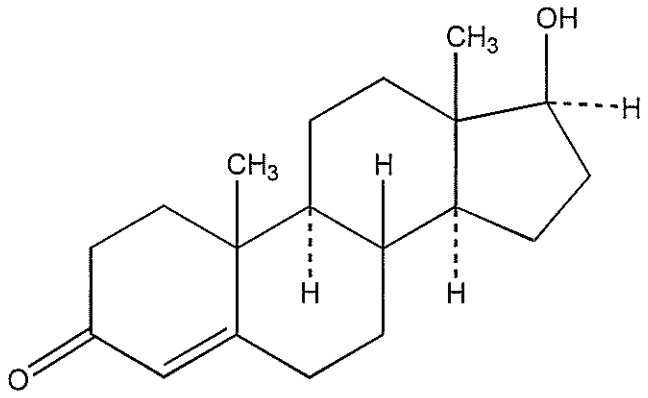
ANDRODERM®

NAME OF THE MEDICINE
Testosterone

The structure of testosterone (17β-hydroxyandrost-4-en-3-one) is given below. The molecular weight of the compound is 288.4 and the CAS number is 58-22-0. Testosterone is a white crystalline powder, or colourless or yellowish-white crystals, practically insoluble in water, freely soluble in alcohol and in methylene chloride, practically insoluble in fatty oils.



Testosterone

DESCRIPTION
Androderm® is a transdermal drug delivery system consisting of a self adhesive patch surrounding a central drug reservoir of testosterone dissolved in an alcohol-based gel. Androderm® provides continuous delivery of testosterone for 24 hours following application to intact, non-scrotal skin (e.g. back, abdomen, thighs, upper arms).

Two strengths of Androderm® Transdermal Patch are available which deliver *in vivo* 2.5 mg or 5 mg of testosterone per day across skin of average permeability.

The Androderm® 2.5 mg/day Transdermal Patch has a 7.5 cm^2 active surface area and contains 12.2 mg testosterone USP. The Androderm® 5 mg/day Transdermal Patch has a 15 cm^2 active surface area and contains 24.3 mg testosterone USP. Each patch also contains ethanol, purified water, glycerol, glyceryl monooleate, methyl laurate, Carbomer Copolymer (Type B), and sodium hydroxide as excipients in the drug reservoir.

PHARMACOLOGY
Androderm® delivers physiological amounts of testosterone producing circulating testosterone concentrations that mimic the normal circadian rhythm of healthy young men.

Testosterone, the primary androgenic hormone is responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterised by low serum testosterone concentrations.

Symptoms associated with male hypogonadism include the following: impotence and decreased sexual desire; fatigue and loss of energy; mood depression; regression of secondary sexual characteristics.

Androgens promote retention of nitrogen, sodium, potassium and phosphorus, decrease urinary excretion of calcium and increase bone mass, increase protein anabolism, decrease protein catabolism, and stimulate muscle growth. They are also responsible for the growth spurt of adolescence and for the eventual termination of linear growth and stimulate the production of red blood cells by enhancing erythropoietin production.

Exogenous administration of androgens inhibits endogenous testosterone release. With large doses of exogenous androgens, spermatogenesis may be suppressed.

Pharmacokinetics

Following Androderm® application to non scrotal skin, testosterone is continuously absorbed during the 24 hour dosing period. The interaction between the testosterone gel formulation and the skin is rate limiting to the systemic absorption of testosterone.

Daily application of Androderm® at approximately 10 pm results in a serum testosterone concentration profile which mimics the normal circadian variation observed in healthy young men. Figure. 1 shows maximum concentrations occur in the early morning hours with minimum concentrations in the evening.

