CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022504/S-005

Trade Name: **AXIRON**

Generic Name: **Testosterone**

Sponsor: **Eli Lilly and Company**

Approval Date: 12/22/2011

Indications: AXIRON is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.

Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022504/S-005

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022504/S-005

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Richard Hoffman, MS
Manager, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Hoffman:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 29, 2011, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Axiron® (testosterone) topical solution.

This "Changes Being Effected" supplemental new drug application proposes to modify Section 6, Adverse Reactions section, subsection 6.1, Clinical Trial Experience of the current USPI for Axiron®.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling

[21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Acting Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Medication Guide

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
12/22/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022504/S-005

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AXIRON safely and effectively. See full prescribing information for AXIRON.

AXIRON (testosterone) topical solution, for topical use CIII

Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- Virilization has been reported in children who were secondarily exposed to topical testosterone products (5.2)
- Children should avoid contact with unwashed or unclothed application sites in men using AXIRON (2.2, 5.2)
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use (2.2, 5.2, 17)

----------INDICATIONS AND USAGE----------

AXIRON® is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired) (1)
- Hypogonadotropic hypogonadism (congenital or acquired) (1)

Important limitations of use: Safety and efficacy of AXIRON in males <18 years old have not been established (8.4)

----------DOSAGE AND ADMINISTRATION----------

- Starting AXIRON dose is 60 mg of testosterone (1 pump actuation of 30 mg of testosterone to each axilla), applied once daily, at the same time each morning. (2.1)
- Apply to clean, dry intact skin of the axilla, not to any other parts of the body including the abdomen or genitals (2.2)
- Dose adjustment: The dose of testosterone may be decreased from 60 mg (2 pump actuations) to 30 mg (1 pump actuation) or increased from 60 mg to 90 mg (3 pump actuations) or from 90 mg to 120 mg (4 pump actuations) based on the serum testosterone concentration from a single blood draw 2 – 8 hours after applying AXIRON and at least 14 days after starting treatment or following dose adjustment. (2.2)
- Patients should wash hands immediately with soap and water after applying AXIRON and cover the application site with clothing after the solution has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)
- The application site and dose of AXIRON are not interchangeable with other topical testosterone products. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

AXIRON (testosterone) topical solution is available as a metered-dose pump. One pump actuation delivers 30 mg of testosterone. Each metered-dose pump is supplied with an applicator. (3)

----------CONTRAINDICATIONS----------

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate (4, 5.1)
- Pregnant or breastfeeding women. Testosterone may cause fetal harm (4, 8.1, 8.3)

----------WARNINGS AND PRECAUTIONS----------

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.1)
- Avoid unintentional exposure of women or children to AXIRON. Secondary exposure to testosterone can produce signs of virilization. AXIRON should be discontinued until the cause of the virilization is identified (2.2, 5.2)
- Exogenous administration of testosterone may lead to azoospermia (5.5)
- Edema with or without congestive heart failure, may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.7).
- Sleep apnea may occur in those with risk factors (5.9)
- Monitor serum testosterone, prostate specific antigen (PSA), liver function, lipid concentrations, hematocrit and hemoglobin periodically (5.1, 5.3, 5.6, 5.10)
- AXIRON is flammable until dry (5.13)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >4%) are skin application site reactions, increased hematocrit, headache, diarrhea, vomiting, and increased serum PSA (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Androgens may decrease blood glucose and insulin requirement in diabetic patients (7.1).
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended (7.2).
- Use of testosterone with Adrenocorticotropic Hormone (ACTH) or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3).

----------USE IN SPECIFIC POPULATIONS----------

- There are insufficient long-term safety data in geriatric patients using AXIRON to assess the potential risks of cardiovascular disease and prostate cancer (8.5).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to topical testosterone products *[see Warnings and Precautions (5.2)]*.**
- **Children should avoid contact with unwashed or unclothed application sites in men using AXIRON *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Patient Counseling Information (17)]*.**

1 INDICATIONS AND USAGE

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

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.
- **Hypogonadotropic hypogonadism (congenital or acquired):** idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Important limitations of use — Safety and efficacy of AXIRON in males <18 years old have not been established *[see Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Dose Adjustment

The recommended starting dose of AXIRON (testosterone) topical solution is 60 mg of testosterone (2 pump actuations) applied once daily.

To ensure proper dosing, serum testosterone concentrations should be measured after initiation of therapy to ensure that the desired concentrations (300 ng/dL-1050 ng/dL) are achieved. The AXIRON dose can be adjusted based on the serum testosterone concentration from a single blood draw 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 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 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 1050 ng/dL at the lowest daily dose of 30 mg (1 pump actuation), AXIRON therapy should be discontinued.

