

PRODUCT MONOGRAPH



ANDROGEL[®]

Testosterone gel

1%

Androgens

BGP Pharma ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

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ANDROGEL®

Testosterone gel
1%

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	1% gel	Alcohol <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

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

ANDROGEL 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 (Endocrine Society Guidelines recommend two separate tests preferably in the morning) before initiating therapy with any testosterone replacement, including ANDROGEL treatment. Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

Geriatrics (>65 years of age):

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

Pediatrics (<18 years of age):

ANDROGEL 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

- **ANDROGEL is not indicated for use in women.**
- **Pregnant and nursing women should avoid skin contact with ANDROGEL 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 ANDROGEL has been applied or clothing exposed to ANDROGEL 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.
- ANDROGEL should not be used in patients with known hypersensitivity to any of its ingredients, including testosterone USP that is chemically synthesized from soy. For a complete listing, see Dosage Forms. Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel, including ANDROGEL.**
- **Children should avoid contact with unwashed or unclothed application sites in men using ANDROGEL.**
- **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 ANDROGEL-treated skin)

Potential for Secondary Exposure to Testosterone

Secondary exposure to testosterone in children and women can occur with testosterone gel 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 behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. 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 testosterone gel.

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 gel should also be brought to the attention of a physician. Testosterone gel 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 ANDROGEL-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using testosterone gel.
- ANDROGEL should only be applied to the shoulders, upper arms, and/ or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); when a shirt is used to cover the application site(s), the transfer of ANDROGEL from the male to the female partner can be completely prevented.
- Patients should wash their hands immediately with soap and water after applying ANDROGEL.
- Patients should cover the application site(s) with clothing (e.g., a shirt) after the gel 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.
- In the events that unwashed or unclothed skin to which ANDROGEL has been applied and/or that the testosterone gel user's unwashed shirts and/ or other fabrics (such as towels and sheets) 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. Studies show that residual testosterone is removed from the skin surface by washing with soap and water.

General

Androgens should be used with caution in patients with pre-existing cardiovascular (e.g., congestive heart failure, ischemic heart disease), renal, or hepatic disease (**see Cardiovascular**).

There is very limited data from clinical trials with ANDROGEL 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.

ANDROGEL 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.

ANDROGEL 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.

Gels are flammable. Following application of ANDROGEL (testosterone gel), allow gel to dry completely before smoking or going near an open flame.

Special Populations

Pregnant Women and Nursing Women:

ANDROGEL is not indicated for use in women, due to lack of evaluation and possible virilising effects (**see CONTRAINDICATIONS**).

Although it is not known how much testosterone transfers into human milk, ANDROGEL is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. (**see CONTRAINDICATIONS**)

Pregnant and nursing women should avoid skin contact with ANDROGEL application sites on men. Testosterone is teratogenic and 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 ANDROGEL has been applied or clothing exposed to ANDROGEL 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):

ANDROGEL 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 and for worsening of lower urinary tract signs and symptoms.

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

Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia (BPH). In men receiving testosterone replacement therapy, careful and regular monitoring of the prostate gland should be consistent with current practices for eugonadal men. Prior to testosterone initiation, at risk patients (those with clinical and familial factors) should be identified and all patients must undergo a detailed examination in order to detect preexisting prostatic cancer.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma (see **Special Populations – Geriatrics**).

Breast

Patients using long-term androgen therapy may be at an increased risk for the development of breast cancer. In men receiving testosterone replacement therapy, careful and regular monitoring of the breast should be conducted.

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 testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. ANDROGEL 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.

Androgens, including AndroGel 1%, may promote retention of sodium and water. In patients suffering from severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause serious complications characterised by edema, with or without congestive cardiac failure, and in such cases, treatment must be stopped immediately. 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 stroke and venous thromboembolic events including deep vein thrombosis and pulmonary embolism 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. If any of these serious adverse events are suspected, treatment with ANDROGEL should be discontinued and appropriate assessment and management initiated.

Dependence/tolerance

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

Endocrine and Metabolism

Androgens have been shown to alter glucose tolerance tests. Diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly (see **Drug-Drug Interactions**).

Hypercalciuria/hypercalcemia (caused by malignant tumors) 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.

Hematologic

Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long-term androgen therapy (see **Monitoring and Laboratory Tests**).

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 of international normalized ratio (INR) and prothrombin time, 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 frequently develop (reported in 1-3% of patients in clinical trials) and occasionally persist in patients being treated for hypogonadism.

Priapism or excessive sexual stimulation may develop.

Oligospermia may occur after prolonged administration or excessive dosage through feedback inhibition of pituitary follicle-stimulating hormone (FSH). (See **ACTIONS & CLINICAL PHARMACOLOGY: Pharmacodynamics – General Androgen Effects**)

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 generally accepted to be approximately 10.4-34.6 nmol/L (300-1000 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);
- 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;
- 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**).

Dose adjustment or discontinuation until normalization of parameters might be necessary.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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.

In a controlled clinical study, 154 patients were treated with ANDROGEL (testosterone gel) for up to 6 months (see **Clinical Studies**). Adverse Events possibly, probably or definitely related to the use of ANDROGEL and reported by $\geq 1\%$ of the patients are listed in Table 1. The four most reported adverse events are: acne (1-8%), lab test abnormal*(3-6%), application site reaction (3-5%), and prostate disorders** (3-5%).

Table 1: Adverse Events Possibly, Probably or Definitely Related to Use of ANDROGEL in the 180-Day Controlled Clinical Trial

<u>Adverse Event</u>	<u>5 g</u> <u>n = 77</u>	<u>7.5 g</u> <u>n = 40</u>	<u>10 g</u> <u>n = 78</u>
Acne	1%	3%	8%
Alopecia	1%	0%	1%
Application Site Reaction	5%	3%	4%
Asthenia	0%	3%	1%
Depression	1%	0%	1%
Emotional Lability	0%	3%	3%
Gynecomastia	1%	0%	3%
Headache	4%	3%	0%
Hypertension	3%	0%	3%
Lab Test Abnormal*	6%	5%	3%
Libido Decreased	0%	3%	1%
Nervousness	0%	3%	1%
Pain Breast	1%	3%	1%
Prostate Disorders**	3%	3%	5%
Testis Disorder***	3%	0%	0%

* *Lab test abnormal* occurred in nine patients with one or more of the following events: elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalemia, decreased HDL, elevated glucose, elevated creatinine, or elevated total bilirubin.

** *Prostate disorders* included five patients with enlarged prostate, one patient with BPH, and one patient with elevated PSA (Prostatic Specific Antigen) results.

*** *Testis disorders* were reported from two patients: one patient with left varicocele and one patient with slight sensitivity of left testis.