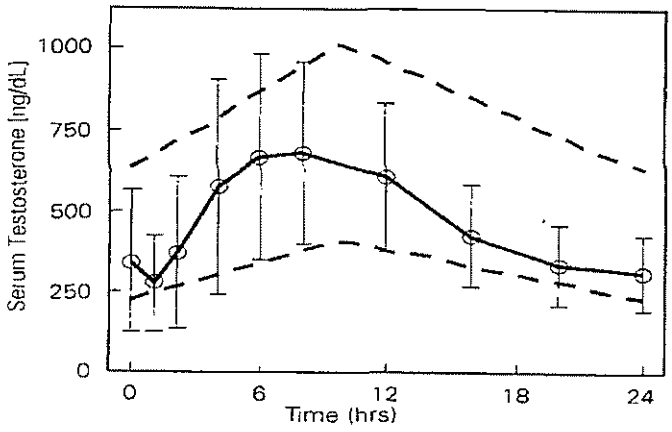


Figure 1: Mean (SD) steady state serum testosterone concentrations during nightly application of Androderm® 2.5 mg/day Transdermal Patch in 29 hypogonadal male patients, 27 patients used 2 systems nightly and 2 patients used 3 systems nightly. Area between the dashed lines shows the 95% confidence interval for the circadian variation observed in healthy young men. Transdermal patch application (t=0) at approximately 10 pm.

Normal range morning serum testosterone concentrations are reached during the first day of dosing. There is no accumulation of testosterone during continuous treatment.

The average morning level of testosterone was 589 ± 209 ng/dL (normal range 306 to 1031 ng/dL). For bioavailable testosterone, dihydrotestosterone and estradiol, values were normalised in 88%, 85% and 77% of patients respectively.

In hypogonadal men, application of two Androderm® 2.5 mg/day Transdermal Patches to the back, abdomen, thighs or upper arms resulted in average testosterone absorption of 4 to 5 mg over 24 hours.

The serum testosterone concentration profiles during application were similar for these sites. Applications to the chest and shins resulted in greater inter individual variability and average 24 hour absorption of 3 to 4 mg.

Upon removal of the Androderm® Transdermal Patches, serum testosterone concentrations decrease with an apparent half life of approximately 70 minutes. Hypogonadal concentrations are reached within 24 hours following system removal.

In a study of 20 hypogonadal patients, two Androderm® 2.5 mg/day Transdermal Patches and a single Androderm® 5 mg/day Transdermal Patch produced equivalent serum testosterone concentration profiles. Average steady state concentrations over 24 hours (Cssavg) were 613 ± 169 and 621 ± 176 ng/dL for the two 2.5 mg and single 5 mg systems, respectively. Cmax values were 925 ± 340 ng/dL for the two 2.5 mg systems and 905 ± 254 ng/dL for the single 5 mg system. Although not statistically significant, more subjects reported adverse reactions with the 5 mg patch than with two 2.5 mg patches. These adverse events included redness, itching and skin irritation at the patch site.

Androderm® therapy suppresses endogenous testosterone secretion via the pituitary/gonadal axis, resulting in a reduction in baseline serum testosterone concentrations compared to the untreated state.

Geriatric

No age related effects on testosterone pharmacokinetics were observed in clinical trials of Androderm® in men up to 65 years of age. In a group of 9 elderly testosterone deficient men (65 to 79 years of age, average baseline testosterone level 184 ± 50 ng/dL), a single application of two Androderm® 2.5 mg systems to the back resulted in an average testosterone level of 591 ± 121 ng/dL with a Tmax of 14.2 ± 4.2 hours. The total testosterone delivered over the 24 hour application time was 3.8 ± 0.6 mg, approximately 20% less than the average amount delivered in younger patients.

INDICATIONS

Androderm® is indicated for testosterone replacement therapy for confirmed testosterone deficiency in males.

CONTRAINDICATIONS

Known hypersensitivity to testosterone or other constituents of the patch.

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate, nephrotic syndrome and hypercalcaemia.

Androderm® has not been evaluated in women and must not be used in women. Testosterone may be harmful to the foetus.

PRECAUTIONS

Geriatric patients, and others with an increased risk of developing prostatic hypertrophy and/or prostate cancer, should be assessed before starting testosterone replacement therapy because testosterone may promote the growth of the prostate and of subclinical prostate cancer. Patients receiving testosterone replacement therapy should be reviewed for prostatic disease in accordance with contemporary clinical practice for their age.