The application site and dose of AXIRON are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

AXIRON is applied to the axilla, preferably at the same time each morning, to clean, dry, intact skin. Do not apply AXIRON to other parts of the body including to the scrotum, penis, abdomen, shoulders or upper arms. After applying the solution, the application site should be allowed to dry completely prior to dressing. Avoid fire, flames or smoking until the solution has dried since alcohol based products, including AXIRON, are flammable.

AXIRON is applied to the axilla using an applicator. When using AXIRON for the first time, patients should be instructed to prime the pump by depressing the pump three (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 (one pump actuation) to dispense 30 mg of testosterone. To dispense the solution, position the nozzle over the applicator cup and carefully depress the pump fully once. Ensure that the liquid is directed into the cup. The cup should be filled with no more than 30 mg (1 pump actuation) of testosterone. Dosing that requires greater than one pump actuation must be applied in increments of 30 mg as is shown in Table 1.

Keeping the applicator upright, patients should place it up into the axilla and wipe steadily down and up into the axilla. 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. The process is then repeated with application of 30 mg of testosterone (1 pump actuation) to the other axilla to achieve a total of 60 mg of testosterone applied. For patients prescribed the 90 mg dose of testosterone, the procedure is the same, but three applications are required. To dose 120 mg of testosterone, four applications are required alternating left and right for each application as shown in Table 1. When repeat application to the same axilla is required, the axilla should be allowed to dry completely before more AXIRON is applied.

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

When deodorants or antiperspirants are used as part of a regular program for personal hygiene, they should not interfere with the efficacy of AXIRON in treating hypogonadism. If patients use an antiperspirant or deodorant (stick or roll-on) then it should be applied prior to the application of AXIRON to avoid contamination of the stick or roll-on product.

Patients should be advised to avoid swimming or washing the application site until two hours following application of AXIRON *[see Clinical Pharmacology (12.3)]*.

To reduce the likelihood of interpersonal transfer of testosterone, the application site should always be washed prior to any skin-to-skin contact regardless of the length of time since application. *[See Warnings and Precautions (5.2)]*.

Table 1: Application Technique

Daily Prescribed 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.

Hands should be washed thoroughly with soap and water after AXIRON has been applied *[see Warnings and Precautions (5.2)]*.

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

- Children and women should avoid contact with the unclothed or unwashed application sites on the skin of men using AXIRON.
- Patients should wash their hands immediately with soap and water after application of 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 direct skin-to-skin contact is anticipated, patients should wash the application site thoroughly with soap and water to remove any testosterone residue.
- In the event that 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.

While interpersonal testosterone transfer can occur with a T-shirt on, it has been shown that transfer can be substantially reduced by wearing a T-shirt and the majority of residual testosterone is removed from the skin surface by washing with soap and water.

3 DOSAGE FORMS AND STRENGTHS

AXIRON is a (testosterone) topical solution available as a metered-dose pump. One pump actuation delivers 30 mg of testosterone. Each metered-dose pump is supplied with an applicator.

4 CONTRAINDICATIONS

- AXIRON is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precaution (5.1)]*.
- 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 Use in Specific Populations (8.1, 8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening of Benign Prostatic Hyperplasia and Potential Risk of Prostate Cancer

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH.
- Patients treated with Androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating treatment. It would be appropriate to reevaluate patients 3 to 6 months after initiation of treatment, and then in accordance with prostate cancer screening practices. *[See Contraindications (4)]*.

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure to testosterone in children and women have been reported with topical testosterone products applied to the abdomen or upper arms, including cases of secondary exposure resulting in virilization of children. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to 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. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AXIRON *[see Dosage and Administration (2.2), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

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 testosterone should also be brought to the attention of a physician. Testosterone therapy should be promptly discontinued at least until the cause of virilization has been identified. *[See Dosage and Administration (2.2)]*.

5.3 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating testosterone treatment. It would be appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.4 Use in Women

Due to lack of controlled studies in women and potential virilizing effects, AXIRON is not indicated for use in women *[see Contraindications (4) and Use in Specific Populations (8.1, 8.3)]*.

5.5 Potential for Adverse Effects on Spermatogenesis

At large doses of exogenous androgens, including AXIRON, 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.

5.6 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. AXIRON is not known to cause these adverse effects.

