AXIRON®

(testosterone) 2% w/v transdermal solution

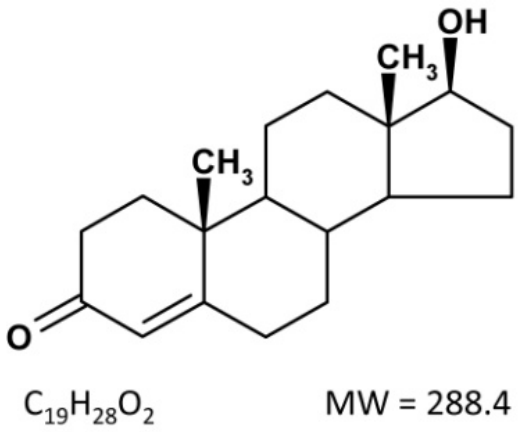
NAME OF THE MEDICINE

AXIRON® (testosterone).

Testosterone AAN is a fragrance free white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. Testosterone has the empirical formula $C_{19}H_{28}O_2$ representing a molecular weight of 288.43. The CAS number for testosterone is 58-22-0.

Pharmacotherapeutic group: Androgens, ATC code: G03BA03

Testosterone has the following structural formula:



$C_{19}H_{28}O_2$ MW = 288.4

DESCRIPTION

AXIRON (testosterone) transdermal solution is a clear, colourless, fragrance free, single phase solution containing 30 mg of testosterone in 1.5 mL of AXIRON solution for transdermal administration through the underarm. The active pharmacologic ingredient in AXIRON is testosterone. The inactive ingredients are ethanol, isopropyl alcohol, octyl salicylate, and povidone.

PHARMACOLOGY

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 erectile dysfunction, 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.

Male hypogonadism has two main aetiological categories: primary hypogonadism, which occurs as a result of testicular failure of any cause (such as Klinefelter's Syndrome or Leydig cell aplasia); and secondary hypogonadism, which results from failure of the hypothalamus or pituitary gland of any cause (such as pituitary tumours) leading to insufficient production of GnRH and/or gonadotrophins (FSH, LH).

Pharmacodynamics

No specific pharmacodynamic studies were conducted using AXIRON.

Pharmacokinetics

Absorption –AXIRON delivers physiologic amounts of testosterone, producing circulating levels of testosterone that approximate normal levels seen in healthy men. AXIRON provides continuous delivery of testosterone over the 24-hour dosing interval following application to the underarm.

In-vitro studies with AXIRON show that 97% of the stated dose is delivered to the skin using the pump and applicator. On the skin, the ethanol and isopropyl alcohol evaporate leaving testosterone and octyl salicylate, and testosterone is released into the systemic circulation over time. In general, steady-state serum concentrations are attained within two weeks of daily dosing.

Distribution — Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 45% of testosterone in plasma is bound to SHBG, 4% remains unbound (free) and the rest is bound to albumin and other proteins.

Metabolism – Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT).
DHT concentration increased in parallel with testosterone concentration during AXIRON treatment. The mean steady-state DHT/T ratio remained within normal limits and ranged from 0.17 to 0.26 across all doses on Days 15, 60, and 120.

Elimination – There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose 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. Inactivation of testosterone occurs primarily in the liver.

CLINICAL TRIALS

AXIRON was evaluated in a multicenter, open label, 120-day trial that enrolled 155 hypogonadal men at 26 clinical research centers. The median age of subjects was 53 years with a range of 19 – 78 years. Of the 144 subjects whose race was recorded, 122 (84.7%) were Caucasian, 13 (9.0%) were Hispanic, 6 (4.2%) were African Americans, 1 (0.7%) was Asian and 2 (1.4%) had race recorded as "Other".

Patients were instructed to apply AXIRON to unclothed, clean, dry, and unbroken skin. The solution was applied to the axillary area. Patients were not instructed to alter their normal grooming routine, e.g., shave under the arm.

During the initial AXIRON treatment period (Days 1-15) 143 patients were treated with 60 mg of testosterone daily. On Day 45 of the trial, patients were maintained at the same dose, or were titrated up or down, based on their 24 hour average serum testosterone concentration measured on

Day 15. On Day 90 of the trial, patients were maintained at the same dose, or were titrated up or down, based on their 24 hour average serum testosterone concentration measured on Day 60.