Hypercalciuria/hypercalcaemia (caused by skeletal metastases) may be exacerbated by androgen treatment.

Testosterone may cause a rise in blood pressure and Androderm® should be used with caution in patients with hypertension.

Oedema, with or without congestive heart failure, may result from androgen treatment in patients with pre-existing cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

Androderm® should be used with caution in patients with ischaemic heart disease, epilepsy and migrane as these conditions may be aggravated. Patients should be monitored for polycythemia and for sleep apnoea.

Carcinogenesis, Mutagenesis and Impairment of Fertility
The potential carcinogenicity of testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical uterine tumours, which metastasised in some cases. There is suggestive evidence that injection of testosterone in some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumours and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

There are rare reports of hepatocellular carcinoma in patients receiving long term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumours in all cases.

Chronic androgen deficiency, however, is a protective factor for prostatic disease and hypogonadal men receiving androgen replacement therapy require surveillance for prostate disease similar to that recommended for eugonadal men of comparable age. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic cancer.

Use in pregnancy and lactation (Category D[†])
Androderm® therapy has not been evaluated in and must not be used in women under any circumstances. Testosterone may have a virilising effect on the female foetus.

Use in children
Androderm® is not indicated for use in children as there has been no clinical experience of its use below the age of 15.

Interactions with other medicines
When used simultaneously with anticoagulants, the anticoagulant effect can increase. Patients receiving oral anticoagulants require close monitoring especially when androgens are started or stopped.

Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

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

Medical procedures – MRI
Skin burns have been reported at the patch site in several patients wearing an aluminised transdermal system during a magnetic resonance imaging scan (MRI). Because Androderm® contains aluminium, it is recommended to remove the system before undergoing an MRI.

[†] *Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

ADVERSE EFFECTS

Transient mild to moderate erythema was observed at the site of application in the majority of patients at some time during treatment.

The following adverse events were observed during clinical trials with Androderm®:

Events are listed within body systems and categorised by frequency according to the following definitions: very common events reported at a frequency of greater or equal to 1/10 patients; common events reported at a frequency of less than 1/10 but greater or equal to 1/100 patients; uncommon events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; rare events reported at a frequency of less than 1/1,000 but greater than or equal to 1/10,000 patients; very rare events reported at a frequency of less than 1/10,000 patients.

Body as a whole:

Common:	Headache
Uncommon:	Body pain, accelerated growth, depression, fatigue, confusion, increased appetite, decreased libido, thinking abnormalities, pelvic pain.

Cardiovascular system:

Uncommon:	Hypertension, peripheral vascular disease.

Central and Peripheral Nervous System:

Uncommon:	Vertigo, paraesthesia

Gastrointestinal:

Common:	Gastrointestinal bleeding

Psychiatric:

Uncommon:	Anxiety

Reproductive:

Common:	Prostatic abnormalities
Uncommon:	Impotence, testicular abnormalities. There was a single case of prostatic carcinoma.

Skin:

Very common:	Pruritus at application site, burns like blister reaction under system.
Common:	Erythema at application site, vesicles at application site, allergic contact dermatitis to the system, rash, induration at application site, burning at application site.
Uncommon:	Acne, bullae at application site, mechanical irritation at application site, rash at application site, contamination at application site.

Urinary tract system:

Uncommon:	Urinary tract infection, dysuria, urinary incontinence, haematuria.

Skin irritancy

Three types of application site reactions occurred: irritation which included mild to moderate erythema, induration or burning; allergic contact dermatitis; and burn-like blister reactions.

Chronic skin irritation caused 5% of patients to discontinue treatment. Mild skin irritation may be ameliorated by treatment of affected skin with over the counter topical hydrocortisone cream or topical antihistamine products.