5.7 Edema

Androgens, including AXIRON, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease *[see Adverse Reactions (6)]*.

5.8 Gynecomastia

Gynecomastia may develop and may persist in patients being treated with androgens, including AXIRON, for hypogonadism.

5.9 Sleep Apnea

The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity and chronic lung disease.

5.10 Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

5.11 Hypercalcemia

Androgens, including AXIRON, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.12 Decreased Thyroxine-binding Globulin

Androgens, including AXIRON, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentration and increased resin uptake of T3 and T4. Free thyroid hormone concentration remain unchanged, however there is no clinical evidence of thyroid dysfunction.

5.13 Flammability

Alcohol based products, including AXIRON, are flammable; therefore, patients should be advised to avoid smoking, fire or flame until the AXIRON dose applied has dried.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Hypogonadal Men

Table 2 shows the treatment emergent adverse reactions that were reported by either >4% of 155 patients in a 120 day, Phase 3 study or by >4% of 71 patients who continued to use AXIRON for up to 180 days. These data reflect the experience primarily with a testosterone dose of 60 mg, which was taken by all patients at the start of the study, and was the maintenance dose for 97 patients. However, the doses used varied from 30 mg to 120 mg.

Table 2: Adverse Reactions Seen With the Use of AXIRON in either the 120 Day Clinical Trial or in the Extension to 180 Days (>4%)

Event	120 Days (155 Patients)	180 Days (71 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 Increased	2 (1%)	3 (4%)

Other less common adverse reactions reported by at least 2 patients in the 120 day trial included: application site edema, application site warmth, increased hemoglobin, hypertension, erythema (general), increased blood glucose, acne, nasopharyngitis, anger and anxiety. Other less common adverse reactions reported in fewer than 1% of patients in the 120 day trial included: asthenia, affect lability, folliculitis, increased lacrimation, breast tenderness, increased blood pressure, increased blood testosterone, neoplasm prostate and elevated red blood cell count.

During the 120 day trial one patient discontinued treatment because of affect lability/anger which was considered possibly related to AXIRON administration.

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.

Following the 120 day study, seventy-one (71) patients entered a two-month extension study with AXIRON. Two patients (3%) had adverse reactions that led to discontinuation of treatment during the period from Day 120 to Day 180. These reactions were: one patient with application site irritation (considered possibly related to AXIRON application) and one patient with dry skin and erythema, but not at the application site (considered not related to AXIRON administration) and application site erythema (considered possibly related to AXIRON administration).

No serious adverse reactions to AXIRON were reported during either the 120 day trial, or the extension to 180 days.

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement.

7.2 Oral anticoagulants

Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]* — AXIRON is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, AXIRON is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation. *[See Contraindications (4)]*.

8.4 Pediatric Use

Safety and efficacy of AXIRON has not been established in males <18 years of age. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AXIRON to determine whether efficacy in those over 65 years of age differs from younger patients. Of the 155 patients enrolled in the pivotal clinical study utilizing AXIRON, 21 were over 65 years of age. Additionally, there were insufficient long-term safety data in these patients utilizing AXIRON to assess a potential incremental risk of cardiovascular disease and prostate cancer.

8.6 Renal Impairment

No formal studies were conducted involving patients with renal impairment.

8.7 Hepatic Impairment

No formal studies were conducted involving patients with hepatic impairment.

8.8 Use in Men with Body Mass Index (BMI) >35 kg/m^2

Safety and efficacy of AXIRON in males with BMI >35 kg/m^2 has not been established.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AXIRON contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

9.2 Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

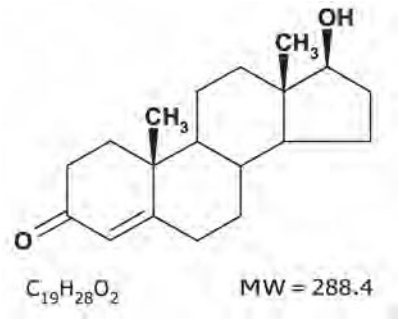
- Taking more drug than intended
- Continued drug use despite medical and social problems
- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drug are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of withdrawal syndrome upon discontinuation of anabolic steroid use

10 OVERDOSAGE

No cases of overdose with AXIRON have been reported in clinical trials. There is one report of acute overdosage by injection of testosterone enanthate: testosterone concentrations of up to 11,400 ng/dL were implicated in a cerebrovascular accident. Treatment of overdosage would consist of discontinuation of AXIRON together with appropriate symptomatic and supportive care.

