PRODUCT MONOGRAPH

<c>AXIRON®

(testosterone topical solution, 2%)

30 mg per actuation

Androgens

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Date of Revision:
May 26, 2015

Submission Control #181753

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Topical	2% solution 30 mg per actuation	Ethanol, isopropyl alcohol, octisalate, povidone

INDICATIONS AND CLINICAL USE

AXIRON is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism).

AXIRON should not be used to treat non-specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other etiologies responsible for the symptoms have not been excluded. Testosterone deficiency should be clearly demonstrated by clinical features and confirmed by biochemical assays before initiating therapy with any testosterone replacement, including AXIRON treatment.

Geriatrics (> 65 years of age):

There are limited clinical study data supporting the use of AXIRON in the geriatric population (see WARNINGS AND PRECAUTIONS and CLINICAL TRIALS).

Pediatrics (<18 years of age):

AXIRON is not indicated for use in children <18 years of age since safety and efficacy have not been established in this patient population (see WARNINGS AND PRECAUTIONS - Special Populations).

CONTRAINDICATIONS

- AXIRON is not indicated for use in women.
- **Pregnant and nursing women should avoid skin contact with application sites on men. Testosterone may cause fetal harm. Testosterone exposure during pregnancy has been reported to be associated with fetal abnormalities (see WARNINGS AND PRECAUTIONS - Potential for Secondary Exposure to Testosterone and Special Populations)**.

In the event that unwashed or unclothed skin to which AXIRON has been applied or clothing exposed to AXIRON comes in direct contact with the skin of a pregnant or nursing woman, the general area of contact on the woman should be immediately washed with soap and water.

- Androgens are contraindicated in men with known or suspected carcinoma of the prostate or breast.
- AXIRON should not be used in patients with known hypersensitivity to any of its ingredients, including testosterone that is chemically synthesized from soy (see DOSAGE FORMS: COMPOSITION AND PACKAGING).

WARNINGS AND PRECAUTIONS

SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to topical testosterone products.**
- **Children should avoid contact with unwashed or unclothed application sites in men using AXIRON.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use.**

(See WARNINGS AND PRECAUTIONS - Potential for Secondary Exposure to Testosterone. Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AXIRON-treated skin)

Potential for Secondary Exposure to Topical Testosterone

Secondary exposure to testosterone in children and women can occur with topical testosterone use in men. Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behaviour, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to topical testosterone. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age.

Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to topical testosterone should also be brought to the attention of a physician. Testosterone should be promptly discontinued until the cause of virilization has been identified.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AXIRON-treated skin:

- AXIRON should only be applied to the underarm, not to any other parts of the body.
- Children and women should avoid contact with unwashed or unclothed application site(s) of men using AXIRON.
- Patients should wash their hands immediately with soap and water after applying AXIRON.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the solution has dried.
- Prior to any situation in which skin-to-skin contact with the application site is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
- When unwashed or unclothed skin to which AXIRON has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

General

- There are very limited data from clinical trials with AXIRON in the geriatric male (>65 years of age) to support the efficacy and safety of prolonged use. Impacts to prostate and cardiovascular event rates and patient important outcomes are unknown.
- If testosterone deficiency has not been established, AXIRON should not be used to improve body composition, bone and muscle mass, increase lean body mass and decrease total fat mass. Efficacy and safety have not been established. Serious long term deleterious health issues may arise.
- AXIRON has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk of serious adverse health effects, this drug should not be used for such purpose.
- If testosterone deficiency has not been established, testosterone replacement therapy should not be used for the treatment of sexual dysfunction.
- Testosterone replacement therapy is not a treatment for male infertility.
- Following application of AXIRON, allow the product to dry completely before smoking or going near an open flame.

Special Populations

Pregnant and Nursing Women:

Pregnant and nursing women should avoid skin contact with AXIRON application sites on men. Testosterone may cause fetal harm. Testosterone exposure during pregnancy has been reported to be associated with fetal abnormalities. In the event that unwashed or unclothed skin to which AXIRON has been applied or clothing exposed to AXIRON comes in

direct contact with the skin of a pregnant or nursing woman, the general area of contact on the woman should be immediately washed with soap and water (see CONTRAINDICATIONS).

Pediatrics (<18 years of age):

AXIRON is not indicated for use in children <18 years of age since safety and efficacy have not been established in this patient population.

Androgen therapy should be used cautiously in males with hypogonadism causing delayed puberty. Androgens can accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child is the greater risk of compromising final mature height. The effect of androgens on bone maturation should be monitored closely by assessing bone age of the wrist and hand on a regular basis.

Geriatrics (>65 years of age):

There are very limited controlled clinical study data supporting the use of testosterone in the geriatric population and virtually no controlled clinical studies on subjects 75 years and over.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma. Testosterone therapy is not recommended without further urological evaluation in patients with a palpable prostate nodule or induration or PSA >4 ng/mL.

Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy.

Carcinogenesis

Prostatic: Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma (see Special Populations - Geriatrics). In men 40 years of age or older with a baseline PSA >0.6 ng/mL, digital examination of the prostate and PSA measurement are recommended before initiating treatment, at 3 to 6 months and then in accordance with clinical guidelines for prostate cancer screening.

Breast: Patients using long-term androgen therapy may be at an increased risk for the development of breast cancer.

Hepatic: Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. AXIRON is not known to produce these adverse effects.

Skeletal: Patients with skeletal metastases are at a risk of exacerbating hypercalcemia/ hypercalciuria with concomitant androgen therapy. Regular monitoring of serum calcium concentrations is recommended in these patients.

Cardiovascular

Testosterone may increase blood pressure and should be used with caution in patients with hypertension.

Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. Diuretic therapy may be required, in addition to discontinuation of the drug.

Post-market studies suggest increased risk of serious cardiovascular events such as myocardial infarction and stroke associated with testosterone therapy. Before starting testosterone therapy, patients should be assessed for any cardiovascular risk factors (e.g., existing ischaemic heart disease) or prior history of cardiovascular events (e.g., myocardial infarction, stroke, or heart failure). Patients should also be closely monitored for possible serious cardiovascular events while on testosterone therapy.

Dependence/Tolerance

AXIRON contains testosterone, a Schedule G controlled substance as defined by the Food and Drugs Act.