Less Common Clinical Trial Adverse Drug Reactions (<1%):

Endocrine disorders	Hirsutism
General Disorders and administration	Peripheral edema
Genitourinary disorders	Impaired urination
Nervous system disorders	Dizziness
Psychiatric disorders	Anxiety, hostility, amnesia
Reproductive system and breast disorders	Penis disorder
Skin and subcutaneous tissue disorders	Dry skin, discolored hair, sweating, paresthesia
Vascular disorders	Vasodilation

The following adverse events possibly related to the use of ANDROGEL occurred in fewer than 1% of patients: amnesia, anxiety, discolored hair, dizziness, dry skin, hirsutism, hostility, impaired urination, paresthesia, penis disorder, peripheral edema, sweating, and vasodilation.

In this clinical trial of ANDROGEL, skin reactions at the site of application were occasionally reported with ANDROGEL, but none was severe enough to require treatment or discontinuation of drug. Six (4%) patients in this trial had adverse events that led to discontinuation of ANDROGEL. These events included the following: cerebral hemorrhage, convulsion (neither of which were considered related to ANDROGEL administration), depression, sadness, memory loss, elevated prostate specific antigen and hypertension. No ANDROGEL patients discontinued due to skin reactions.

In an uncontrolled pharmacokinetic study of 10 patients, two had adverse events associated with ANDROGEL; these were asthenia and depression in one patient and increased libido and hyperkinesia in the other. In further studies in 17 patients, there was one instance each of acne, erythema at the thoracic level and benign prostate adenoma associated with a 2.5% testosterone gel formulation applied dermally.

One hundred and sixty-two (162) patients have received ANDROGEL for up to 3 years in a long-term follow-up study for patients who completed the controlled clinical trial. Table 2 summarizes those adverse events possibly, probably or definitely related to the use of ANDROGEL and reported by 2 or more subjects in at least one treatment group during long-term exposure to ANDROGEL.

Table 2: Incidence of Treatment-Emergent Adverse Events Possibly, Probably or Definitely Related to the Use of ANDROGEL in the 3 Year Open-Label Extension Clinical Trial

<u>Adverse Event Category/Classification</u>	<u>Treatment Group</u> n = 162 (%)
Lab Test Abnormal *	15 (9.3)
Skin Dry	3 (1.9)
Application Site Reaction	9 (5.6)
Acne	5 (3.1)
Pruritus	3 (1.9)
Enlarged Prostate	19 (11.7)
Carcinoma of Prostate	2 (1.2)
Urinary symptoms **	6 (3.7)
Gynecomastia	4 (2.5)
Testis Disorder ***	3 (1.9)
Anemia	4 (2.5)

* *Lab test abnormal* occurred in fifteen patients with one or more of the following events: elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/LDL ratio, elevated triglycerides, elevated HDL, or elevated serum creatinine.

***Urinary symptoms* included nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream.

****Testis disorder* included three patients. There were two patients with a non-palpable testis and one patient with slight right testicular tenderness.

Two patients reported serious adverse events considered possibly related to treatment: deep vein thrombosis (DVT) and prostate disorder requiring a transurethral resection of the prostate (TURP). Nine patients discontinued treatment due to adverse events possibly related to treatment with ANDROGEL, including two patients with application site reactions, one with kidney failure, and five with prostate disorders (including increase in serum PSA in 4 patients and increase in PSA with prostate enlargement in a fifth patient). All patients who discontinued due to an increase in serum PSA did so by Day 357.

During the initial 6-month study, the mean change in PSA values had a statistically significant increase of 0.26 ng/mL. Serum PSA was measured every 6 months thereafter. While there were no statistically significant increases in mean PSA from 6 months through 36 months of ANDROGEL treatment for the overall group of 162 patients enrolled in the long-term extension study, there were increases in serum PSA seen in approximately 18% of individual patients. In the long-term extension study, the overall mean change from baseline in serum PSA values for the entire group was 0.11 ng/mL.

Twenty-nine (29) (18%) patients met the per-protocol criterion for increase in serum PSA value, defined as a value $\geq 2X$ the baseline value or any single absolute value ≥ 6 ng/mL. Twenty-five of these patients met this criterion by virtue of a post-baseline value at least twice the baseline value. In most of these cases (22/25), the maximum serum PSA value attained was ≤ 2 ng/mL. The first occurrence of a pre-specified, post-baseline increase in serum PSA was seen at or prior to Month 12 in most of the patients who met this criterion (23 of 29; 79%).

Four patients met this criterion by having a serum PSA ≥ 6 ng/mL and in these, maximum serum PSA values were 6.2 ng/mL, 6.6 ng/mL, 6.7 ng/mL, and 10.7 ng/mL (in ANDROGEL-treated patients). In two of these ANDROGEL-treated patients, prostate cancer was detected on biopsy. The first patient's PSA levels were 4.7 ng/mL and 6.2 ng/mL at baseline and at Month 6/Final, respectively. The second patient's PSA levels were 4.2 ng/mL, 5.2 ng/mL, 5.8 ng/mL, and 6.6 ng/mL at baseline, Month 6, Month 12, and Final, respectively.

Abnormal Hematologic and Clinical Chemistry Findings

Table 3: Laboratory test results of clinical concern appearing at Day 90 or Final visit but not Baseline

Lab source/ test	Criteria for very low and very high lab test results	Day 90						Final Visit								
		Very low values			Very high values			Very low values				Very high values				
		T-Gel 50	T-Gel 100	T-patch	T-Gel 50	T-Gel 100	T-patch	T-Gel 50	T-Gel 75	T-Gel 100	T-patch	T-Gel 50	T-Gel 75	T-Gel 100	T-patch	
CHEM																
Glucose	VL: <=40; VH: >=175	0 (0%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	1 (3%)	0 (0%)	0 (0%)	
Potassium (K)	VL: <=3; VH: >=6	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	
Calcium (CA)	VL: <=8.2; VH: >=12	1 (1%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Inorganic phosphorus	VL: <=1.7; VH: >=9	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
AST (SGOT)	VH: >=2.6 ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	
Triglycerides	VH: >=450	0 (0%)	0 (0%)	0 (0%)	2(3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	
HEMA																
WBC	VL: <2.5; VH: >16	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Hemoglobin	VL: <9.4; VH: >18	0 (0%)	0 (0%)	0 (0%)	1 (1%)	3 (4%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (3%)	1 (1%)	1 (1%)	
Hematocrit	VL: <37; VH: >56	1 (1%)	1 (1%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (4%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	
IMMU																
Prostate specific anti	VH: >5.5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	

Only patients with lab test results meeting the criteria for Clinical Concern for the first time at Day 90 or Final visit are included in this table

VL= Very Low lab test result, VH= Very High lab test result; ULN= Upper Limit of Normal.