11 DESCRIPTION

AXIRON (testosterone) topical solution is a clear, colorless, single phase solution containing 30 mg of testosterone in 1.5 mL of AXIRON solution for topical administration through the axilla. The active pharmacologic ingredient in AXIRON is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:



The inactive ingredients are ethanol, isopropyl alcohol, octisalate, and povidone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), 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. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism 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).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using AXIRON.

12.3 Pharmacokinetics

Absorption — AXIRON delivers physiologic circulating testosterone that approximate normal concentration range (i.e., 300 - 1050 ng/dL) seen in healthy men following application to the axilla.

On the skin, the ethanol and isopropyl alcohol evaporate leaving testosterone and octisalate. The skin acts as a reservoir from which testosterone is released into the systemic circulation over time (*see* Figure 1). In general, steady-state serum concentrations are achieved by approximately 14 days of daily dosing.

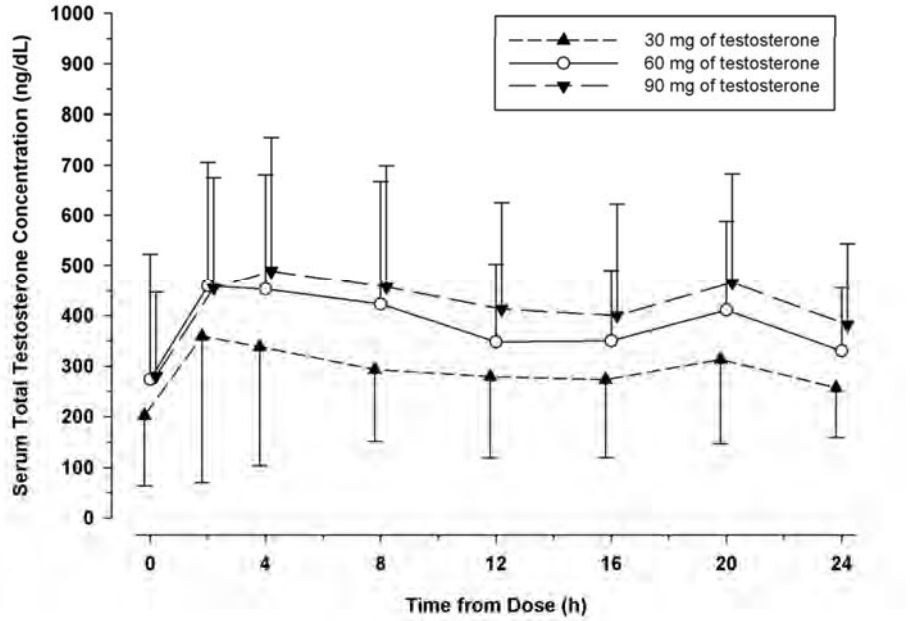


Figure 1: Mean (±SD) Serum Testosterone Concentrations on Day 7 in Patients Following AXIRON Once-Daily Application of 30 mg, 60 mg, or 90 mg of Testosterone

When AXIRON treatment is discontinued after achieving steady-state, serum testosterone concentrations returned to their pretreatment concentrations by 7 – 10 days after the last application.

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 —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.

Excretion — 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 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.

Potential for testosterone transfer: The potential for testosterone transfer from males dosed with AXIRON to healthy females was evaluated in a clinical study conducted with a 2% testosterone formulation. 10 males were treated with 60 mg (2 pump actuations) of testosterone in each axilla (the maximum testosterone dose of 120 mg). At 2 hours after the application of AXIRON to the males, the females rubbed their outer forearms for 15 minutes on the axilla of the males. The males had covered the application area with a T-shirt. Serum concentrations of testosterone were monitored in the female subjects for 72 hours after the transfer procedure. Study results show a 13% and 17% increase in testosterone exposure ($AUC_{[0-24]}$) and maximum testosterone concentration (C_{max}), respectively, compared to baseline in these females. In a prior clinical study conducted with a 1% testosterone formulation under similar study conditions, direct skin-to-skin transfer showed a 131% and 297% increase in testosterone exposure ($AUC_{[0-72]}$) and maximum testosterone concentration (C_{max}), respectively, compared to when men had covered the application area with a T-shirt.

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. *[See Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.

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. *[See Dosage and Administration (2.2), and Patient Counseling Information (17.4)]*.

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. *[See Dosage and Administration (2.2) and Patient Counseling Information (17.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, 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 tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Testosterone was negative in the in vitro Ames and in the in vivo mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Studies in Hypogonadal Men

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.

