PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

NATESTO®

Testosterone nasal gel
4.5% w/w

Androgens

Acerus Biopharma Inc.
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Date of Revision:
April 4, 2019

Imported by:
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Submission Control No: 223106

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intranasal	Nasal gel / 4.5% w/w	Castor Oil *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

NATESTO should not be used to treat non-specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other etiologies responsible for the symptoms have not been excluded. Testosterone deficiency should be clearly demonstrated by clinical features and confirmed by biochemical assays before initiating therapy with any testosterone replacement, including NATESTO 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 clinical study data supporting the use of NATESTO in the geriatric population (see **WARNINGS AND PRECAUTIONS** and **CLINICAL TRIALS**).

Pediatrics (< 18 years of age):
NATESTO 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

- NATESTO should not be used in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container, including testosterone USP, as

this is chemically synthesized from soy. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- NATESTO is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate (see **WARNINGS AND PRECAUTIONS**).
- NATESTO is not indicated for use in women.
- NATESTO is contraindicated in women who are or who may become pregnant, or who are breast-feeding. NATESTO may cause fetal harm when administered to a pregnant woman. NATESTO may cause serious adverse reactions in nursing infants. Exposure of a fetus or nursing infant to androgens may result in varying degrees of virilization. If a pregnant woman is exposed to NATESTO, she should be apprised of the potential hazard to the fetus (see **Special Populations – Pregnant and Nursing Women**).

WARNINGS AND PRECAUTIONS

General

Nasal Adverse Reactions and Limited Long-Term Information on Nasal Safety:
Nasal adverse reactions, including nasopharyngitis, rhinorrhea, epistaxis, nasal discomfort and nasal scabbing, were reported in the clinical trial experience with NATESTO. All nasal adverse reactions except one (a single case of upper respiratory infection) were reported as mild or moderate in severity; however, long-term clinical trial data on nasal safety is available in a limited number of subjects [see **Adverse Reactions**]. Patients should be instructed to report any nasal symptoms or signs to their health care professional. In that circumstance, health care professionals should determine whether further evaluation (e.g., otorhinolaryngology consultation) or discontinuation of NATESTO is appropriate.

Use in Patients with Chronic Nasal Conditions and Alterations in Nasal Anatomy:
Due to lack of clinical data on the safety or efficacy, NATESTO **is not recommended for use** in the following patients:
•History of nasal disorders;
•History of nasal or sinus surgery;
•History of nasal fracture within the previous 6 months or nasal fracture that caused a deviated anterior nasal septum;
•Mucosal inflammatory disorders (e.g, Sjogren's syndrome); and
•Sinus disease.

There are very limited data from clinical trials with NATESTO 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.

NATESTO 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.

NATESTO 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 a 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.

Carcinogenesis and Mutagenesis
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.

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

Androgens, including NATESTO 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. Diuretic therapy may be required, in addition to discontinuation of the drug.

Some post-market retrospective studies equivocally 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 NATESTO should be discontinued and appropriate assessment and management initiated.

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

Genitourinary
Patients with Benign Prostatic Hyperplasia (BPH) treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.

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

Increases in hematocrit, reflective of increases in red blood cell mass, may require discontinuation of NATESTO. 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 (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**).

Hepatic/Biliary/Pancreatic
Hepatic:
Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. NATESTO is not known to produce these adverse effects. Nonetheless, patients should be instructed to report any signs or symptoms of hepatic dysfunction (e.g., jaundice). If these occur, promptly discontinue NATESTO while the cause is evaluated.

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

Sexual Function/Reproduction
- Gynecomastia may develop and occasionally persist in patients being treated with androgens, including NATESTO, for hypogonadism.
- Priapism or excessive sexual stimulation may develop.
- Oligospermia may occur after prolonged administration or excessive dosage through feedback inhibitory pituitary follicle-stimulating hormones (FSH). (see **ACTIONS & CLINICAL PHARMACOLOG – Pharmacodynamics: General Androgen 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.

Special Populations

Pregnant and Nursing Women and Use in Women:
NATESTO is not indicated for use in women, due to lack of evaluation and possible virilizing effects (see **CONTRAINDICATIONS**).

NATESTO is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. 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. Exposure of a female fetus to androgens may result in varying degrees of virilization.

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

Pediatrics (< 18 years of age):
NATESTO 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. Of the 306 patients enrolled in the Phase 3 clinical trial utilizing NATESTO, 60 were 65 years of age or older, and 9 were 75 years of age or older. There are insufficient long-term safety data in geriatric patients to assess the potential for increased risks of cardiovascular disease and prostate cancer.

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

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

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

Currently there is no consensus about age-specific testosterone levels. The normal serum testosterone level for young eugonadal men is approximately 10.4-36.4 nmol/L (300-1050 ng/dL). However, it should be taken into account that physiological 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).
- 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.
- 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. Changes in the serum lipid profile may occur. Changes in serum lipid profile may require discontinuation of testosterone therapy.
- Diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly (see **Drug-Drug Interactions**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the Phase 3 clinical study of 306 patients treated with NATESTO, the most common adverse events reported were local nasal reactions at the site of gel application. The most frequently observed were rhinorrhea, epistaxis and nasal discomfort which were mild and transient in the majority of cases.