Of the 135 patients who completed the 120 day treatment, 123 patients did so with no deviation from the protocol.

The primary endpoint was the proportion of subjects having serum total testosterone levels in the normal range (10.4-36.4 nmol/l) at day 120.

Table 1 summarises the proportion of subjects having average testosterone concentrations within the normal range on Days 15, 60 and 120.

Table 1: Proportion of subjects who had an average Serum Total Testosterone in the range 10.4 to 36.4 nmol/L and completed 120 days of treatment (N=138[a])

Evaluation Time	Proportion of Subjects with C_{avg} in the range 10.4 to 36.4 nmol/L (95% CI)
Day 15	76.1% (69.0%, 83.2%)
Day 60	84.8% (78.8%, 90.8%)
Day 120	84.1% (77.9%, 90.2%)

[a] Three patients who withdrew from the study due to adverse reactions are included as treatment failures.

On day 120, 75% of responding patients finished the study on the starting dose of 60 mg of testosterone, while 2% had been titrated to 30 mg, 17% had been titrated to 90 mg and 6% had been titrated to the 120 mg dose.

By day 120, average serum testosterone concentration was within normal range for 67% (2/3) of those who titrated down to the 30 mg dose, 90% (87/97) of those on the 60 mg dose, 80% (20/25) of those who titrated up to 90 mg and 70% (7/10) of those who titrated up to the 120 mg dose. Table 2 below summarises the testosterone concentration data in the patients who completed 120 days.

Table 2: Baseline-unadjusted Arithmetic Mean (±SD) Steady-State Serum Testosterone Concentrations on Days 15, 60 and 120 in Patients Who Completed 120 Days of Treatment

	Dose of AXIRON				
	30 mg	**60 mg**	**90 mg**	**120 mg**	**Overall**
Day 15	**[N=0]**	**[N=135]**	**[N=0]**	**[N=0]**	**[N=135]**
C_{avg} (nmol/L)	--	15.8 (±7.8)	--	--	15.8 (±7.8)
C_{max} (nmol/L)	--	25.8 (±17.4)	--	--	25.8 (±17.4)
Day 60	**[N=1]**	**[N=105]**	**[N=29]**	**[N=0]**	**[N=135]**
C_{avg} (nmol/L)	11.9 (--)	18.1 (±7.2)	12.8 (±4.8)	--	16.9 (±7.1)
C_{max} (nmol/L)	17.0 (--)	31.2 (±23.0)	22.4 (±13.3)	--	29.1 (±21.5)
Day 120	**[N=3]**	**[N=97]**	**[N=25]**	**[N=10]**	**[N=135]**
C_{avg} (nmol/L)	17.1 (±8.3)	17.6 (±6.1)	14.4 (±5.7)	13.5 (±5.6)	16.7 (±6.1)
C_{max} (nmol/L)	27.0 (±14.4)	29.1 (±15.1)	23.0 (±11.7)	22.8 (±12.2)	27.5 (±14.5)

Figure 1 depicts the pharmacokinetic profiles of total testosterone in patients completing 120 days of AXIRON treatment administered as 60 mg of testosterone for the initial 15 days followed by possible titration according to follow-up testosterone measurements.