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.

On day 60, 84.8% of subjects had total testosterone concentrations in the normal range. Of those who had sufficient data for analysis on day 120, 84.1%, had their average serum testosterone concentration in the normal range of 300 – 1050 ng/dL.

Table 3 summarizes the proportion of subjects having average testosterone concentrations within the normal range on Days 60 and 120.

Table 3: Proportion of subjects who had an average Serum Total Testosterone in the range 300 to 1050 ng/dL and completed 120 days of treatment (N=138[a])

Evaluation Time	Statistics	Value
Baseline Testosterone	Mean (SD)	194.6 ng/dL (92.9 ng/dL)
Day 15	Normal[b]	76.1%[c]
	95% CI	(69.0%, 83.2%)
Day 60	Normal[b]	84.8%
	95% CI	(78.8%, 90.8%)
Day 120	Normal[b]	84.1%
	95% CI	(77.9%, 90.2%)

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

[b] Normal represents the percentage of patients with average testosterone concentration in the range of 300 – 1050 ng/dL.

[c] On Day 15, 72.2% of the 90 subjects in the US study population had an average serum testosterone in the range of 300 ng/dL – 1050 ng/dL.

Of the 135 patients who completed the 120 day treatment, 123 patients did so with no deviation from the protocol. By day 120, average serum testosterone concentration was within normal range for 67% of those who titrated down on the 30 mg dose, 89% of those on the 60 mg dose, 86% of those who titrated up to 90 mg and 70% of those who titrated up to the 120 mg dose. Table 4 below summarizes the testosterone concentration data in the patients who completed 120 days.

Table 4: 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} (ng/dL)	--	456 (±226)	--	--	456 (±226)
C_{max} (ng/dL)	--	744 (±502)	--	--	744 (±502)
Day 60	**[N=1]**	**[N=105]**	**[N=29]**	**[N=0]**	**[N=135]**
C_{avg} (ng/dL)	343 (--)	523 (±207)	368 (±138)	--	488 (±204)
C_{max} (ng/dL)	491 (--)	898 (±664)	646 (±382)	--	840 (±620)
Day 120	**[N=3]**	**[N=97]**	**[N=25]**	**[N=10]**	**[N=135]**
C_{avg} (ng/dL)	493 (±239)	506 (±175)	415 (±165)	390 (±160)	480 (±177)
C_{max} (ng/dL)	779 (±416)	839 (±436)	664 (±336)	658 (±353)	792 (±417)

Figure 2 summarizes 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.

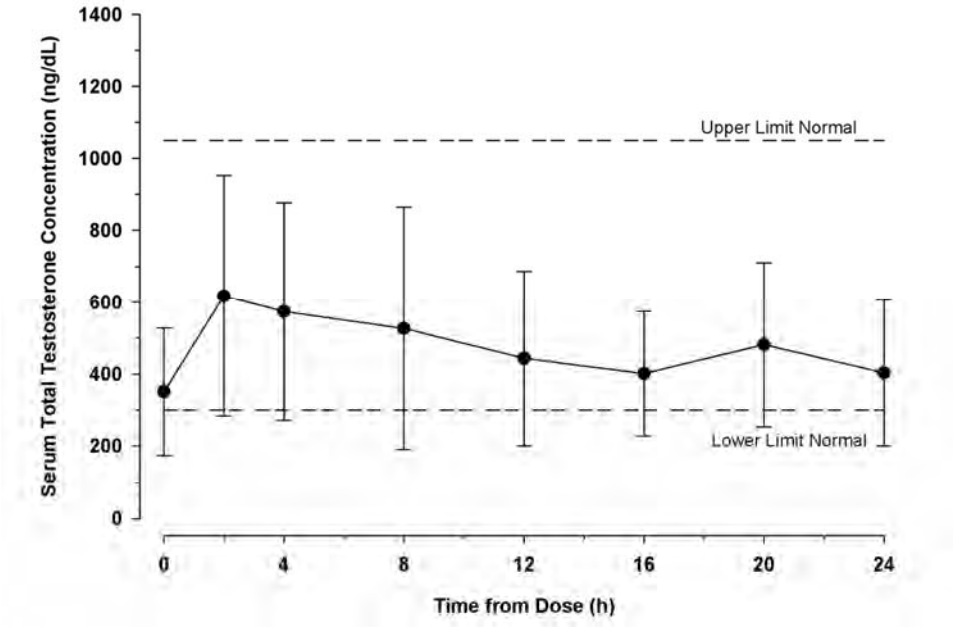


Figure 2: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 120 (30, 60, 90 or 120 mg testosterone) in Patients Who Completed 120 Days (N=135) of AXIRON Once-Daily Treatment

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AXIRON (testosterone) topical 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.