Endocrine and Metabolism

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

Hypercalciuria/hypercalcemia (caused by malignant tumours) may be exacerbated by androgen treatment. Androgens should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in patients at risk of hypercalciuria/ hypercalcemia. Hypercalcemia may occur in immobilized patients. If this occurs, the drug should be discontinued.

Genitourinary

Men with benign prostatic hyperplasia (BPH) treated with androgens are at an increased risk for worsening signs and symptoms.

Hematologic

Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long-term androgen therapy (see Monitoring and Laboratory Tests). Men with hematocrit levels >50% should undergo further clinical evaluation before consideration of

testosterone therapy. If hematocrit is >54%, testosterone therapy should be discontinued until hematocrit decreases to a safe level.

Oral alkylated derivatives of testosterone such as methandrostenolone, have been reported to decrease the anticoagulant requirement of patients receiving oral anticoagulants (e.g. warfarin). Patients receiving oral anticoagulants therapy require close monitoring, especially when androgens are started or stopped (see Drug-Drug Interactions).

Respiratory

The treatment of hypogonadal men with testosterone may potentiate sleep apnea, particularly for those with risk factors such as obesity or chronic lung diseases.

Sexual Function/Reproduction

- Gynecomastia may develop and occasionally persist in patients being treated with androgens for hypogonadism.
- Priapism or excessive sexual stimulation may develop.
- Oligospermia may occur after prolonged administration or excessive dosage.

Skin

Changes in body hair distribution, significant increase in acne, or other signs of virilization of the female partner or in any person (including children) exposed to skin-to skin contact, should be brought to the attention of a physician.

Application site reactions associated with the use of transdermal testosterone may manifest as skin irritation (including erythema, induration or burning).

Monitoring and Laboratory Tests

The patient should be monitored (including serum testosterone levels) on a regular basis to ensure adequate response to treatment.

Currently there is no consensus about age-specific testosterone levels. The normal serum testosterone level for young eugonadal men is approximately 10.4-36.4 nmol/L (300-1050 ng/dL). However, it should be taken into account that physiologically testosterone levels (mean and range) decrease with increasing age. Men with levels below their laboratory's reference range and who are experiencing symptoms are candidates for testosterone replacement therapy and should be evaluated as such.

The following laboratory tests, performed routinely, are recommended to ensure that adverse experience is detected and addressed:

- Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia). Men with hematocrit level >50% should undergo further clinical evaluation before considering testosterone therapy.

- Liver function tests, to detect hepatotoxicity associated with the use of androgens.
- Prostate specific antigen (PSA), Digital Rectal Examination (DRE), especially if the patient presents with progressive difficulty with urination or a change in voiding habits. In men 40 years of age or older who have a baseline PSA >0.6 ng/mL, a digital examination of the prostate and PSA measurement are recommended before initiating treatment, at 3 to 6 months, and then in accordance with evidence-based guidelines for prostate cancer screening.
- Lipid profile, total cholesterol, LDL, HDL, and triglycerides.
- Diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly (see Drug-Drug Interactions).

ADVERSE REACTIONS

Clinical Trials in Hypogonadal Men

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 shows the incidence of treatment emergent adverse reactions reported by patients treated with AXIRON for up to 120 days (N=155) or 180 days (N=71), with doses ranging from 30 mg to 120 mg per day in a Phase 3 Study. These data reflect the experience primarily with a dose of 60 mg testosterone, which was taken by all patients at the start of the study, and was the maintenance dose for 117 of 155 subjects.

Table 1. Treatment-Emergent Adverse Reactions in Patients Treated with AXIRON for up to 120 Days (N=155) and up to 180 Days (N=71), with Doses Ranging from 30 to 120mg per day.

Adverse Event	AXIRON Therapy 120 Days (N=155)	AXIRON Therapy 180 Days (N=71)
	№ (%) Patients	№ (%) Patients
Application Site Irritation	11 (7%)	6 (8%)
Application Site Erythema	8 (5%)	5 (7%)
Headache	8 (5%)	4 (6%)
Hematocrit Increased	6 (4%)	5 (7%)
Diarrhea	4 (3%)	3 (4%)
Vomiting	4 (3%)	3 (4%)
PSA Increase	2 (1%)	3 (4%)

Other less common adverse reactions often associated with topical applications and/or testosterone reported by at least 2 subjects were: application site edema, application site warmth,

increased hemoglobin, increased prostate specific antigen (PSA), increased blood pressure, increased blood testosterone, increased blood glucose, acne, anger and anxiety. Adverse reactions reported in fewer than 1% of patients in the 120 day trial included: asthenia, affect lability, increased blood testosterone, erythema (general), folliculitis, anxiety, increased lacrimation, breast tenderness, hypertension, neoplasm prostate and elevated red blood cell count.

Adverse events (AEs) tended to be reported early during therapy and were transient. Severity of most adverse events was reported as mild, with some moderate and very few severe.

Five patients discontinued the 120 day trial and its extension to 180 days due to AEs. These were *(a)* superficial thrombophlebitis, *(b)* malignant melanoma, *(c)* dry skin and erythema, *(d)* affect lability and anger, and *(e)* application site irritation. Events *(d)* and *(e)* were considered probably related to testosterone treatment. There were other discontinuations due to abnormal laboratory findings. Seven patients had hematocrit levels that exceeded 54% at one or more sampling periods. All patients had a hematocrit of <51% at study entry. Five of these 7 patients discontinued the study.

Seventy-one (71) patients continued AXIRON treatment for a further two months to assess the occurrence of skin safety events. Skin irritation was generally mild and after 6 months of treatment, the incidence was similar to the incidence for those treated for 120 days.

No patients reported serious adverse events (SAEs) considered related to treatment during either the 120 day trial, or the extension to 180 days. Three cases of non-treatment related SAEs were observed in these trials: appendicitis, hepatitis C and prostate cancer.

During the 120 day clinical trial, there was an increase in mean PSA values of 0.13 ± 0.68 ng/mL from baseline. At the end of the 180 day extension clinical trial, there was an overall increase in mean PSA values of 0.1 ± 0.54 ng/mL.

Post-Market Adverse Drug Reactions

According to the literature and post marketing experience, the following is a list of adverse drug reactions that may be related to AXIRON and/or testosterone treatment:

Blood and Lymphatic System Disorders: increased blood creatinine; polycythemia.