Post-Market Adverse Drug Reactions

Secondary Exposure to Testosterone in Children

Cases of secondary exposure to testosterone resulting in virilization of children have been reported in postmarket surveillance. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or of the penis, premature development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases with a reported outcome, these signs and symptoms were reported to have regressed with removal of the testosterone gel exposure. 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. In some of the cases, direct contact with the sites of application on the skin of men using testosterone gel was reported. In at least one reported case, the reporter considered the possibility of secondary exposure from items such as the testosterone gel user's shirts and/ or other fabric, such as towels and sheets (see **WARNINGS AND PRECAUTIONS**).

In addition to those adverse events reported during clinical trials, the following adverse reactions have been identified during post-marketing use of ANDROGEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Table 4: Adverse Drug Reactions from Postmarketing experience of ANDROGEL and Known Reactions of General Testosterone Treatment:

MedDRA System Organ Class (SOC)	Adverse Drug Reaction
Blood and the lymphatic system disorders:	Polycythemia, (elevated hemoglobin, hematocrit) erythropoiesis abnormal and red blood cell count increased
Cardiovascular disorders:	Tachycardia, atrial fibrillation, hypertension, vasodilation (hot flushes) and venous thromboembolism, including deep vein thrombosis and pulmonary embolism.
Endocrine disorders:	Abnormal accelerated growth Male pattern baldness, hirsutism
Gastrointestinal disorders:	Nausea, vomiting, diarrhea, abdominal pain, gastrointestinal bleeding
General disorders and administration site conditions:	Edema, malaise, asthenia, fatigue, application site reaction (eg. discoloured hair, dry skin, burning, induration, rash, dermatitis, blister, erythema, paresthesia, pruritus)
Genitourinary disorders:	Dysuria, hematuria, incontinence, bladder irritability
Hepatobiliary disorders:	Hepatic neoplasms, peliosis hepatic,
Immune system disorders:	Allergic reaction, hypersensitivity reaction
Investigations:	Weight increase, fluctuating testosterone levels, testosterone decreased, abnormal liver function tests (e.g. transaminases, elevated gamma-glutamyltransferase {GGTP}, bilirubin) lipid abnormalities (hyperlipidemia, elevated triglycerides, decreased high density lipoprotein (HDL))
Metabolism and nutrition disorders:	Increased appetite, electrolyte changes (nitrogen, potassium, phosphorus, sodium), urine calcium decrease, glucose tolerance impaired, elevated cholesterol
Musculoskeletal and connective tissue disorders:	Myalgia, arthralgia
Neoplasms Benign, Malignant and Unspecified (Cysts and Polyps)	Prostate cancer (see Warnings and Precautions)
Nervous system disorders:	Insomnia, headache, dizziness, sleep apnea, amnesia
Psychiatric disorders:	Personality disorder, confusion, anger, aggression, depression, anxiety, decreased libido, cognitive disturbance, emotional lability, nervousness
Reproductive system and breast disorders:	Enlarged prostate (benign), free prostate-specific antigen increased, testicular atrophy, epididymitis, oligospermia, priapism, impotence, precocious puberty, gynecomastia, mastodynia

Respiratory, thoracic and mediastinal disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Pruritus, rash, urticaria, vesiculo-bullous rash, seborrhea, acne, alopecia,

In addition, one patient reported experiencing serum sickness and another patient reported experiencing both a hepatoma and polycystic kidneys.

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 ANDROGEL.

Corticosteroids:

The concurrent administration of testosterone with adrenocorticotrophic hormone (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. Therefore more frequent monitoring of the international normalized ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy. 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

ANDROGEL is a transparent or slightly opalescent colourless gel with an odour of alcohol containing 1% testosterone. ANDROGEL provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

A daily application of ANDROGEL (testosterone gel) 5 g, 7.5 g, or 10 g delivers 50 mg, 75 mg, or 100 mg of testosterone, respectively, per day, to the skin's surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period. ANDROGEL delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (10.3 – 36.2 nmol/L or 300 – 1000 ng/dL) seen in healthy men.

Recommended Dose and Dosage Adjustment

The recommended starting and usual dose of ANDROGEL is 5 g (to deliver 50 mg of testosterone) (4 pump actuations, two 25 mg packets or one 50 mg packet) applied topically once daily in the morning, (preferably at the same time every day) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen.

As some patients may benefit from higher doses, serum testosterone levels should be measured after initiation of therapy to assist in proper dosing. To ensure proper dosing, serum testosterone concentrations should be measured at intervals. If the desired clinical response is not achieved or if the serum testosterone concentration is below the lower limit of the normal range (10.3 nmol/L or 300 ng/dL), the daily ANDROGEL 1% dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g for adult males as instructed by the physician. If the serum testosterone concentration exceeds the normal range, the daily testosterone dose may be decreased. If the serum testosterone concentration consistently exceeds the normal range at a daily dose of 50 mg testosterone, ANDROGEL 1% therapy should be discontinued. In addition, serum testosterone concentrations should be assessed periodically.

ANDROGEL is available in either 2.5 g or 5.0 g gel unit-dose packets or a 60 actuation metered-dose pump. The pump delivers 1.25 g of gel for each time the pump mechanism is fully depressed (actuation).

Pediatrics (<18 years of age):

ANDROGEL 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).

Administration

If using the metered-dose ANDROGEL pump, patients should be instructed to prime the new pump prior to using it for the first time. To do so, with the canister in the upright position, slowly and fully depress the actuator. Up to five depressions may be needed before all of the air is removed from the pump and gel is discharged. The first two actuations which deliver gel, should be discarded to assure precise dose delivery. Discard this portion of gel in household trash in a manner that prevents accidental application or ingestion by household members, especially nursing/pregnant women and children. It is only necessary to prime the pump before the first dose. After priming, patients should completely depress the pump once (1 actuation) for every 1.25 g of gel required to achieve the daily prescribed dosage. The gel should be delivered directly into the palm of the hand and then applied to the desired application sites, either one actuation at a time or upon completion of all actuations, required for the daily dose.

Alternatively, the product can be applied directly to the application sites. Application directly to the sites may prevent loss of product that may occur during transfer from the palm of the hand onto the application sites.

For specific dosing guidelines when using the ANDROGEL pump, refer to the chart below:

Prescribed Daily Dose	Number of Full Pump Actuations
5.0 g	4
7.5 g	6
10.0 g	8

If using the unit-dose ANDROGEL packet, one half (½) of the contents of the packet should be squeezed into the palm of the hand and immediately applied to the application sites. Once the first half of the packet has been applied, the second half of the packet should be applied in the same manner. Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water immediately after ANDROGEL has been applied.

Fire, flames or smoking should be avoided until the gel has dried since alcohol based products including ANDROGEL are flammable.