The adverse drug reactions observed in at least 2% of patients are listed below in Table 1, shown by system organ class and in order of decreased frequency.

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.

NATESTO was evaluated in a multicenter, open-label clinical study that included 90-Day Treatment period and two, open-label safety extension periods of 90 and 180 days, respectively. A total of 306 hypogonadal men with morning testosterone concentrations ≤ 300 ng/dL received NATESTO (see **Clinical Studies**).

90-Day Treatment Period

Table 1 summarizes the most common (experienced by ≥2% of patients in any treatment group) Adverse Drug Reactions during the 90-day Treatment Period.

Table 1: Summary of Adverse Drug Reactions (≥2% of Patients in Any Treatment Group)– Treatment Period.

System Organ Class Preferred Term	22.0 mg (N=143) n (%)	22.0/33.0mg* (N=85) n (%)	33.0 mg (N=78) n (%)	Total (N=306) n (%)
Investigations	2 (1.4)	6 (7.1)	5 (6.4)	13 (4.2)
PSA increased**	0 (0.0)	2 (2.4)	2 (2.6)	4 (1.3)
Weight increased	0 (0.0)	2 (2.4)	0 (0.0)	2 (0.7)
Musculoskeletal and connective tissue disorders	1 (0.7)	0 (0.0)	2 (2.6)	3 (1.0)
Myalgia	0 (0.0)	0 (0.0)	2 (2.6)	2 (0.7)
Nervous system disorders	8 (5.6)	3 (3.5)	7 (9.0)	18 (5.9)
Parosmia	6 (4.2)	2 (2.4)	2 (2.6)	10 (3.3)
Dysgeusia	1 (0.7)	1 (1.2)	2 (2.6)	4 (1.3)
Respiratory, thoracic and mediastinal disorders	24 (16.8)	21 (24.7)	14 (17.9)	59 (19.3)
Rhinorrhoea	6 (4.2)	7 (8.2)	2 (2.6)	15 (4.9)

System Organ Class Preferred Term	22.0 mg (N=143) n (%)	22.0/33.0mg* (N=85) n (%)	33.0 mg (N=78) n (%)	Total (N=306) n (%)
Epistaxis	4 (2.8)	4 (4.7)	3 (3.8)	11 (3.6)
Nasal discomfort	4 (2.8)	1 (1.2)	3 (3.8)	8 (2.6)
Nasal dryness	5 (3.5)	1 (1.2)	2 (2.6)	8 (2.6)
Nasal congestion	1 (0.7)	3 (3.5)	2 (2.6)	6 (2.0)
Upper-airway cough syndrome	1 (0.7)	2 (2.4)	1 (1.3)	4 (1.3)
Skin and subcutaneous tissue disorders	6 (4.2)	3 (3.5)	4 (5.1)	13 (4.2)
Scab	3 (2.1)	2 (2.4)	3 (3.8)	8 (2.6)

*Patients who were uptitrated from 22.0mg to 33.0mg at Day 45;
***PSA increase was considered an adverse reaction by meeting one of two pre-specified criteria: (1) increase from baseline serum PSA greater than 1.4 µg/L, or (2) serum PSA greater than 4.0 µg/L

90-Day Extension Period

During the 90-Day Safety Extension Period, the most common system organ classes of Adverse Drug Reactions were respiratory, thoracic and mediastinal disorders (8.5%), investigations and skin subcutaneous tissue disorders (2.6% each).

The most frequently reported Adverse Drug Reactions in each treatment group during the 90-Day Safety Extension Period were the following:

- 22.0 mg group: nasal discomfort (4.2%); and rhinorrhea, and scab (2.5% each);
- 33.0 mg group: epistaxis and PSA increased (2.6% each).

180-Day Extension Period

During the 180-Day Safety Extension Period, the most common system organ classes of Adverse Drug Reactions were respiratory, thoracic, and mediastinal disorders (8.1%), skin and subcutaneous tissue disorder (5.4%) and nervous system disorders (4.1%).

The most frequently reported Adverse Drug Reactions in each treatment group during the 180-Day Safety Extension were the following:

- 22.0 mg group: scab (5.9%), nasal discomfort, rhinalgia and rhinorrhea, parosmia and migraine (2.9%).
- 33.0 mg group: epistaxis (7.5%), scab (5.0%) and parosmia (2.5%).

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

Adverse Drug Reactions occurring in less than 1% of patients are presented in Table 2 below.