Cardiovascular disorders: tachycardia, atrial fibrillation, pulmonary embolism, and deep vein thrombosis.

Endocrine Disorders: increase in male pattern hair distribution; hirsutism.

General Disorders and Administration Site Conditions: malaise.

Hepatobiliary Disorders: abnormal liver enzyme/liver function tests, including bilirubin.

Investigations: decreased HDL.

Metabolism and Nutrition Disorders: electrolyte changes (potassium, sodium, chloride, inorganic phosphate,) during high dose or prolonged treatment; increased appetite.

Musculoskeletal System Disorders: muscle spasms; muscle cramps; muscle pain.

Nervous System Disorders: amnesia; hyperesthesia; smell disorder; taste disorder.

Psychiatric Disorders: depression; mood disorders; nervousness; hostility.

Renal and Urinary Disorders: impaired urination; urinary tract infection, urinary tract obstruction.

Reproductive System and Breast Disorders: mastodynia, sensitive nipples; prostatic disorders; spontaneous penile erection; libido changes; increased frequency of erections; priapism; reduction in the size of the testicles/testicular atrophy.

Respiratory System Disorders: dyspnea.

Skin and Subcutaneous Disorders: alopecia; urticaria; seborrhea; discoloured hair.

Vascular Disorders: decreased diastolic blood pressure; flushing; vasodilation.

DRUG INTERACTIONS

Drug-Drug Interactions

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

Propranolol: In a published pharmacokinetic study of an injectable testosterone product, administration of testosterone cypionate led to an increased clearance of propranolol in the majority of men tested. It is unknown if this would apply to AXIRON.

Corticosteroids: The concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation; thus these drugs should be administered cautiously, particularly in patients with cardiac, renal or hepatic disease.

Anticoagulants: Androgens may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinemia.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Literature reports indicate that some herbal products (e.g. St John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore may decrease plasma testosterone levels.

Drug-Laboratory Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing and Dose Adjustment

The recommended starting dose of AXIRON (testosterone) topical solution is 60 mg of testosterone (2 pump actuations) applied once daily. AXIRON is a metered-dose pump capable of dispensing 90 mL of solution in 60 metered pump actuations. Each pump actuation delivers 30 mg of testosterone in 1.5 mL of solution.

The usual dose of AXIRON topical solution is 60 mg of testosterone (2 pump actuations) applied once daily to the skin of the underarm, preferably at the same time each morning, to clean, dry, intact skin.

Serum testosterone concentrations should be measured after initiation of therapy and at least 14 days after starting treatment or following dose adjustment and between 2-8 hours after administration, to ensure that the desired concentrations of 10.4-36.4 nmol/L (300-1050 ng/dL) are achieved.

If the measured serum testosterone concentration is below 10.4 nmol/L (300 ng/dL), the daily testosterone dose may be increased from 60 mg (2 pump actuations) to 90 mg (3 pump actuations) or from 90 mg to 120 mg (4 pump actuations). If the serum testosterone concentration exceeds 36.4 nmol/L (1050 ng/dL), the daily testosterone dose should be decreased from 60 mg (2 pump actuations) to 30 mg (1 pump actuation) as instructed by a physician. If the serum testosterone concentration consistently exceeds 36.4 nmol/L (1050 ng/dL) at the lowest daily dose of 30 mg (1 pump actuation), AXIRON therapy should be discontinued.

Administration Instructions

AXIRON is a solution applied to the underarm, using a no-touch applicator. AXIRON should not be applied to any other parts of the body. After applying the solution, the application site should be allowed to dry for about 2 minutes before putting on clothing. Avoid fire, flames or smoking until the solution has dried since alcohol based products, including AXIRON, are flammable.

Patients may use underarm deodorant or antiperspirant before or after applying AXIRON as part of their normal daily routine. Antiperspirants or deodorants have no significant effect on the absorption of testosterone from AXIRON (see CLINICAL TRIALS). If patients are to use a "stick" or "roll-on" type of-antiperspirant or deodorant, it should be applied prior to using AXIRON, to avoid contamination of the stick or roll-on product.

When using AXIRON for the first time, patients must be instructed to prime the pump by depressing the pump 3 times, discard any product dispensed directly into a basin, sink or toilet and then wash the liquid away thoroughly. This priming should be done only prior to the first use of each pump. After priming, patients should completely depress the pump one time (1 actuation) to dispense 30 mg of testosterone directly into the applicator cup.

Keeping the applicator upright, patients should place it up into the underarm and wipe steadily *down and up* into the underarm. If the solution drips or runs, it can be wiped back up with the applicator cup. The solution should not be rubbed into the skin with fingers or hand.

Covering the treatment application area with clothing [e.g., a shirt] when the testosterone solution has dried is an effective method to reduce testosterone interpersonal transfer.

In-vitro studies with AXIRON show that 97% of the stated dose is delivered to the skin using the pump and applicator system. Dosing that requires greater than one pump actuation must be applied in increments of 30 mg as shown in Table 2.

Table 2. AXIRON Application Technique

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

To achieve a total dose of 60 mg testosterone, this process is repeated with application of 30 mg testosterone (1 pump actuation) to the other underarm. For patients prescribed the 90 mg dose of testosterone, the procedure is the same, but 3 applications are required. To dose 120 mg of testosterone, 4 applications are required, alternating left and right axilla for each application. When repeated application to the same axilla is required, the underarm should be allowed to dry completely before more AXIRON is applied.

After use, the applicator should be rinsed under running water and patted dry with a tissue. The applicator and cap are then replaced on the bottle for storage.

Hands should be washed thoroughly with soap and water after applying AXIRON (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms of a testosterone overdose are not known. No specific antidote is available. Treatment of overdosage would consist of washing the application site and discontinuation of AXIRON, together with appropriate symptomatic and supportive care.

ACTION AND CLINICAL PHARMACOLOGY

AXIRON (testosterone) topical solution is a clear, colourless, fragrance-free solution containing 30 mg of testosterone in 1.5 mL of AXIRON solution for topical administration through the axilla. AXIRON provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen.