Special Notes on Administration:

The physician or health care professional should advise patients of the following:

- ANDROGEL should not be applied to the scrotum.
- ANDROGEL should be applied daily to clean, dry, healthy, intact skin.
- Currently it is unknown how long showering or swimming should be delayed after application of ANDROGEL. For optimal absorption of testosterone, it appears reasonable to wait at least 5-6 hours after application prior to showering or swimming. Nevertheless,

showering or swimming after just 1 hour should have a minimal effect on the amount of ANDROGEL absorbed if done very infrequently.

Transference of ANDROGEL to another person can be completely prevented when application site is covered with a long-sleeved shirt (cotton-polyester blend).

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

Secondary exposure to testosterone in children and women can occur with the use of testosterone gel in men. Cases of secondary exposure to testosterone have been reported in children with signs and symptoms including enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior.

- Physicians should advise patients of the reported signs and symptoms of secondary exposure which may include the following:
 - In children; unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior.
 - In women; changes in hair distribution, increase in acne, or other signs of testosterone effects.
- The possibility of secondary exposure to testosterone gel should be brought to the attention of a healthcare provider.
- Testosterone gel should be promptly discontinued until the cause of virilization is identified.

Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone from testosterone gel in men:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using testosterone gel.
- **To minimize the potential for transfer** to others, patients using ANDROGEL should apply the product as directed and strictly adhere to the following:
 - **Wash hands** with soap and water after application.
 - **Cover the application site(s)** with clothing after the gel has dried.
 - **Wash the application site(s) thoroughly** with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated.
 - In the events that unwashed or unclothed skin to which ANDROGEL has been applied and/or that the testosterone gel user's unwashed shirts and/ or other fabrics (such as towels and sheets) 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. Studies show that residual testosterone is removed from the skin surface by washing with soap and water.

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. Symptomatic and supportive treatment should be given.

One case of acute testosterone enanthate overdose following an injection has been reported in the literature. This was a case of a cerebrovascular accident in a patient with a high plasma testosterone concentration of 11,400 ng/dl (395 nmol/l).

ACTION AND CLINICAL PHARMACOLOGY

ANDROGEL (testosterone gel) contains 1% testosterone and provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen.

Pharmacodynamics

Testosterone and Hypogonadism

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 chord thickening; alterations in body musculature; and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/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, 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.

General Androgen Effects

Drugs in the androgen class also promote retention of nitrogen, sodium, water, 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 centers. 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

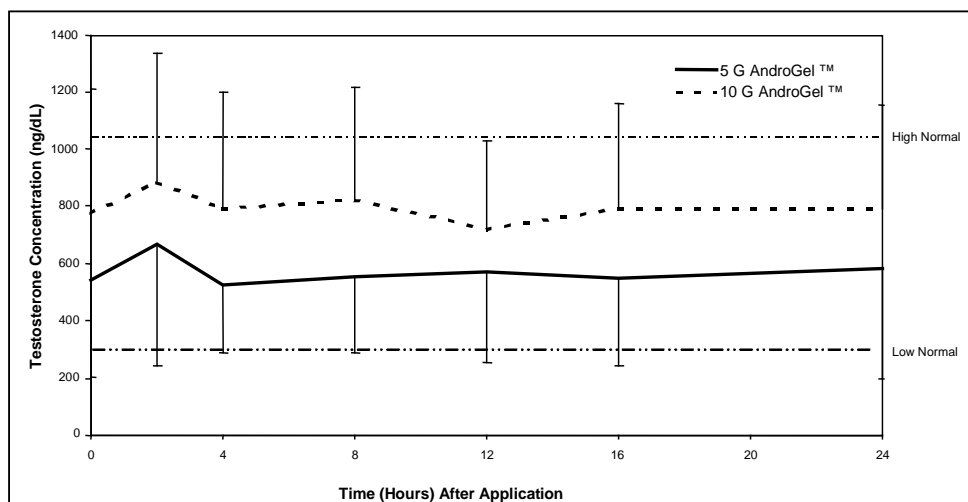
Absorption

ANDROGEL (testosterone gel) is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. In a study with the 10 g dose (to deliver 100 mg testosterone), all patients showed an increase in serum testosterone within 30 minutes, and eight of nine patients had a serum testosterone concentration within normal range by 4 hours after the initial application. Absorption of testosterone into the blood continues for the entire 24-hour dosing interval. Serum concentrations approximate the steady state level by the end of the first 24 hours and are at steady state by the second or third day of dosing.

Approximately 10% of testosterone from the applied ANDROGEL dose is absorbed across the skin during 24 hours, resulting in about 9-14% bioavailability of testosterone from the T-gel formulation. Nearly 1% of absorbed testosterone appears in the systemic circulation as dihydrotestosterone (DHT). There is no accumulation of testosterone or its metabolites such as estradiol and DHT, during continuous treatment.

With single daily applications of ANDROGEL, follow-up measurements 30, 90 and 180 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the eugonadal range. Similar trends were observed in patients followed up to 3 years. Figure 1 summarizes the 24-hour pharmacokinetic profiles of testosterone for hypogonadal men (<300 ng/dL) maintained on 5 g or 10 g of ANDROGEL (to deliver 50 or 100 mg of testosterone, respectively) for 30 days. The average (\pm SD) daily testosterone concentration produced by ANDROGEL 10 g on Day 30 was 27.5 (\pm 10.2) nmol/L and by ANDROGEL 5 g, 19.6 (\pm 9.1) nmol/L.

Figure 1. Mean (SD) Steady-State Serum Testosterone Concentrations on Day 30 in Patients Applying ANDROGEL Once Daily



Distribution

Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and nonbioactive androgen.

Metabolism

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from ten to 100 minutes.

When ANDROGEL treatment is discontinued after achieving steady state, serum testosterone levels remain in the normal range for 24 to 48 hours but return to their pretreatment levels by the fifth day after the last application.

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT). Testosterone is metabolized to DHT by steroid 5 α reductase located in the skin, liver, and the urogenital tract of the male. Estradiol is formed by an aromatase enzyme complex in the brain, fat, and testes. DHT binds with greater affinity to SHBG than does testosterone. In many tissues the activity of testosterone depends on its reduction to DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription and cellular changes related to androgen action. In reproductive tissues, DHT is further metabolized to 3- α and 3- β androstanediol.

DHT concentrations increased in parallel with testosterone concentrations during testosterone gel treatment. After 90 days of treatment, mean DHT concentrations remained generally within the normal range for testosterone gel-treated subjects.

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 ANDROGEL, 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 ANDROGEL 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

ANDROGEL pumps or packets 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

ANDROGEL (testosterone gel) for topical use is a transparent or slightly opalescent colourless gel with an odour of alcohol. One gram of gel contains 10 mg of testosterone

Availability of Dosage Forms

ANDROGEL is supplied in a non-aerosol, metered-dose pump. The pump is composed of plastic and stainless steel and a LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each ANDROGEL pump is capable of dispensing sixty 1.25 g doses.