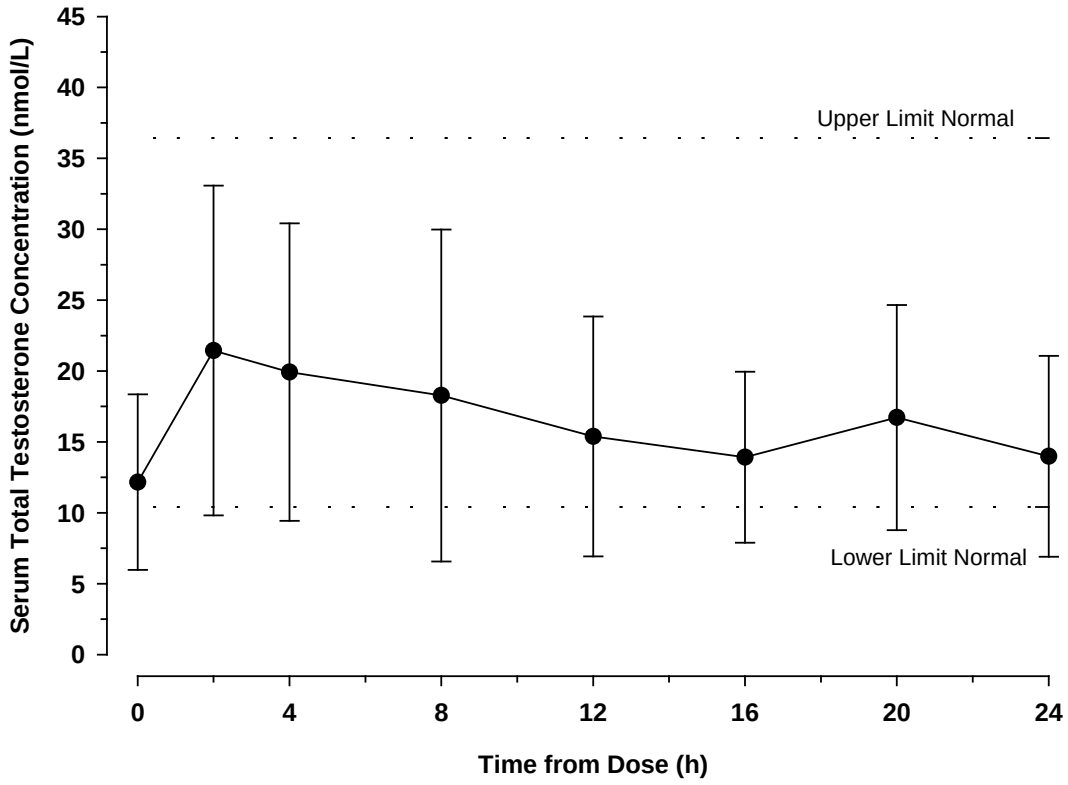


Figure 1: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 120 (30, 60, 90 or 120 mg testosterone) in Patients Who Completed 120 Days (N=135) of AXIRON Once-Daily Treatment

The secondary pharmacokinetic endpoints characterised the distribution of testosterone levels above and below the normal range in this study The proportion of patients with Cmax <52.1 nmol/L was always greater than 90%, and at Day 120 it was 94.8%. Five patients during the 120 days of treatment had a C_{max} >86.8 nmol/L; these occurrences were not associated with an adverse event, and were sustained only on rare occasions. The proportion of patients with a C_{min} <10.4 nmol/L at Day 120 was 64.4%. However, these patients had a total testosterone below 10.4 nmol/Lfor a relatively short duration which generally occurred at the end of the dosing interval

Clinical endpoints were measured in the form of changes from baseline on the Psychosexual Daily Questionnaire (PDQ) and SF-36 questionnaire.

For the PDQ, there were statistically significant improvement on all sexual desire and enjoyment, sexual activity and sexual performance variables tested. A decrease was observed in the mean scores for angry (Day 60 and Day 120), irritable, sad/blue, tired, nervous (Day 60) and negative mood and an increase was observed in the mean scores for alert, full of pep/energetic, friendly, well/good and positive mood.

There was a statistically significant increase in the SF-36 mental and physical component scores from day 1 to day 60 and from day 1 to day 120. The mean physical component score increased from 50.55 on day 1 to 52.58 on day 60 (p=0.0082) and 52.3 on day 120 (p=0.0254), while the mean mental component score increased from 46.79 on day 1 to 51.28 on day 60 (p<0.0001), and 51.26 on day 120 (p<0.001).