Mechanism of Action

Testosterone and dihydrotestosterone (DHT), endogenous androgens, are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without erectile dysfunction, fatigue and loss of energy, mood depression/ disorder and depressive symptoms, regression of some secondary sexual characteristics and osteoporosis, weakness, irritability and decreased motivation. Although causality has not been established, there are associations between hypogonadism and depression, osteoporosis, metabolic syndrome, type 2 diabetes, cardiovascular disease and increased mortality in men. Hypogonadism is a risk factor for osteoporosis in men.

Male hypogonadism (congenital or acquired) has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

Pharmacodynamics

General Androgen Effects:

Drugs in the androgen class also promote retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium.

Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein. Androgens have been reported to stimulate the production of red blood cells by enhancing erythropoietin production.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth brought about by fusion of the epiphyseal growth centres. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process.

During exogenous administration of androgens, endogenous testosterone release may be inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

Pharmacokinetics

Absorption

AXIRON delivers physiologic circulating testosterone that approximates the normal concentration range of 10.4-36.4 nmol/L (300-1050 ng/dL) seen in healthy men. AXIRON provides continuous delivery of testosterone over the 24-hour dosing interval following application to the underarm.

AXIRON is a solution that dries rapidly. On the skin, the ethanol and isopropanol evaporate leaving testosterone and octisalate. The skin acts as a reservoir from which testosterone is released into the systemic circulation over time. At steady state, maximum observed serum concentration of testosterone is achieved at approximately a median time of 6 hours. In general, steady-state serum concentrations are attained within approximately one week of daily dosing.

With daily application of AXIRON 60 mg, follow-up measurements 15, 60 and 120 days after starting treatment have confirmed that mean serum testosterone concentrations are generally maintained within the eugonadal range (Figure 1). In patients on a once-daily dose of 60 mg AXIRON, the average (±SD) daily testosterone concentration (C_{avg}) was 15.8 (±7.7) nmol/L [456 (±226) ng/dL] and 17.6 (±6.1) nmol/L [506 (±175) ng/dL] on Day 15 and Day 120, respectively.

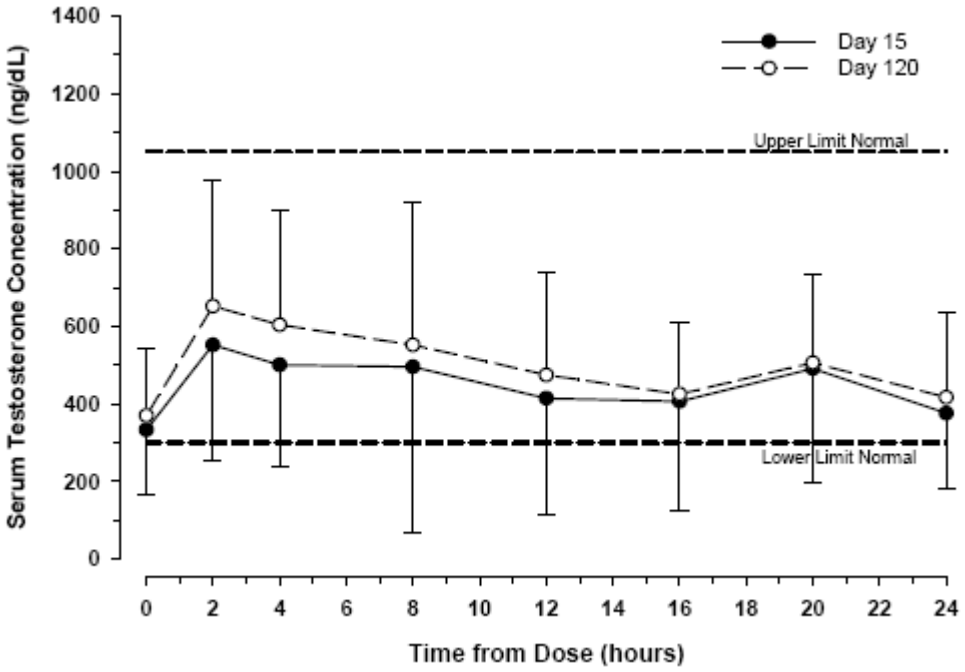


Figure 1: Mean (±SD) Serum Testosterone Concentrations on Day 15 and Day 120 in Patients Following Once-Daily Application of AXIRON 60 mg

Distribution

Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins

Metabolism

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT).

DHT concentrations increased in parallel with testosterone (T) concentrations during AXIRON treatment with mean concentrations maintained in the normal range on Days 15, 60 and 120. 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.

Excretion

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

Special Populations and Conditions

In patients treated with AXIRON, there are no observed differences in the average daily serum testosterone concentration at steady-state based on age, cause of hypogonadism or body mass index.

Since no formal studies were conducted involving patients with renal or hepatic insufficiencies, the use of AXIRON is not recommended in men with serious liver or kidney disorders.

STORAGE AND STABILITY

Store at controlled room temperature (15-30°C).

SPECIAL HANDLING INSTRUCTIONS

Avoid fire, flames or smoking near the package since alcohol based products, including testosterone topical solution 2%, are flammable.

Disposal: Used AXIRON bottles and applicators should be discarded in household trash in a manner that prevents accidental application or ingestion by household members, especially nursing/pregnant women and children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AXIRON (testosterone topical solution, 2%) is supplied as a clear, colourless, single phase solution containing 30 mg of testosterone in 1.5 mL of solution for topical administration to the underarm. It is dispensed in a metered-dose pump containing 110 mL capable of dispensing 90 mL of solution in 60 metered pump actuations. Each metered-dose pump is supplied with an applicator. The applicator head is made of silicone.