ANDROGEL is also supplied in unit-dose aluminum foil packets in cartons of 30. Each packet has 2.5 g or 5.0 g of gel and contains 25 mg or 50 mg of testosterone, respectively.

ANDROGEL is supplied as follows:

<u>Strength</u>	<u>Package Size</u>
1% (25 mg testosterone)	30 packets: 2.5 g gel per packet
1% (50 mg testosterone)	30 packets: 5.0 g gel per packet
1%	Two 60-actuation metered-dose pumps: 1.25 g gel per actuation

Active Ingredient:

Testosterone USP

Non-medicinal ingredients:

Isopropyl myristate NF, Alcohol, Carbopol 980 NF, NaOH 0.1 N, Purified Water USP

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

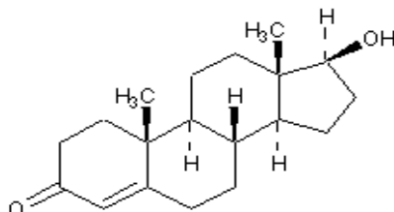
Drug Substance

Proper name: Testosterone USP

Chemical name: 17 β - hydroxyandrost-4-en-3-one
Androst-4-en-3-one, 17- hydroxy-, (17 β)-

Molecular formula and molecular mass: C₁₉H₂₈O₂

Structural formula:



Testosterone

Physicochemical properties:

Molecular Weight: 288.42

Description: white to practically white crystalline powder

Solubility: Soluble in acetone, dioxane and vegetable oils
In water: practically insoluble
In dehydrated alcohol: 1 in 6 of dehydrated alcohol
In chloroform: 1 in 2 of chloroform
In ether: 1 in 100 of ether

CAS Registry No: 58-22-0

Melting point: 153°- 157°C

CLINICAL TRIALS

ANDROGEL was evaluated in a multicenter, randomized, parallel-group, active-controlled, 180-day trial in 227 hypogonadal men (age = 18 to 68 years). The study was conducted in 2 phases. During the Initial Treatment Period (Days 1-90), 73 patients were randomized to ANDROGEL 5 g daily (to deliver 50 mg testosterone), 78 patients to ANDROGEL 10 g daily (to deliver 100 mg testosterone), and 76 patients to a non-scrotal testosterone transdermal system (5 mg daily). The study was double-blind for doses of ANDROGEL but open-label for active control. Patients who were originally randomized to ANDROGEL and who had single-sample serum testosterone levels above or below the normal range on Day 60 were titrated to 7.5 g daily (to deliver 75 mg testosterone) on Day 91. During the Extended Treatment Period (Days 91-180), 51 patients continued on ANDROGEL 5 g daily, 52 patients continued on ANDROGEL 10 g daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received ANDROGEL 7.5 g daily. Upon completion of the initial study, 162 patients elected to enter and receive treatment in an open-label, long-term extension study of ANDROGEL for an additional period of 3 years. Patients in the original trial and in the long-term extension study were treated with ANDROGEL for up to 42 months.

Mean peak, trough and average serum testosterone concentrations within the normal range (10.3 - 36.2 nmol/L) were achieved on the first day of treatment with doses of 5 g and 10 g. In patients continuing on ANDROGEL 5 g and 10 g, these mean testosterone levels were maintained within the normal range for the 180-day duration of the study. Figure 2 summarizes the 24-hour pharmacokinetic profiles of testosterone administered as ANDROGEL for 30, 90 and 180 days. Testosterone concentrations were maintained as long as the patient continued to properly apply the prescribed ANDROGEL treatment.

Figure 2: Mean Steady-State Testosterone Concentration in Patients with once-Daily ANDROGEL Therapy

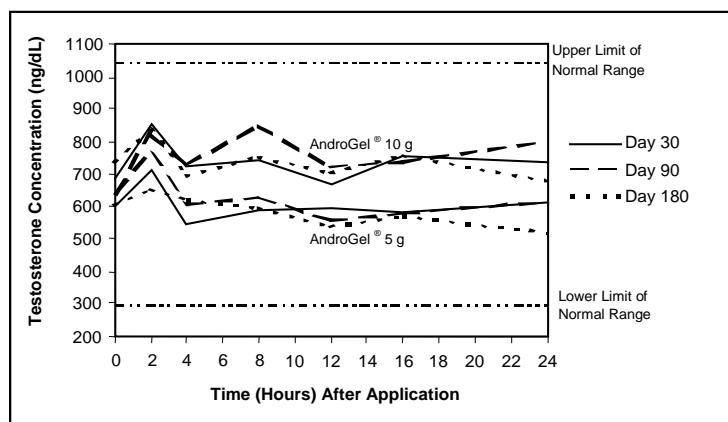


Table 5 summarizes the mean testosterone concentrations on Treatment Day 180 for patients receiving 5 g, 7.5 g, or 10 g of ANDROGEL. The 7.5 g dose produced mean concentrations intermediate to those produced by 5 g and 10 g of ANDROGEL.

Table 5: Mean (\pm SD) Steady-State Serum Testosterone Concentrations During Therapy (Day 180) nmol/L

	5 g	7.5 g	10 g
	N = 44	N = 37	N = 48
Cavg	19.3 \pm 7.8	20.9 \pm 10.7	24.7 \pm 7.3
Cmax	28.8 \pm 12.0	31.3 \pm 16.3	37.6 \pm 15.1
Cmin	12.9 \pm 5.7	14.1 \pm 7.6	16.8 \pm 5.4

Of 129 hypogonadal men who were appropriately titrated with ANDROGEL and who had sufficient data for analysis, 87% achieved an average serum testosterone level within the normal range on Treatment Day 180.

An open-labelled, randomized, non-placebo controlled, parallel-group, active-controlled trial indicated that ANDROGEL (5 g/day and 10 g/day) resulted in statistically significant increases in blood testosterone levels which were maintained in the eugonadal range through Days 30, 90, and 180. Treatment for 90 days was associated with an increase in total body lean mass and a decrease in total body fat. Bone mineral density (BMD) in both hip and spine increased from Baseline to Day 180 with the 10 g dose of ANDROGEL. These observed changes were maintained through the 180 day treatment period and sustained for a period of 24 months. Patients treated for up to 24 months with either 5 g, 7.5 g, or 10 g of ANDROGEL experienced a sustained improvement of bone mineral density of the spine and hip.

Subjective assessments by patients using a self-administered non-validated questionnaire indicated that ANDROGEL (5 g/day and 10 g/day) treatment for 90 days was associated with a perceived improvement in some hypogonadal symptoms (measured by sexual motivation, sexual activity and enjoyment of sexual activity, penile erection, mood and fatigue) when compared to the baseline score.