Five patients (4%) developed allergic contact dermatitis after 3 to 8 weeks treatment that required discontinuation. These reactions were characterised by pruritus, erythema, induration and in some instances vesicles or bullae, which recurred with each system application. Re-challenge with components of the system showed ethanol sensitisation in four patients. One patient's reaction was attributed to testosterone. None of these patients had adverse sequelae related to oral alcohol ingestion or to injectable testosterone use. Older patients may be more prone to develop allergic contact dermatitis.

Fourteen patients (12%) had burn-like blister reactions that involved bullae, epidermal necrosis or the development of ulcerated lesions. These reactions typically occurred once, at a single application site; five patients experienced a single recurrence. None withdrew from the clinical trials. These reactions occurred at a rate of approximately 1 in 6,500 system applications (1 in 3,250 treatment days). The majority of these lesions were associated with system application over bony prominences or on parts of the body that may have been subject to prolonged pressure during sleep or sitting (e.g. over the deltoid region of the upper arm, the greater trochanter of the femur, or the ischial tuberosity). The more severe lesions healed over several weeks with scarring in some cases. Such lesions could be treated as burns.

Other known undesirable effects associated with testosterone treatments include male pattern baldness, seborrhoea, excessive frequency and duration of penile erections and nausea.

Oligospermia may occur at high doses.

Prolonged testosterone administration may cause electrolyte disturbances, e.g. retention of sodium, chloride, potassium, calcium, inorganic phosphates and water.

DOSAGE AND ADMINISTRATION

Dosage

The usual dose is one Androderm® 5 mg/day Transdermal Patch applied nightly (approximately 10.00pm) and worn for 24 hours, providing approximately 5 mg testosterone per day.

The dose can be adjusted up to 7.5 mg/day (i.e., one 5 mg/day and one 2.5 mg/day patches or three 2.5 mg/day patches) nightly or down to 2.5 mg/day (i.e., one 2.5 mg/day patch) nightly depending on the serum testosterone measured in the morning after the application. Measurement of serum testosterone should be repeated taking care to ensure proper patch adhesion and correct time of application before the dose is adjusted.

Treatment in non-virilised patients may be initiated with one Androderm® 2.5 mg/day Transdermal Patch applied nightly. The dose should be adjusted as appropriate.

Three patches per day may be required for men with a higher body weight (>130kg).

The duration of treatment and frequency of testosterone measurements is determined by the physician.

Application of Androderm®

The adhesive side of the patch should be applied to a clean, dry area of the skin on the back, abdomen, upper arms, or thighs.

Bony prominences, such as the shoulder and hip areas, should be avoided as this may predispose to skin blister reactions. Absorption is more variable if applied to skin on the chest and shins.

<u>Do not</u> apply to the scrotum

The sites of application should be rotated, with an interval of 7 days between applications to the same site. The area selected should not be oily, damaged or irritated.

The patch should be applied immediately after opening the pouch and removing the protective release liner.

The patch should be pressed firmly in place, making sure there is good contact with the skin, especially around the edges.

Instructions for use/handling
Androderm® may be discarded with household waste in a manner that avoids accidental contact by others.

Damaged patches should not be used.

OVERDOSAGE
This is not likely due to the mode of administration. Serum testosterone has a half life of 70 minutes and therefore falls rapidly once patches are removed.

In case of overdose, immediately contact the Poisons Information Centre for advice (In Australia, call 13 11 26. In New Zealand, call 0800 764 766).

PRESENTATIONS AND STORAGE CONDITIONS
Each Androderm® 2.5 mg/day Transdermal Patch contains 12.2 mg testosterone USP for delivery of 2.5 mg testosterone per day. Each patch is individually pouched and supplied in cartons of 60.

Each Androderm® 5 mg/day Transdermal Patch contains 24.3 mg testosterone USP for delivery of 5 mg testosterone per day. Each patch is individually pouched and supplied in cartons of 5 and 30. (Not registered in New Zealand)

Store below 25°C. Shelf life under these conditions is two years.

The drug reservoir may be burst by excessive heat or pressure.

Apply to skin immediately upon removal from the protective pouch. Do not store outside the pouch provided.

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