Active Ingredient: testosterone

Non-medicinal ingredients: ethanol, isopropyl alcohol, octisalate, povidone.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

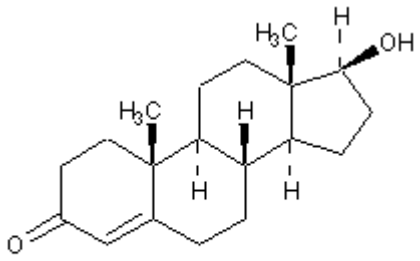
Proper name: Testosterone

Chemical name: 17 β- hydroxyandrost-4-en-3-one

Molecular formula: $C_{19}H_{28}O_2$

Molecular Weight: 288.43

Structural formula:



Testosterone

Physicochemical Properties:

Description:	White to practically white crystalline powder
Solubility:	Soluble in acetone, dioxane and vegetable oils
- water:	practically insoluble
- dehydrated alcohol:	1 in 6 of dehydrated alcohol
- chloroform:	1 in 2 of chloroform
- ether:	1 in 100 of ether
CAS Registry No:	58-22-0
Melting point:	153°- 157°C

CLINICAL TRIALS

Clinical Studies in Hypogonadal Men

AXIRON was evaluated in a multicenter, open label, 120-day trial that enrolled 155 hypogonadal men. Patients were instructed to apply AXIRON to unclothed, clean, dry, and unbroken skin. The solution was applied to the underarm area. Patients were not instructed to alter their normal grooming routine, e.g., shave under the arm. During the initial treatment period (Days 1-15) 143 patients were treated with AXIRON 60 mg once daily. At Day 45 of the trial, patients were maintained at the same dose, or were titrated up or down, based on their calculated 24 hour average serum testosterone levels measured on Day 15. At Day 90 of the trial, patients were maintained at the same dose, or were titrated up or down, based on their calculated 24 hour average serum testosterone levels measured on Day 60. At day 120, 75% of responding patients finished the study on the starting dose of AXIRON 60 mg, while 2% were on 30 mg, 17% on 90 mg and 6 % on the 120 mg dose.

Of those who had sufficient data for analysis at day 120, 84.1%, had their average serum testosterone level in the normal range of 10.4- 36.4 nmol/L (300-1050 ng/dL). At day 15, 76.1% of subjects had total testosterone levels in the normal range and by Day 60 this proportion had risen to 84.8%. For subjects requiring dose escalation to 90 mg (N=20) or 120 mg (N=7) to achieve levels in the eugonadal range, mean testosterone concentrations at Day 120 were comparable to those in subjects maintained at 60 mg once-daily. In addition, following dose escalation, there was no increase in the observed frequency of values exceeding a level of 1050 ng/dL.

Table 3 summarizes the mean testosterone concentrations on Days 15, 60 and 120 for those patients who responded to treatment with AXIRON.

Table 3. Mean (±SD) Steady-state Serum Testosterone Concentrations on Days 15, 60 and 120 in those Patients who Responded to Treatment on Day 120.

	Day 15 (N = 116)	Day 60 (N = 116)	Day 120 (N = 116)
C_{avg} (nmol/L)	15.7 (± 5.8)	17.3 (± 7.1)	17.5 (± 4.8)
C_{max} (nmol/L)	25.2 (± 15.1)	29.9 (± 22.5)	28.5 (± 11.6)
C_{min} (nmol/L)	9.2 (± 3.7)	9.5 (± 4.3)	10.1 (± 3.7)

Treatment with AXIRON produced significant improvements from baseline in multiple sexual function parameters as measured by patient responses to a questionnaire completed prior to commencing treatment and after 15, 60 and 120 days of treatment. These parameters included sexual desire and enjoyment, sexual activity and sexual performance. In addition, the overall mean summary scores showed a significant increase in positive mood and a significant decrease in negative mood.

Sexual desire amongst all patients who completed the trial increased by 79% from baseline, and overall sexual activity, increased from baseline by 68%, 86% and 104% after 15, 60 and 120 days of treatment respectively. Patients reported a 26% increase from baseline in "the degree of penile erection" as well as a 35% increase in the score for "satisfactory duration of erection".

Patients showed a significant improvement in general well being after 60 and 120 days of treatment compared to baseline (i.e. prior to commencing treatment), as measured by the patients completing a SF-36 general health survey.

Potential for Testosterone Transfer

The potential for dermal testosterone transfer from males to females was evaluated in 2 clinical studies. In an initial study, 4 groups (each of 6 males) were treated with a total of 60 mg (30 mg to each underarm) of a 1% formulation of testosterone solution. After the males applied the testosterone, three groups of females then rubbed their outer forearms on the underarms of the males for 15 minutes at 2 hours, 6 hours or 12 hours, respectively. In the fourth group of females, the rubbing procedure occurred 2 hours after dosing but the males wore shirts during the 15 minutes of contact. Blood levels of testosterone were monitored in the female subjects for 72 hours after the rubbing procedure. Under these study conditions, when a shirt did not cover the mens' underarms, the women had serum testosterone concentrations that were above baseline at all time points. When a shirt covered the mens' underarms, there was no significant increase above baseline in the womens' serum testosterone concentrations.

In a confirmatory study with a similar design and using the maximum dose of AXIRON (testosterone 2% solution), 10 males were treated with AXIRON (60mg in each underarm) followed by wearing long-sleeved, cotton T shirts. Two hours after the application of AXIRON, women rubbed their outer forearms on the underarm of the males for 15 minutes. Total testosterone levels were assessed in the female subjects for 24 hours. While there was a small increase in serum testosterone concentration (13%) from baseline in the women, their testosterone levels remained within the normal range for women.

Use of Deodorants and Antiperspirants

The interaction of deodorants and antiperspirants with AXIRON was evaluated in 3 clinical trials with females dosed with AXIRON.

In the first trial, the impact on testosterone delivery of deodorant and antiperspirant use before and after application of a formulation closely related to that of AXIRON was examined. This study was conducted using a 1% testosterone formulation rather than the 2% formulation that represents the final AXIRON formulation. Despite the difference in testosterone concentration, the data from this study are considered relevant to the final formulation. In the first half of the trial 4 groups of 6 healthy female subjects applied a deodorant spray immediately before or after, 30 minutes after or 8 hours after application of the 1% testosterone formulation to a single underarm. In the second half of the trial, the same groups applied an antiperspirant stick immediately before or after, 30 minutes after or 8 hours after application of the 1% testosterone formulation to a single underarm. Systemic levels of testosterone were monitored in all subjects for 72 hours and no significant differences were observed between those subjects who applied a

deodorant or antiperspirant and a control group (n=6) in which no deodorant or antiperspirant was applied.

In the second trial, two groups of 6 healthy female subjects applied a combined deodorant/antiperspirant spray (6 subjects) or stick (6 subjects) to a single underarm 2 minutes before the application of a 30 mg dose of AXIRON to the same underarm. A further 5 healthy female subjects applied a deodorant spray to a single underarm 2 minutes prior to the application of a 30 mg dose of AXIRON to the underarm. A control group of 5 subjects applied no deodorant or antiperspirant product to their underarm before the application of a 30 mg dose of AXIRON to a single underarm.