NDC 0002-1975-90

16.2 Storage and Handling

Keep AXIRON out of reach of children.

Store at 25°C (77°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature.

Used AXIRON bottles and applicators should be discarded in household trash in a manner that prevents accidental exposure of children or pets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide.

Patients should be informed of the following information:

17.1 Use in Men with Known or Suspected Prostate or Breast Cancer

Men with known or suspected prostate or breast cancer should not use AXIRON. *[See Contraindications (4) and Warnings and Precaution (5.1)]*.

17.2 Potential for Secondary Exposure to Testosterone and Steps to Prevent Secondary Exposure

Cases of secondary exposure to testosterone in children and women have been reported with topical testosterone products applied to the abdomen, shoulders or upper arms, including cases of secondary exposure resulting in virilization of children, with signs and symptoms including enlargement of the penis or clitoris, premature development of pubic hair, increased erections, aggressive behavior and advanced bone age. Inappropriate changes in genital size or premature development of pubic hair or libido in children, or changes in hair distribution, increase in acne, or other signs of testosterone effects in adult women should be brought to the attention of a physician and the possibility of secondary exposure to AXIRON also should be brought to the attention of a physician. AXIRON should be promptly discontinued at least until the cause of virilization is 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 axilla, not to any other part of the body.
- Children and women should avoid contact with the unwashed skin of the axilla or unclothed application sites of men where AXIRON has been applied.
- Patients should wash their hands immediately with soap and water after application of AXIRON.
- Patients should cover the axilla application site(s) with clothing (e.g., a shirt) after waiting 3 minutes for the solution to dry.
- Prior to any situation in which direct skin-to-skin contact of the axilla is anticipated, patients should wash the axilla to which AXIRON has been applied thoroughly with soap and water to remove any testosterone residue.
- In the event that 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.

[See Dosage and Administration (2.2), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].

17.3 Potential Adverse Reactions with Androgens

Patients should be informed that treatment with Androgens may lead to adverse reactions which include:

- Changes in urinary habits such as increased urination at night, trouble starting your urine stream, passing urine many times during the day, having an urge that you have to go to the bathroom right away, having urine accident, being unable to pass urine and having a weak urine flow.
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- Too frequent or persistent erections of the penis.
- Nausea, vomiting, changes in skin color, or ankle swelling.

17.4 Patients Should be Advised of these Application Instructions

- The pump should be primed by depressing it 3 times prior to its first use. No priming is needed with subsequent uses of that pump.
- AXIRON should NOT be applied to the scrotum, penis, abdomen, shoulders or upper arms.
- With testosterone doses greater than 60 mg, which require two applications of AXIRON to the same axilla, the product should be allowed to dry after the first application before the second is applied.
- AXIRON should be applied once daily at approximately the same time each day. AXIRON should be applied to clean, dry skin.
- Patients may use an antiperspirant or deodorant spray before applying AXIRON. If patients use a stick or roll-on antiperspirant or deodorant, then it should be applied prior to application of AXIRON to avoid contamination of the stick or roll-on product.
- Avoid swimming or washing the application site until two hours following application of AXIRON *[see Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.
- Avoid splashing in the eyes. In case of contact with eyes, flush thoroughly with water. If irritation persists, seek medical advice.

Literature revised December 2011

Marketed by: Lilly USA, LLC Indianapolis, IN 46285, USA

PV 8151 AMP

Medication Guide

AXIRON® (AXE-e-RON) CIII

(testosterone) topical solution

Read this Medication Guide before you start using AXIRON and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AXIRON?

AXIRON can transfer from your body to others. This can happen if other people come into contact with the area where the AXIRON was applied.

Signs of puberty that are not expected (for example, pubic hair) have happened in young children who were accidentally exposed to testosterone through skin to skin contact with men using topical testosterone products like AXIRON.