Effect of showering/washing - In a parallel designed clinical study to evaluate the effect of washing on the testosterone systemic exposure, two groups of 6 healthy premenopausal female subjects were each dosed with 30 mg (1 pump actuation) of testosterone to a single axilla. The application sites of each group were washed with soap and water 2 hours or 6 hours after the application of AXIRON. A control group of 6 female subjects applied 30 mg (1 pump actuation) of testosterone to a single axilla and did not wash the application site. Blood samples were collected for 72 hours from all subjects following dosing with AXIRON. A decrease of up to 35% of testosterone exposure ($AUC_{[0-72]}$) was observed when applications sites were washed 2 hours and 6 hours after AXIRON application. Patients should be advised to avoid swimming or washing the application site until 2 hours following application of AXIRON.
In a clinical study conducted with a 2% testosterone formulation to evaluate the effect of washing on the residual amount of testosterone at the axilla, 10 healthy male subjects received 60 mg (2 pump actuations) of testosterone to each axilla (the maximum testosterone dose of 120 mg). Following 5 minutes of drying time, the left axilla was wiped with alcohol towelettes which were assayed for testosterone content. Subjects were required to shower with soap and water 30 minutes after application. The right axilla was then wiped with alcohol towelettes which were assayed for testosterone content. A mean (SD) of 3.1 (2.8) mg of residual testosterone (i.e., 92.6% reduction compared to when axilla was not washed) was recovered after washing this area with soap and water.

Use of deodorants and anti-perspirants - In a parallel designed clinical study evaluating the effect of deodorants and antiperspirants in healthy premenopausal females dosed with AXIRON, each subject applied either a combined deodorant/antiperspirant spray (6 subjects) or stick (6 subjects) or a deodorant spray (6 subjects) to a single axilla 2 minutes before the application of 30 mg (1 pump actuation) of testosterone to the same axilla. A control group of 6 subjects only applied 30 mg (1 pump actuation) of testosterone to a single axilla. Blood samples were collected for 72 hours from all subjects following AXIRON administration. Although a decrease of up to 33% of testosterone exposure ($AUC_{[0-72]}$) was observed when antiperspirants or deodorants are used 2 minutes prior to AXIRON application, underarm deodorant or antiperspirant spray or stick products may be used 2 minutes prior to AXIRON application as part of normal, consistent, and daily routine."

Absorption of AXIRON from application sites other than the axilla has not been assessed. In an early clinical pharmacology study with a lower strength testosterone formulation, absorption from the inner arm was only about 54% of that from the axilla. AXIRON should be applied to the axilla, and should not be applied to other sites.

INDICATIONS

Androgen replacement therapy for confirmed testosterone deficiency in males.

CONTRAINDICATIONS

- AXIRON is contraindicated in men with known or suspected carcinoma of the breast or prostate *[see Precautions]*.
- AXIRON is contraindicated in women who are, or who may become pregnant, or who are breastfeeding. AXIRON may cause fetal harm when administered to a pregnant woman. AXIRON may cause serious adverse reactions in nursing infants. If a pregnant woman is exposed to AXIRON, she should be apprised of the potential hazard to the fetus. *[See Precautions]*.
- Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

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

AXIRON should not be used by women, due to possible virilising effects.

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

AXIRON 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 2 separate blood testosterone measurements.

There is limited experience of the use of AXIRON 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.

Testosterone concentrations should be monitored when switching the patient from another testosterone product to AXIRON.

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

With large doses of exogenous androgens, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

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 case, treatment must be stopped immediately. There are no studies undertaken to demonstrate the efficacy and safety of Axiron in patients with renal or hepatic impairment.

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.

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

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.

AXIRON is not a treatment for male sterility or impotence in men with normal serum testosterone levels.

Athletes should be informed that AXIRON 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.

The cutaneous solution is flammable. Patients should be advised to avoid naked flame or smoking until the AXIRON dose applied, has dried.

Potential for transfer

Testosterone solution 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 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.

The physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). AXIRON should not be prescribed to patients with a major risk of non-compliance with safety instructions (e.g. severe alcoholism, drug abuse, severe psychiatric disorders and children).

As a result, the following precautions are recommended:

For the patient:

- Wash hands thoroughly with soap and water after applying the solution.
- Cover the application area with clothing once the solution has dried.
- Wash before any situation in which skin-to-skin contact is foreseen.

For people not being treated with AXIRON:

- 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 application site during the contact period or to shower before sexual intercourse.

Furthermore, it is recommended to wear clothing covering the application site during contact periods with children in order to avoid transference to children.

Pregnant women must avoid any contact with AXIRON application sites. In case of pregnancy of the partner, the patient must reinforce his attention to the precautions for use.