Blood samples were collected for 72 hours from all subjects following dosing with AXIRON. The pre-application of either the deodorant/antiperspirants or the deodorant did not significantly affect overall systemic exposure to testosterone.

In the pivotal phase 3 study, data collected at day 120 demonstrated that application of antiperspirant/deodorant does not adversely affect the efficacy of the product. There was no significant difference in the response rate in those patients who did or did not use deodorant/antiperspirant and the response in both of these groups was not significantly different from the overall response rate. In this trial, patients were instructed to apply deodorant/antiperspirant immediately prior to the application of AXIRON.

Effect of Showering/Washing

Two groups of 5 healthy female subjects were each dosed with 30 mg AXIRON in a single underarm. 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 5 female subjects applied a 30 mg dose of AXIRON to a single underarm and did not wash the application site. Blood samples were collected for 72 hours from all subjects following dosing with AXIRON. Washing the application site did not significantly reduce the subjects' overall systemic exposure to total testosterone.

In the pivotal phase 3 study, among subjects who showered or washed a minimum of 2 hours after dosing on Days 15, 60 and 120 there was no evidence to suggest that washing had any negative impact on the efficacy of AXIRON.

TOXICOLOGY

Single-Dose Toxicity

Testosterone was administered to Swiss Webster mice in a single 5000 mg/kg dose oral toxicity study using testosterone gel. All 10 animals showed some instances of lethargy during the first four hours following dosing. No other signs of toxicity or deaths occurred during the 14-day post dosing observation period. The LD50 was greater than 5000 mg/kg.

Repeat-Dose Toxicity

A repeat dose study with testosterone enanthate in male rats was undertaken to evaluate the effects on male fertility, testes, and the seminal vesicles. Testosterone enanthate was administered at doses of 0, 1.2 or 2.4 mg/kg, subcutaneous (sc), three times a week for eight weeks. Testosterone and dihydrotestosterone (DHT) plasma levels were significantly elevated in relation to the dose administered. Mean testosterone and DHT plasma levels for the control, the low dose group, the high dose groups were 0.53 ng/mL, 2.43 ng/mL, and 4.28 ng/mL, respectively. Treated males appeared to mate normally, however, fertility of high-dose animals was decreased relative to that of low-dose and control animals. Testis weights were reduced and seminal vesicle weights increased in animals of both treatment groups.

Low testosterone levels were detected in castrated Sprague-Dawley (SD) male rats. Testosterone implants containing testosterone propionate (35 mg delivering 0.39 mg/day) were administered subcutaneously for 11 weeks. Plasma testosterone levels were significantly increased in the treatment group relative to placebo controls. Control castrates had testosterone plasma levels below the limits of detection while testosterone levels in the treatment group were within the normal range (approximately 1.5 ng/mL).

Genotoxicity

Published literature on the genotoxic potential of testosterone indicated that testosterone did not induce sperm abnormalities or micronuclei in mice treated *in vivo* and was not mutagenic to bacteria.

Carcinogenicity

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumours, which metastasized in some cases. There is suggestive evidence that injection of testosterone into 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.

Effects on the Prostate

An induction of prostate adenocarcinomas in male rats following the chronic administration of testosterone has been reported. Testosterone was given chronically by subcutaneous administration in pellets (1-3 pellets, each containing 10 mg testosterone propionate) to Noble (Nb) strain rats. A 20% incidence of prostate carcinoma in rats whose mean exposure to testosterone was 64 weeks was seen. When the treatment regimen included estrogen and testosterone, the incidence of prostate adenocarcinoma was not significantly different from the group receiving testosterone alone. The latency period for the appearance of this tumour type was reduced.

In another study, Lobund-Wistar strain of rats were used to study the incidence of prostate cancer with testosterone treatment. Thirty milligrams of testosterone was administered subcutaneously via silastic implants. Reported results indicate that testosterone treatments increased the incidence of prostate adenocarcinomas to 40% (13 of 32) in the rat. The tumour promotional effects of testosterone in combination with high fat (20%) diet in Lobund-Wistar rats showed testosterone and a high-fat diet contributed to an increased incidence of prostatic tumours and a shortened latency period over low-fat (5%) diet controls.

Reproductive and Developmental Toxicity

Effects on exogenously dosed male animals The effects of exogenously administered testosterone on the reproductive tract of male dogs was reported . Mixed testosterone esters (testosterone phenylpropionate, testosterone isocaproate, testosterone decanoate, and testosterone propionate) were administered as a single 5 mg/kg SC dose to male dogs producing long-lasting effects on semen quality. Sperm motility was observed to decline from three weeks after treatment with the maximum effect occurring between 30 and 80 days post-dosing. Sperm morphology was also adversely affected in treated animals and a decrease in live spermatozoa occurred from one month after treatment. There was a significant decline in the mean total output of spermatozoa in treated males.

Testosterone administration has been demonstrated to be anti-spermatogenic in animals and humans. Male rabbits treated with ~200% of the physiological dose of testosterone via implants were shown to be azoospermic. The implants were designed to deliver 50%, 100% or ~200% the physiological amount of testosterone as that produced by the normal rabbit testes in situ during a 24-hour period. Combination treatment with implants of testosterone and estradiol or progesterone has been shown to consistently produce sterility in male rats for up to eight months, whereas testosterone alone reduced fertility, but did not induce sterility. Combinations of androgens and progestins produce rapid and significant effects on semen quality, and have also been suggested for use in male contraception in dogs. DHT has been demonstrated to be more effective than testosterone in producing infertility in male rats. Testosterone treatment in rats has been reported to reverse the anti-fertility effects of prior treatments with gonadotrophin releasing hormone (GnRH) antagonists. The administration of testosterone (20 mg, SC for three days, then every three days for 90 days) to obese male Zucker rats has shown a four-fold increase in the number of litters sired relative to untreated controls. Testosterone treatment of these animals also reduced food consumption and weight gains.