- **Women and children should avoid contact with the unwashed or unclothed area where AXIRON has been applied. If a woman or child makes contact with the application area, the contact area on the woman or child should be washed well with soap and water right away.**
- To lower the risk of transfer of AXIRON from your body to others, you should follow these important instructions:
    - Apply AXIRON **only** to your armpits.
    - Wash your hands **right away** with soap and water after applying AXIRON.
    - After the solution has dried, **cover the application area with clothing.** Keep the area covered until you have washed the application area well or have showered.
    - **If you expect another person to have direct skin-to-skin contact with your armpits, first wash the application area well with soap and water.**

Stop using AXIRON and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have occurred through accidental exposure to AXIRON:

Signs and symptoms in **children** may include:

- enlarged penis or clitoris
- early development of pubic hair
- increased erections or sex drive
- aggressive behavior

Signs and symptoms in **women** may include:

- changes in body hair
- a large increase in acne

What is AXIRON?

AXIRON is a prescription medicine that contains testosterone. AXIRON is used to treat adult males who have low or no testosterone.

Your healthcare provider will test your blood before you start and while you are taking AXIRON.

It is not known if AXIRON is safe and effective in children younger than 18 years old. Improper use of AXIRON may affect bone growth in children.

AXIRON is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your AXIRON in a safe place to protect it. Never give AXIRON to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and it is against the law.

AXIRON is not meant for use in women.

Who should not use AXIRON?

Do not use AXIRON if you:

- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or are breast-feeding. AXIRON may harm your unborn or breast-feeding baby.

  Women who are pregnant or who may become pregnant should avoid contact with the area of skin where AXIRON has been applied.

Talk to your healthcare provider before taking this medicine if you have any of the above conditions.

What should I tell my healthcare provider before using AXIRON?

Before you use AXIRON, tell your healthcare provider if you:

- have breast cancer
- have or might have prostate cancer
- have urinary problems due to an enlarged prostate
- have heart problems
- have kidney or liver problems
- have problems breathing while you sleep (sleep apnea)
- have any other medical conditions

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using AXIRON with other medicines can affect each other.
Especially tell your healthcare provider if you take:

- insulin
- medicines that decrease blood clotting
- corticosteroids

Know the medicines you take. Ask your healthcare provider or pharmacist for a list of all of your medicines if you are not sure. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use AXIRON?

- 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.
- Your healthcare provider may change your AXIRON dose. Do not change your AXIRON dose without talking to your healthcare provider.
- **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.
- You can use an antiperspirant or deodorant before applying AXIRON. If you use antiperspirant or deodorant, then it should be applied at least 2 minutes before you apply AXIRON.
- **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.**

Applying Axiron

AXIRON
Figure 1

- 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.

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

Find Your Dose as Prescribed by Your Doctor	Each application equals 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.

- Before applying AXIRON, make sure that your armpit is clean, dry and that there is no broken skin.

- Remove the cap and the applicator cup from the pump. Then, position the nozzle over the applicator cup and depress the pump gently (*see* Figure 2).

Figure 2

- To apply the AXIRON solution, keep the applicator upright, place it up into the armpit application site and wipe steadily down and up (*see* Figure 3).
- 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.

Figure 3

- Let the application site dry completely before putting on a shirt.
- 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 and make sure you store the bottle safely.
- 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.**

What are the possible side effects of AXIRON?

See also "What is the most important information I should know about AXIRON?"

AXIRON can cause serious side effects including:

- **If you already have enlargement of your prostate gland your signs and symptoms can get worse while using AXIRON.** This can include:
  - increased urination at night
  - trouble starting your urine stream
  - having to pass urine many times during the day
  - having an urge that you have to go to the bathroom right away
  - having a urine accident
  - being unable to pass urine or weak urine flow
- **Possible increased risk of prostate cancer.** Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use AXIRON.
- **In large doses AXIRON may lower your sperm count.**
- **Swelling of your ankles, feet, or body.**
- **Enlarged or painful breasts.**
- **Problems breathing while you sleep (sleep apnea).**
- **Blood clots in the legs.** This can include pain, swelling or redness of your legs.

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of AXIRON include:

- skin redness or irritation where AXIRON is applied
- increased red blood cell count
- headache
- diarrhea
- vomiting
- increase in blood level of Prostate Specific Antigen (a test used to screen for prostate cancer)

Other side effects include more erections than are normal for you or erections that last a long time.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of AXIRON. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AXIRON?

Store AXIRON at 15°C to 30°C (59°F to 86°F)

When it is time to throw away the bottle, safely throw away all parts of the AXIRON dispenser including bottle applicator cup and cap. Be careful to prevent accidental exposure of children or pets.

Keep AXIRON away from fire.

General information about AXIRON

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AXIRON for a condition for which it was not prescribed. Do not give AXIRON to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about AXIRON. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about AXIRON that is written for health professionals.

For more information, go to www.axiron.com or call 1-800-545-5979.

What are the ingredients in AXIRON?