Effects on Fertility

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

Use in Pregnancy

Pregnancy category D.

AXIRON is contraindicated in women who are or who anticipate becoming pregnant (see Contraindications). Pregnant women must avoid any contact with AXIRON application sites (see Dosage and Administration). Exposure of a fetus to androgens may result in varying degrees of virilisation. In the event of contact, women are advised to wash with soap and water as soon as possible.

Use in Lactation

AXIRON is contraindicated during breast-feeding (see *Contraindications*). In the event of accidental contact, women are advised to immediately wash with soap and water.

Carcinogenicity

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 promote the growth of certain hormone-dependent tissues and tumours.. Subcutaneous implantation of testosterone produced cervical-uterine tumours in female mice, which metastasised in some cases. Metastasising prostatic adenocarcinomas occurred in male rats after chemical induction and subcutaneous implantation of testosterone. 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. Hepatocellular carcinoma has been reported in patients receiving long-term therapy with androgens.

Hypogonadal men receiving androgen replacement therapy require surveillance for prostatic disease similar to that recommended for eugonadal men of comparable age.

Genotoxicity

The genotoxic potential of testosterone has not been fully investigated in a comprehensive battery of genotoxicity studies. However, testosterone was found not to be clastogenic when tested *in vitro* in assays with hamster lung fibroblasts or in mouse or hamster embryo fibroblasts, or in *in vivo* chromosome aberration assays in mouse bone marrow cells and spermatocytes. Testosterone was also negative in assays for unscheduled DNA synthesis in rat and human hepatocytes.

INTERACTIONS WITH OTHER MEDICINES

Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated hemoglobin have been reported with androgens. In diabetic patients, medication requirements may change.

When androgens are used simultaneously with anti-coagulants, the anti-coagulant effects may be increased. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored, particularly in patients with cardiac, renal or hepatic disease.

Effects on Ability to Drive and Operate Machinery
No studies on the effects on the ability to drive and use machines have been performed.

Effects on Laboratory Tests
Androgens may decrease levels of thyroxine-binding globulin resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

ADVERSE EFFECTS

The most commonly reported adverse reactions in a clinical trial extending up to 120 days with AXIRON were administration site reactions (14.9 %). The majority of these reactions were mild and did not lead to discontinuation of therapy.

The table below lists the adverse reactions reported during the a phase III open label clinical trial in 155 men with hypogonadism treated for up to 120 days with AXIRON.

Frequency estimate: Very common (≥1/10), Common (≥1/100 to <1/10) and Uncommon (≥1/1000 to <1/100).

Very common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)
Infections and Infestations		
		Folliculitis
Metabolism and Nutrition Disorders		
	Hypercholesterolemia, Glucose dysregulation[1]	Hyperhidrosis, Hypertriglyceridemia, Weight increased
Psychiatric disorders		
	Anger, Anxiety, Mood swings, Insomnia	
Nervous system disorders		
	Dizziness, Migraine, Headache	Paraesthesia
Vascular Disorders		
	Increased blood pressure	
Gastrointestinal Disorders		
	Diarrhoea, Nausea, Vomiting	

Skin and Subcutaneous Tissue Disorders		
	Acne, Epidermal and dermal conditions[2]	
Reproductive and Breast Disorders		
		Breast tenderness, Neoplasm prostate
Investigations		
	Haematology investigations[3], PSA increased	Blood testosterone increased
General disorders and Administration Site Conditions		
Administration site reactions[4]		

(1) Glucose dysregulation includes blood glucose increased, glycosylated haemoglobin increased and Type 2 diabetes.
(2) Includes hyperkeratosis, dry skin, rash, rash papular, pruritis, skin tightness, pigmentation disorder, erythema (all) and erythema
(3) Includes haematocrit increased, RBC increased and haemoglobin increased
(4) Includes application site irritation, application site erythema, application site oedema and application site warmth.