The relationship between testosterone induced decreased spermatogenic activity and fertility, pregnancy outcome and offspring was reported in a published study, in which groups of six male rats received testosterone by subdermal implants at one of the following doses: 0, 15, 30, 60, 90, 120, 240 µg/day. Testosterone administration to male rats produced biphasic effects. Low doses produced decreases in spermatogenesis due to suppression of gonadotropins and subsequent decreases in intra-testicular testosterone, whereas higher doses of testosterone have been shown to maintain spermatogenesis by presenting high serum levels of the hormone. Serum testosterone levels were not significantly different among treatment and control groups, however reported levels were highest among the group receiving 240 µg/day (4.1 ng/ml versus 2.5 ng/ml). Testosterone is also capable of maintaining spermatogenesis in the hypophysectomized animal. Testes weights were significantly reduced in groups receiving 90, 120 or 240 µg/day testosterone. Decreased spermatozoa reserves of less than five million were shown to be infertile in individual animals. It was further demonstrated in rats that a decrease in epididymal spermatozoal reserves mediated by testosterone did not cause an observed increase in teratogenic incidences in their progeny as compared with that of controls.

Local Tolerance

The dermal irritation potential of transdermal testosterone was evaluated in rabbits, with and without use of a semiocclusive dressing. Results indicated that topical testosterone gel was irritating to rabbit dorsal skin when the application site was covered for a 4 hour contact period. Dermal irritation was not observed when the application site was left uncovered, which simulates the actual clinical use of the product.

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PART III: CONSUMER INFORMATION

<c>AXIRON®
(testosterone topical solution, 2%)

30 mg per actuation

This leaflet is part III of a three-part "Product Monograph" published when AXIRON was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AXIRON. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Your doctor has prescribed AXIRON because your body is not making enough testosterone. The medical term for this condition is hypogonadism.

What it does:

AXIRON delivers medicine into your bloodstream through your skin. AXIRON helps raise your testosterone to normal levels.

When it should not be used:

- If you have or it is suspected that you have prostate or breast cancer.
- If you have a known allergy to any of its components [the active ingredient is testosterone, which may be synthesized from soy; (see "*What the nonmedicinal ingredients are*" in this section)].

AXIRON should NOT be used by women. Pregnant and breast feeding women are especially at risk and should avoid skin contact with application sites on men. Testosterone may cause harm to your unborn baby. Testosterone exposure during pregnancy has been reported to be associated with fetal abnormalities. If skin contact with unwashed or unclothed application sites of men using AXIRON and/ or with clothing or other fabrics exposed to AXIRON occurs, pregnant or nursing women should immediately wash the area of contact with soap and water.

What the medicinal ingredient is:

Testosterone

What the nonmedicinal ingredients are:

Ethanol, isopropyl alcohol, octisalate, povidone.

What dosage forms it comes in:

AXIRON is available as a metered-dose pump with an applicator, capable of dispensing 90 mL of solution in 60 pump actuations. Each pump actuation delivers 30 mg of testosterone in 1.5 mL of solution. The applicator head is made of silicone.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

AXIRON can be transferred to another person when skin-to-skin contact with application site occurs.

- **Signs of puberty (unexpected sexual development) have been reported in children who were exposed to topical testosterone.**
- **Keep children away from unwashed or unclothed application sites of men using AXIRON and from unwashed clothing or other fabrics exposed to AXIRON.**
- **Men who use AXIRON must strictly follow the instructions for use to lower the risk of transferring AXIRON to another person.**

You should prevent AXIRON from transferring to another person, especially **pregnant or breast feeding women, or children** by taking the following precautions:

- Children and women should avoid contact with the application sites on men using AXIRON.
- Wash hands immediately with soap and water after application of AXIRON.
- Cover the application site(s) with clothing (such as a shirt) after AXIRON has dried.

If direct skin-to-skin contact is anticipated, wash the application site(s) thoroughly with soap and water to remove any AXIRON left on the application site(s).

- In the event that an unwashed or uncovered AXIRON application site and/ or unwashed clothing or other fabrics exposed to AXIRON does come in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

In children, signs of testosterone exposure can include unexpected sexual development such as inappropriate enlargement of the penis or clitoris, development of pubic hair, increased erections, or aggressive behaviour. In women, signs of testosterone exposure include changes in body hair distribution, significant increase in acne, or other signs of the development of masculine traits. Any of these changes should be brought immediately to the attention of a doctor. The possibility of exposure to testosterone should be discussed with the doctor.

AXIRON must not be used by children under the age of 18.

There is very little information from clinical trials with testosterone in the older male (>65 years of age) to support safe use of AXIRON for a long period of time.

You should not use testosterone in an attempt to reduce weight and increase muscle, or improve athletic performance as it may cause serious health problems.

You should not use testosterone to treat sexual dysfunction or male infertility.

Before using AXIRON, talk to your doctor if you have:

- difficulty urinating due to an enlarged prostate. Older patients may have a higher risk of developing an enlarged prostate or prostate cancer;
- prostate cancer (confirmed or suspected);
- liver, kidney or heart disease;
- high blood pressure (hypertension);
- diabetes;
- breathing problems during sleep (sleep apnea);
- heart or blood vessel problems or a history of these problems such as heart attacks, stroke or blood clot in the lungs or legs.

Drug Abuse and Dependence:
AXIRON contains testosterone, which is a controlled substance under Schedule G of the Food and Drugs Act.

Precautions while using AXIRON:
Following application of AXIRON, allow it to dry completely before smoking or going near an open fire.

INTERACTIONS WITH THIS MEDICATION

Be sure to tell your doctor about all other prescription and nonprescription medicines you are taking, if any. Drugs that may interact with AXIRON include:

- insulin
- corticosteroids
- propranolol
- anti-clotting medications (e.g. warfarin).

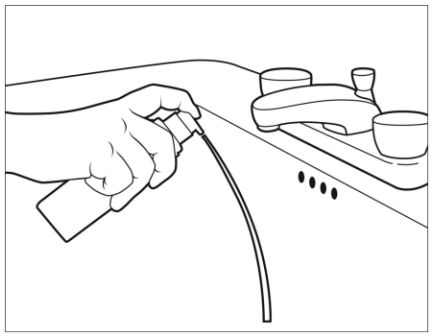
PROPER USE OF THIS MEDICATION

- It is important that you apply AXIRON exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much AXIRON to apply and when to apply it.
- **AXIRON is to be applied to the armpits only.** Do not apply AXIRON to any other parts of your body such as your stomach area (abdomen), penis, scrotum, shoulders or upper arms.
- Do not apply AXIRON with your fingers or hands.
- Apply AXIRON at about the same time each morning. AXIRON should be applied after showering or bathing.
- Avoid swimming or bathing for at least 2 hours after you apply AXIRON.
- If you use deodorant or antiperspirant, apply it **before** applying AXIRON; this will help avoid contamination of the stick or roll-on product.
- **AXIRON is flammable until dry. Let AXIRON dry before smoking or going near an open flame.**
- Avoid splashing in the eyes. In case of contact with eyes, flush thoroughly with water. If irritation persists, seek medical advice.
- Never share your AXIRON with anyone.