DHT concentrations increased in parallel with testosterone concentrations at ANDROGEL doses of 5 g/day and 10 g/day, but the DHT/T ratio stayed within the normal range, indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E₂) concentrations increased significantly within 30 days of starting treatment with ANDROGEL 5 or 10 g/day and remained elevated throughout the treatment period but remained within the normal range for eugonadal men. Serum levels of SHBG decreased very slightly (1 to 11%) during ANDROGEL treatment. Reductions in mean FSH and LH levels were observed in all patients exposed to ANDROGEL, but the gonadotropin reductions were more pronounced in

men with hypergonadotropic hypogonadism. Serum levels of LH and FSH fell in a dose- and time- dependent manner during treatment with ANDROGEL.

Compliance rate was over 93% and 96% for subjects receiving ANDROGEL 5g/ day and 10g/ day, respectively, during Days 1 – 90 and remained at that level during Days 91 – 180.

Potential for Phototoxicity:

The phototoxic potential of ANDROGEL was evaluated in a double-blind, single-dose study in 27 subjects with photosensitive skin types. The Minimal Erythema Dose (MED) of ultraviolet radiation was determined for each subject. A single 24 (+1) hour application of duplicate patches containing test articles (placebo gel, testosterone gel, or negative control) was made to naïve skin sites on Day 1. On Day 2, each subject received five exposure times of ultraviolet radiation, each exposure being 25% greater than the previous one. Skin evaluations were made on Days 2-5. Exposure of test and control article application sites to ultraviolet light did not product increased inflammation relative to non-irradiated sites, indicating no phototoxic effect.

Potential for testosterone transfer to female partner:

The potential for dermal testosterone transfer following ANDROGEL use was evaluated in a clinical study between males dosed with ANDROGEL and their untreated female partners. Two to 12 hours after ANDROGEL (10 g) application by the male subjects, the couples (N=38 couples) engaged in daily, 15-minute sessions of vigorous skin-to-skin contact so that the female partners gained maximum exposure to the ANDROGEL application sites. Under these study conditions, all unprotected female partners had a serum testosterone concentration greater than 2 times the baseline value at Day 7 when women were exposed at 2 hours and less so at 6 or 12 hours, after the application by the male. When a shirt covered the application site(s), the transfer of testosterone from the males to the female partners was completely prevented.

TOXICOLOGY

Testosterone was administered to rabbits in a 10-day dermal toxicity study using a gel formulation. Skin irritation at higher dosages was observed; however, there was no significant organ histopathology.

Testosterone propionate was administered intramuscularly in sesame oil to mature (approximately 2 year old) male and female dogs (2/sex) for 6 months at a dosage of 11 mg/kg. Animals were injected twice each week during the 6 month period. During the first 4 weeks of dose administration, dogs had an increase in body weight as well as a decrease of urine volume and decreased urinary excretion of nitrogen, sodium, potassium and phosphorus. Urine also contained glucose and protein. Throughout the study, serum cholesterol and phospholipids were decreased approximately 60% compared to pre-dose concentrations. At necropsy, renal changes (thickening of the glomerular capsule and degeneration of the tubular epithelial cells) were observed.

Reports on the effects of testosterone in *in vitro* and *in vivo* models for mutagenic potential have not been located in the literature.

The ability of testosterone to produce tumors of the prostate gland has been examined in several studies. Pollard *et al* used male L-W rats, which are susceptible to prostatic cancer. Animals were treated with testosterone propionate administered as a subcutaneous depot in silastic tubing. The dosage was 50 mg of testosterone propionate every 2 months; each treatment group contained 24 animals. Histopathological examination of the prostate, testes, kidneys, lungs, adrenals, pancreas, thyroid, thymus and pituitary was performed.

Mean serum testosterone concentrations were 16.1 ng/mL and 8.0 ng/mL at 2 weeks and 2 months after testosterone was implanted, respectively, demonstrating that animals were exposed to testosterone throughout the test period. Control animals had a mean serum testosterone concentration of 1.4 ng/mL. After 14 months of treatment, 24% of the rats treated with testosterone had developed macroscopic prostate adenocarcinomas while an additional 16% had microscopic *in situ* neoplasia. None of the control rats had macroscopic tumors, but control animals did have microscopic evidence of *in situ* neoplasia. Moreover, gross or microscopic evidence of adenocarcinomas in DHT-treated rats was not observed.

In another study, castrated F344 rats were treated with 3,2'-dimethyl-4-aminobiphenyl (DMBA) to induce prostatic tumors and then administered testosterone propionate or DHT implanted in silastic tubing. Additional groups were coadministered ethinyl estradiol. Male rats (20/group) approximately 6 weeks old and weighing 120 g were administered DMBA at 50 mg/kg subcutaneously every 2 weeks for a total of 10 injections. Animals were then castrated. After 40 weeks hormone treatment, animals were sacrificed and underwent gross and histopathological examination.

No control animals had tumors of the prostate or seminal vesicles. The 18 evaluated animals given testosterone had a total of 21 adenocarcinomas with one in the ventral prostate, 3 in the lateral prostate, 1 in the dorsal prostate and 9 in the anterior prostate. Eight adenocarcinomas of the seminal vesicles were observed. Tumors in the liver (44% in the treated versus 10% in control animals) were statistically significantly ($p < 0.05$) increased. In addition, tumors of the small and large intestine, lung, preputial gland and subcutaneous tissue were present but not significantly increased over control animal tumors. Testosterone plus estrogen produced a synergistic effect on tumor incidence. Treatment with DHT did not have a carcinogenic effect nor did DHT plus estrogen have a synergistic effect.

In conclusion, the administration of testosterone following DMBA treatment produced invasive carcinomas in the lateral and anterior prostate and seminal vesicles, whereas animals not receiving hormone supplement or those treated with DHT had no proliferative lesions. The incidence of liver tumors was also increased in testosterone-treated rats.

Other studies reported in the literature confirm the findings that exposure to testosterone leads to an increase in various tumors. For example, a study in female mice demonstrated that animals with implanted testosterone had an increase in cervical-uterine tumors, some of which

metastasized. Other studies in Noble (Nb) rats showed that testosterone coadministered with estradiol produced a 100% incidence of prostate cancer in these animals.

Segment I: Fertility and General Reproduction Performance

Because testosterone is an endogenous hormone required for the formation of male reproductive organs, alterations in testosterone concentrations during fetal development as well as postnatally lead to changes in morphology of fetuses and morphology and behavior of treated animals.