According to the literature, additional undesirable reactions that are possibly or probably related to testosterone use are shown in the following table:

System Organ Class	**Adverse Reaction**
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	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	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 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
General Disorders and Administration Site Conditions	Hypersensitivity reactions, Asthenia, Malaise
Investigations	Decreased HDL

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

DOSAGE AND ADMINISTRATION

Use in adult and elderly men
The recommended starting dose of AXIRON is 60mg of testosterone (3 ml or one pump actuation of 30mg testosterone applied to each underarm) once daily at approximately the same time each day. AXIRON should not be applied to other parts of the body.

The application should be administered onto clean, dry and intact underarm skin.

To ensure proper dosing, serum testosterone concentrations should be measured after initiation of therapy to ensure that the desired concentrations are achieved. A single blood sample should be taken 2 – 8 hours after applying AXIRON and at least 14 days after starting treatment or following dose adjustment.

If the measured serum testosterone concentration is below the normal range, the daily AXIRON dose may be increased from 60 mg testosterone (3 ml, equivalent to two pump actuations) to 90 mg (4.5 ml, equivalent to three pump actuations) or from 90 mg (4.5 ml) up to a maximum of 120 mg (6ml, equivalent to four pump actuations). If the serum testosterone concentration exceeds the normal range, the daily dose may be decreased by 30 mg (1.5 ml). Therapy should be discontinued if the serum testosterone concentration consistently exceeds the normal range at the lowest daily dose of 30 mg (1.5 ml, equivalent to one pump actuation).

Hepatic or renal impairment
No formal studies were conducted with AXIRON involving patients with renal or hepatic impairment. (See Precautions)

Paediatric population
The safety and efficacy of AXIRON in children and adolescents aged under 18 years of age has not been established.

Method of administration

For cutaneous use

AXIRON is a solution applied to the underarm using an applicator (refer to Applicator Instructions for Use inside pack). Patients should not apply AXIRON with their fingers or hands. Deodorants or antiperspirants do not interfere with the therapeutic effects of AXIRON. Therefore, patients may use deodorant or antiperspirant with AXIRON as part of their normal, daily routine. If patients are to use an antiperspirant or deodorant, then it should be applied prior to application of AXIRON.

Patients should be advised not to dispense more than one pump actuation (1.5 ml) into the applicator cup at any one time. Higher doses are achieved by repeating the application.

Daily Prescribed Dose	Number of Pump Actuations	Application
30 mg testosterone (1.5 ml)	1 (once daily)	Apply once to one underarm only (left OR right)
60 mg testosterone (3.0 ml)	2 (once daily)	Apply once to the left underarm and then apply once to the right underarm.
90 mg testosterone (4.5 ml)	3 (once daily)	Apply once to the left and once to the right underarm, wait for the product to dry, and then apply again once to the left OR right underarm.
120 mg testosterone (6.0 ml)	4 (once daily)	Apply once to the left and once to the right underarm, wait for the product to dry, and then apply again once to the left AND once to the right underarm.

Patients should be advised that after applying the solution, the application site should be allowed to dry for three minutes prior to dressing. Avoid fire, flames or smoking until the solution has dried since AXIRON is flammable.

The patient should be advised to wash their hands well with soap and water after AXIRON has been applied.

As washing after AXIRON administration removes testosterone from the skin, patients should be advised not to wash, shower or swim for at least 2 hours after applying AXIRON. If washing does occur up to 2 hours after the application, the absorption of testosterone may be reduced.

OVERDOSAGE

No cases of overdose with AXIRON have been reported in clinical trials. Treatment of overdose would consist of discontinuation of AXIRON together with appropriate symptomatic and supportive care.
In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26; in New Zealand call 0800 764 766) for advice.

PRESENTATION AND STORAGE CONDITIONS

AXIRON (testosterone) transdermal solution is available as a metered-dose pump containing 110 mL of solution. The pump is capable of dispensing 90 mL of solution in 60 metered pump actuations. One pump actuation delivers 30 mg of testosterone in 1.5 mL of solution. Each metered-dose pump is supplied with an applicator. Neither the bottle nor the applicator cup contains latex.
Keep AXIRON out of reach of children.
Store below 25°C. Store in the original package.

NAME AND ADDRESS OF THE SPONSOR

Eli Lilly Australia Pty. Limited
112 Wharf Road,
West Ryde NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

15 May 2012

DATE OF MOST RECENT AMMENDMENT

15 May 2012