<u>Applying AXIRON</u>:

AXIRON Parts

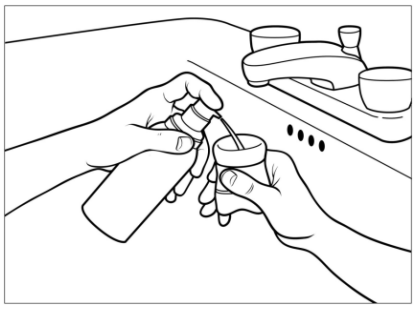
- Before using a new bottle of AXIRON for the first time, you will need to prime the pump. To prime the AXIRON pump gently push down on the pump 3 times. Do not use any AXIRON that came out while priming. Wash it down the sink to avoid accidental exposure to others. Your AXIRON pump is now ready to use.



PRIME THE PUMP

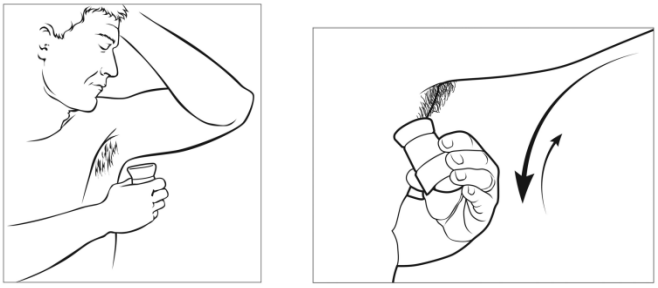
- Before applying AXIRON, make sure that your armpit is clean, dry and that there is no broken skin. It is not necessary to shave the skin.

- Remove the cap and the applicator cup from the pump. Then, position the nozzle over the applicator cup and depress the pump gently:



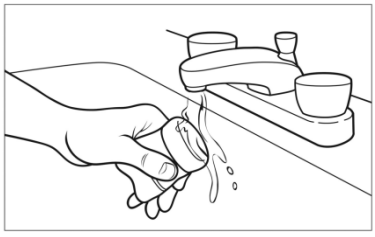
PUMP

- To apply the AXIRON solution, keep the applicator upright, place it up into the armpit application site and wipe steadily down and up:



SWIPE

- If AXIRON drips or runs, wipe it back up with the applicator cup. Do not rub in the solution with your fingers or hand once it has been applied.
- After you have finished applying AXIRON, rinse the applicator cup with room temperature running water, and then pat it dry with a tissue. Carefully replace the applicator cup and cap back onto the bottle.



WASH

- Clean up any spilled solution from surfaces such as the sink or floor to make sure others do not come into contact with it.
- Wash your hands with soap and water right away.
- Let the application site dry completely (about 2 minutes) before putting on a shirt.

Usual dose:

Use AXIRON exactly as your healthcare provider tells you to use it. Your healthcare provider will tell you the dose of AXIRON that is right for you. Your healthcare provider may change your AXIRON dose. Do not change your AXIRON dose without talking to your healthcare provider.

Apply your dose correctly by following the application instructions in the table below.

Daily Prescribed Dose	Each application requires 1 depression of the pump.
30 mg	Apply 1 application once to one armpit only (left OR right).
60 mg	Apply 2 applications: one to the left armpit and then one to the right armpit.
90 mg	Apply 3 applications: one to the left and one to the right armpit, wait for the product to dry, and then apply again one to the left OR right armpit.
120 mg	Apply 4 applications: one to the left and one to the right armpit, wait for the product to dry, and then apply again one to the left AND one to the right armpit.

Overdose:

If you use more AXIRON than the recommended dose (an overdose), wash the skin with soap and water where AXIRON was applied and contact your doctor, or pharmacist or hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose and your next dose is more than 12 hours away, take the dose that you missed. If your next dose is less than 12 hours away, it is best to wait. Resume your normal dosing the next day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, AXIRON can have side effects. The following side effects have been reported for products containing testosterone:

- Skin irritation or redness or rash at the application site;
- increased prostatic specific antigen (PSA);
- enlarged prostate (benign prostatic hyperplasia);
- an increase in red blood cell count, (hematocrit and hemoglobin); this might lead to an increased risk of blood clots.
- acne;
- change in mood, depression;
- prolonged or painful erection;
- sleep disturbances caused by breathing problems;

- aggression or aggressive behaviour;
- breast enlargement and breast pain;
- loss of hair and baldness;
- high blood pressure;
- weight gain;
- headache, dizziness;
- increased or irregular heart rate, blood clot in the lungs or the legs.

Signs of puberty (unexpected sexual development) have been reported in children who were exposed to topical testosterone. See WARNINGS AND PRECAUTIONS.

Changes in body hair distribution, significant increase in acne, or other signs of the development of masculine traits in the female partner or in any person (including children) exposed to skin-to skin contact, should be brought to the attention of a doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common			
Urinary symptoms (i.e. change in frequency/ colour, dribbling, pain on urination straining, weak stream, small amounts)		✓	
Uncommon			
Breast enlargement or breast pain		✓	
Swelling of ankles and legs (in patients with heart, kidney or liver damage)			✓
Erections that are too frequent or continue for too long		✓	
Liver problems, with symptoms such as nausea, vomiting, along with yellowed or darkened skin.			✓
Heart attack and stroke			✓

This is not a complete list of side effects. For any unexpected effects while taking AXIRON, contact your doctor or pharmacist.

HOW TO STORE IT

Store AXIRON at room temperature (15°C-30°C).

Keep out of reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

- Fax toll-free to 1-866-678-6789, or

- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at

www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972 or visit the website at www.lilly.ca.

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto Ontario, M1N 2E8.

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Last revised: May 26, 2015