In order to assess the effect of testosterone administration on fertility, adult male rats (6/group) were treated with testosterone in capsules implanted subcutaneously for 90 days. Implants were reported by size rather than dosage and were 0.5, 1, 2, 3, 4 and 8 cm in length. Each male was paired for mating with 4 females over a 2 week period. Weights of sexual accessory tissues increased at the largest dosage while the weights of the testes decreased at the 3 highest dosages which also had the largest decrease in sperm counts. The 4 cm group had the greatest reduction in sperm count (15% of control). However, testosterone treatment had little effect on mating behavior as assessed by the number of vaginal plugs. Females mated with males treated with 3 or 4 cm dosages were sperm-positive but had a greatly lowered number of pregnancies. Animals that had litters had no difference in number of fetuses, fetal weights, post-implantation loss or malformations nor was there a difference in the sex ratio of the offspring. It appears that reduced sperm count could still lead to pregnancy but that rats with sperm did not necessarily become pregnant. In addition, there was no effect of testosterone on the offspring from the females mated to the treated males.

Segment II: Teratology Studies

Testosterone propionate in sesame oil was administered subcutaneously to pregnant DS mice and Wistar rats (approximately 13/group). Dose administration occurred from Days 8 through 12 of gestation at 7.5, 15 or 30 µg/kg/day for mice and 6.25, 125, 250, 500 or 1000 µg/kg/day for rats. There was little effect on fetal viability in mice; in rats, however, the number of viable fetuses was reduced in a dose-dependent fashion at dosages greater than 125µg/kg/day. No fetuses survived at 500 and 1000 µg/kg/day. In the mouse, the hind limb appeared to be most sensitive to the effects of testosterone propionate. There were also anomalies of the neural arches, cervical vertebrae and ribs with delayed ossification of the sternabrae. There were essentially no compound-related effects observed in the rat fetuses.

Rat embryo death was demonstrated in a study with female SD rats who were administered either 10 mg testosterone, estradiol, or Dianabol (8/group) as a subcutaneous implant from Day 10 of gestation until delivery or Day 27 of gestation, at which time all remaining rats were sacrificed. All of the embryos were resorbed in each rat administered either testosterone or estradiol, indicating that testosterone or estradiol at these levels was not compatible with the maintenance of viable fetuses.

Segment III: Perinatal and Postnatal Studies

Testosterone was studied for its effect on the female offspring of dams treated during pregnancy. Pregnant rats received a single injection of 5 mg testosterone on a single gestation day from 16 to 22; the female offspring of these dams were examined for morphology and behavior. The anogenital distance at 25 days after birth was significantly increased if testosterone was given on Gestation Days 16 to 18. In addition, vaginal opening was significantly delayed if testosterone was given between Gestation Day 16 and 20. Vaginal morphology, primarily enlarged clitoris, was observed in all treated groups. Offspring from dams receiving testosterone during Gestation Days 18 to 22 had decreased lordotic behavior.

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PART III: CONSUMER INFORMATION

 **ANDROGEL**[®]
Testosterone gel 1%

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

- One 5.0 g packet contains 50 mg of testosterone
- One full press of the pump delivers 1.25 g of gel which contains 12.5 mg of testosterone.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
ANDROGEL 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 testosterone gel.**
- **Keep children away from unwashed or unclothed application sites of men using ANDROGEL and from unwashed clothing or other fabrics exposed to ANDROGEL.**
- **Men who use ANDROGEL must strictly follow the instructions for use to lower the risk of transferring ANDROGEL to another person.**

ABOUT THIS MEDICATION**What the medication is used for:**

Your doctor has prescribed ANDROGEL because your body is not making enough testosterone. The medical term for this condition is hypogonadism. This should be confirmed by two separate blood testosterone measurements.

What it does:

ANDROGEL delivers medicine into your bloodstream through your skin. ANDROGEL 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 non-medicinal ingredients are**" in this section)].

ANDROGEL 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 ANDROGEL and/or with clothing or other fabrics exposed to ANDROGEL occurs, pregnant or nursing women should immediately wash the area of contact with soap and water.

What the medicinal ingredient is:

Testosterone USP

What the non-medicinal ingredients are:

Alcohol, purified water, sodium hydroxide, Carbopol 980 and isopropyl myristate.

What dosage forms it comes in:

ANDROGEL is a gel containing 1% testosterone. It is supplied either in a pump or foil packets:

- One 2.5 g packet contains 25 mg of testosterone

You should prevent ANDROGEL 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 ANDROGEL.
- ANDROGEL should be applied only to the areas of the shoulders, upper arms, and/or abdomen that will be covered by a short sleeve T-shirt.
- Wash hands immediately with soap and water after application of ANDROGEL.
- Cover the application site(s) with clothing (such as a shirt) after ANDROGEL has dried.
- If direct skin-to-skin contact is anticipated, wash the application site(s) thoroughly with soap and water to remove any ANDROGEL left on the application site(s).
- In the event that an unwashed or uncovered ANDROGEL application site and/or unwashed clothing or other fabrics exposed to ANDROGEL 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.

ANDROGEL must not be used by children under the age of 18. If you are suffering from severe heart, liver or kidney disease, treatment with testosterone may cause serious complications in the form of water retention in your body, sometimes accompanied by congestive heart failure (inadequate pumping of the heart with build-up of fluid in body tissues).

Testosterone may cause a rise in blood pressure. Therefore, ANDROGEL should be used with caution if you are suffering from high blood pressure.

In patients receiving long-term ANDROGEL therapy, the physician may prescribe regular blood tests, such as testosterone, complete blood count, liver function tests and lipid profile. Testosterone increases red blood cell count which theoretically could increase the risk of blood clots .

Your physician may also monitor your prostate gland for any negative effects of testosterone therapy by performing digital rectal examinations.

There is very little information from clinical trials with testosterone in the older male (>65 years of age) to support safe use 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 ANDROGEL, 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;
- have prostate cancer (confirmed or suspected);
- have liver, kidney or heart disease;
- have high blood pressure (hypertension);
- have diabetes;
- have breathing problems during sleep (sleep apnea).
- have 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:

ANDROGEL contains testosterone, which is a controlled substance under Schedule G of the Food and Drugs Act.

Precautions while using ANDROGEL:

Following application of ANDROGEL, allow gel to dry completely before smoking or going near an open flame.