Active ingredient: testosterone.

Inactive ingredients: ethanol, isopropyl alcohol, octisalate, and povidone.

The bottle or applicator cup does not contain latex.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Literature issued November 2010

Marketed by: Lilly USA, LLC Indianapolis, IN 46285, USA

NL PV 8160 AMP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022504/S-005

MEDICAL REVIEW(S)

Memorandum

Date: August 11, 2011

Regarding: Changes to Axiron Label

Application: NDA 22504

Sponsor: Eli Lilly

Lilly has submitted a CBE0 labeling supplement for their testosterone solution, Axiron. They propose to modify two paragraphs of the label.

Modification 1

The Adverse Reactions (section 6) portion of the label currently contains the following paragraph:

> *"During the 120 day clinical trial there was an increase in mean PSA values of 0.13 ± 0.68 ng/dL 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/dL. Neither change was statistically significant."*

They propose to modify this statement as follows:

> *"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. ~~Neither change was statistically significant~~."*

The proper units for serum PSA are ng/ml.

The reason for removing the last sentence is that they were unable to locate in the application the statistical analysis on which the statement is based. They concluded that no statistical analysis was conducted to support the statement that the "changes were not statistically different" and lacking that support, they wish to remove the statement.

Comment: *These modifications are reasonable.*

Modification 2

Also found within section 6 of the label is the following paragraph:

> *"Other less common adverse reactions reported by at least 2 patients in the 120 day trial included: application site edema, application site warmth, increased hemoglobin, increased blood pressure, increased blood testosterone, increased blood glucose, acne, nasopharyngitis, anger and anxiety. Other less common adverse reactions reported in fewer than 1% of patients in the 120 day trial*

included: asthenia, affect lability, erythema (general), folliculitis, anxiety, increased lacrimation, breast tenderness, hypertension, neoplasm prostate and elevated red blood cell count."

They propose to modify this paragraph as follows:

"Other less common adverse reactions reported by at least 2 patients in the 120 day trial included: application site edema, application site warmth, increased hemoglobin, ~~increased blood pressure, increased blood testosterone~~, hypertension, erthyema (general), increased blood glucose, acne, nasopharyngitis, anger and anxiety. Other less common adverse reactions reported in fewer than 1% of patients in the 120 day trial included: asthenia, affect lability, ~~erythema (general),~~ folliculitis, ~~anxiety,~~ increased lacrimation, breast tenderness,~~hypertension,~~ increased blood pressure, increased blood testosterone, neoplasm prostate and elevated red blood cell count."

Their rationale for the changes is:

"The first sentence states that these are events reported by at least 2 subjects. Data Table 14.3.1.2.1b in CSR MTE08/09 (starting on page 537) indicates that only one subject each reported "increased blood pressure" and "increased blood testosterone". Thus, these terms were moved from the first sentence to the second sentence since the latter reflects 'adverse events reported in fewer than 1% of patients' (i.e., 1 patient).

"Data Table 14.3.1.2.1a in MTE08/09 (starting at page 531) indicates that "anxiety" (n=2, 1.3%), "hypertension" (n=3, 1.9%) and "erythema (general)" (n=2, 1.3%), were reported at a rate > 1%. Thus, "hypertension" and "erythema (general)" were moved from the second sentence to the first sentence, since this sentence discusses 'adverse events reported by at least 2 patients'. Finally, "anxiety" was already noted within the first sentence (the correct location); therefore, it was simply removed from the second sentence."

Comment: *These changes are reasonable and are supported by the trial data.*

Recommended Regulatory Action

The Axiron label should be modified as requested by the Sponsor.

Donald McNellis, M.D.
Medical Officer
Division of Reproductive and Urologic Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONALD R MCNELLIS
08/11/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022504/S-005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022504/S-005

CBE-0 SUPPLEMENT

Eli Lilly and Company
Attention: Richard Hoffman, MS
Manager, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Hoffman:

We have received your July 29, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 022504

SUPPLEMENT NUMBER: 005

PRODUCT NAME: Axiron® (testosterone) topical solution

DATE OF SUBMISSION: July 29, 2011

DATE OF RECEIPT: July 29, 2011

This supplemental application, submitted as a "Changes Being Effected" supplement, proposes the following change(s):

- Correct errors noted within Section 6 (Adverse Reactions) of the current USPI for Axiron®.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 27, 2011, in accordance with 21 CFR 314.101(a).

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call Jeannie Roule, Regulatory Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
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JENNIFER L MERCIER
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