OF FIRST APPROVAL

28 August 2025

10 DATE OF REVISION OF THE TEXT

28 August 2025