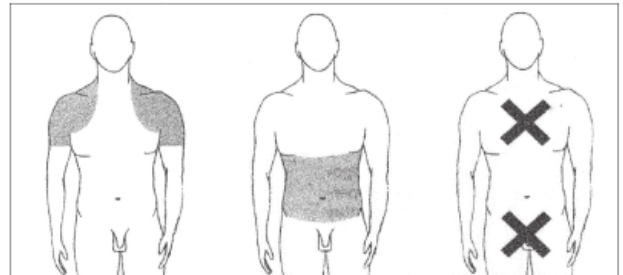
INTERACTIONS WITH THIS MEDICATION

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

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

PROPER USE OF THIS MEDICATION

1. **Apply ANDROGEL at the same time each day, (preferably in the morning).** Apply the proper amount of gel every morning as instructed by your doctor. The amount of testosterone you need may be adjusted by your doctor. Always follow your doctor's recommendations.
2. **Be sure your skin is completely dry before applying ANDROGEL.** For example, if you take a bath or shower in the morning, apply ANDROGEL *after* your bath or shower once your skin is completely dry.
3. **Apply ANDROGEL *only* to your abdomen (stomach area), shoulders, and/or upper arms, as shown in the following diagram.**



- Use a circular motion to rub in the gel for several seconds. Applying ANDROGEL only to the areas shown helps ensure that your body will absorb the right amount of testosterone. ANDROGEL may be applied to the same areas of the body each day. It is not necessary to alternate application sites.
 - **Never apply ANDROGEL to your genitals (penis and scrotum) or to damaged skin.**
 - Apply ANDROGEL only to healthy, normal skin. Avoid skin with open sores, wounds, sunburn, or irritation.
4. **Following application of ANDROGEL, allow gel to dry completely before smoking or going near an open flame.**

5. **Wash your hands immediately following application.**
 - It is important to wash your hands with soap and water right away to reduce the chance that any ANDROGEL will spread from your hands to other people.
 - If, however, you expect direct skin contact with someone else, you should wash your application site(s) with soap and water before that encounter. This will reduce the chance that any ANDROGEL will transfer to the other person.

6. **Let ANDROGEL dry for a few minutes before you dress.**
 - This prevents your clothing from absorbing or wiping the gel off your skin, ensuring that your body will absorb the correct amount of testosterone.
 - **Wait 5 to 6 hours before showering or swimming.** To ensure that ANDROGEL is fully absorbed into your system, you should generally wait five to six hours after application before showering or swimming. However, once in a while you may shower or swim as soon as one hour after applying ANDROGEL. Although this is not recommended, if done infrequently, it will have little effect on the overall amount of ANDROGEL that is absorbed by your body.
 - Transference of ANDROGEL to another person can be completely prevented when the application site is covered with a long-sleeved shirt (cotton-polyester blend).

7. **It is important that you read and follow the directions below on how to use ANDROGEL properly:**
 - See Section A if you are using the ANDROGEL pump
 - See Section B if you are using the ANDROGEL packets

Section A: Using the ANDROGEL pump

- i) **Priming the pump:**
Before using a new pump for the first time, you must prime the pump to remove the air. Up to five depressions may be needed before all of the air is removed and gel is discharged. The first two depressions that deliver any amount of gel are to be discarded by thoroughly rinsing down the sink or discarding in the household trash in a manner that prevents accidental application or ingestion by household members, especially nursing/pregnant women and children.

- ii) **Determining the number of full depressions (presses of the pump) needed for each dose:**
Each full press of the pump delivers 1.25 g of ANDROGEL. Please refer to the chart below to determine the number of full depressions required for the daily dose prescribed by your doctor:

Prescribed Daily Dose	Number of Full Pump Depressions
5.0 g	4
7.5 g	6
10.0 g	8

iii) Number of days of treatment per pump (after priming):

The ANDROGEL pump contains enough gel to allow for priming and a set number of precise doses. Please refer to the chart below to determine the number of days of treatment each pump will provide based on your individual dose. Discard the pump afterwards.

Prescribed Daily Dose	Number of Days of Treatment per Pump (after priming)
5.0 g	15
7.5 g	10
10.0 g	7.5

iv) Applying ANDROGEL to your skin:

Fully press the pump the appropriate number of times to deliver the daily dose prescribed by your doctor. The gel should be delivered directly into the palm of your hand and then applied to the desired application sites, either one pump depression at a time or upon completion of all pump depressions required for the daily dose. Alternatively, the product can be applied directly to the application sites. Application directly to the sites may prevent loss of product that may occur during transfer from the palm of the hand onto the application sites.

Section B: Using the ANDROGEL packet

- i) **Opening the packet:**
Open one ANDROGEL aluminum foil packet by folding it along the top edge and carefully tearing it open.

- ii) **Applying ANDROGEL to your skin:**
 - Gently squeeze the gel from the bottom of the packet toward the top.
 - Squeeze out half (1/2) of the contents of the packet and apply it to the areas of your body *shown in the diagram*. Use a circular motion to rub in the gel for several seconds. Once you have applied this first half to your skin, squeeze out the second half and apply it in the same manner. Discard the empty packet in the household trash in a manner that prevents accidental application or ingestion by household members, especially nursing/pregnant women and children.

What should I do if I get ANDROGEL in my eyes?

If you get ANDROGEL in your eyes, rinse your eyes right away with warm clean water to flush out any ANDROGEL. Seek medical attention if discomfort persists.

Missed Dose

If you miss a dose, **do not double your next dose** the next day to catch up. If your next dose is less than 12 hours away, it is best to wait. Do not take the skipped dose. If it is more than 12 hours until your next dose, take the dose that you missed. Resume your normal dosing the next day.

Overdose

Contact your doctor or pharmacist or poison control centre immediately if you suspect an overdose.

If you use more ANDROGEL than the recommended dose (an overdose), wash the skin with soap and water where ANDROGEL was applied and contact your doctor or pharmacist .

What to do if someone is exposed to the medication:

If someone else is exposed to ANDROGEL either by direct contact with the gel itself or indirectly because of contact with your treated skin, that person should wash his or her area of contact thoroughly with soap and water as soon as possible. The longer the gel is in contact with the skin before washing, the greater is the chance that the other person will absorb some testosterone.

This is particularly important for women, especially pregnant or nursing women, and children. Children have naturally low levels of testosterone and could be harmed by higher levels. Pregnant women are at an even higher risk because increased testosterone levels may cause harm or abnormalities in the unborn baby.

Never share your ANDROGEL with anyone.

- 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 testosterone gel. 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/color, dribbling, pain on urination straining, weak stream, small amounts)		√	
Common (after prolonged use)	Breast enlargement or breast pain		√	
Uncommon	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-			√

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ANDROGEL 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);
- 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;

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	
Heart attack (symptoms include sharp or crushing chest pain or heaviness, coughing blood, or sudden shortness of breath)			√
Stroke (symptoms include sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm or leg)			√

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

HOW TO STORE IT

Store ANDROGEL (testosterone gel) at room temperature (15 -30°C).

Keep out of reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

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 0701E

Ottawa, ON 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 the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The most recent version of this document plus the full Product Monograph, prepared for health professionals can be found at:

www.mylan.ca

or by contacting the sponsor, BGP Pharma ULC, Etobicoke, Ontario, M8Z 2S6 at:
1-844-596-9526

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