Table 2: Clinical Trial Adverse Drug Reactions (<1%) Grouped by System Organ Class

System Organ Class	Preferred Term
Endocrine Disorders	Endocrine Disorder, Hyperthyroidism
Eye Disorders	Dry Eye, Eye Pruritus, Glaucoma
Gastrointestinal Disorders	Dyspepsia, Gastroesophageal Reflux Disease, Retching, Vomiting
General Disorders and Administration Site Conditions	Pyrexia, Chills, Fatigue, Nodule, Oedema Peripheral,
Immune System Disorders	Hypersensitivity
Infections and Infestations	Rhinitis, Ear Infection, Nasal Vistibulitis, Pharyngitis
Injury, Poisoning and Procedural Complications	Excoriation, Sensation of a Foreign Body
Investigations	Blood Creatine Phosphokinase Increased, Blood Luteinising Hormone Decreased, Weight Increased, Blood Follicle Stimulating Hormone Decreased, Blood Glucose Increased, Blood Prolactin Decreased, Blood Thyroid Stimulating Hormone Increased, Electrocardiogram QT Prolonged, Haematocrit Increased, Neutrophil Count Increased, Oestradiol Increased, QRS Axis Abnormal
Metabolism and Nutrition Disorders	Decreased Appetite, Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia
Musculoskeletal and Connective Tissue Disorders	Myalgia, Arthralgia, Pain In Extremity
Nervous System Disorders	Headache, Anosmia, Burning Sensation, Depressed Level Of Consciousness, Migraine, Paraesthesia
Psychiatric Disorders	Anger, Abnormal Dreams
Renal and Urinary Disorders	Hematuria, Nocturia, Urinary Retention
Reproductive System and Breast Disorders	Prostatomegaly, Ejaculation Disorder, Erectile Dysfunction, Testicular Atrophy
Respiratory, Thoracic and Mediastinal Disorders	Increased Viscosity Of Nasal Secretion, Nasal: Obstruction, Discharge Discolouration, Oedema, Septum Deviation, Septum Ulceration, Ulcer, Cough, Dysponoea, Haemoptysis, Intranasal Paraesthesia, Paranasal Sinus Hypersecretion, Respiratory Tract Congestion, Sinus Congestion
Skin and Subcutaneous Tissue Disorders	Acne, Pruritus, Dandruff, Dry Skin, Erythema, Hyperhydrosis, Night Sweats, Petechiae, Skin Fissures
Vascular Disorders	Hot Flush, Hypertension

PSA increased
In patients who received NATESTO three times daily, mean serum PSA concentrations increased by 0.10 ng/dL, 0.06 ng/dL and 0.18 ng/dL after 90, 180 and 360 days, respectively.

Discontinuations due to Adverse Reactions
Among all subjects (n=306) who received NATESTO at any dose in the 90-day clinical study and its 90- and 180-day extension periods, a total of 6 subjects withdrew from treatment for the following adverse reactions, reported by 1 subject each: nasal discomfort, headache, dysgeusia, PSA increased, allergic reaction (hives, swollen lips and tongue), and 1 patient with myalgia, arthralgia, fever, chills and petechiae.

Increased Hematocrit
Among all subjects (n=306) who received NATESTO at any dose in the 90-day clinical study and its 90- and 180-day extension periods, a total of 4 subjects had a hematocrit level >55%. These 4 patients had baseline hematocrits of 48% and 51%. In no case did hematocrit exceed 58%.

Nasal Adverse Events
Among all subjects (n=306) who received NATESTO at any dose in the 90-day clinical study and its 90- and 180-day extension period, the following treatment emergent adverse events were reported: nasopharyngitis (8.2%), rhinorrhea (7.8%), epistaxis (6.5%), nasal discomfort (5.9%), parosmia (5.2%), nasal scab (5.2%), upper respiratory infection (4.2%), nasal dryness (4.2%), and nasal congestion (3.9%).

Post-Market Adverse Drug Reactions

In addition to those adverse events reported during clinical trials, the following reactions have been identified as possibly being related to testosterone use. 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.

MedDRA System Organ Class (SOC)	**Adverse Drug Reaction**
Blood and Lymphatic System Disorders	Increased blood creatinine; polycythemia
Cardiovascular Disorders	Tachycardia, atrial fibrillation, pulmonary embolism, myocardial infarction, stroke and deep vein thrombosis.
Endocrine Disorders	Increase in male pattern hair distribution; hirsutism
General Disorders and Administration Site Conditions	Malaise
Hepatobiliary Disorders	Abnormal liver enzyme/liver function tests, including bilirubin
Investigations	Decreased HDL
Metabolism and Nutrition Disorders	Electrolyte changes (potassium, sodium, chloride, inorganic phosphate) during high

MedDRA System Organ Class (SOC)	Adverse Drug Reaction
	dose or prolonged treatment; increased appetite
Musculoskeletal System Disorders	Muscle spasms; muscle cramps; muscle pain
Nervous System Disorders	Amnesia; hyperesthesia; smell disorder; taste disorder
Psychiatric Disorders	Depression; mood disorders; nervousness; hostility
Renal and Urinary Disorders	Impaired urination; urinary tract infection, urinary tract obstruction
Reproductive System and Breast Disorders	Mastodynia, sensitive nipples; prostatic disorders; spontaneous penile erection; libido changes; increased frequency of erections; priapism; reduction in the size of the testicles/testicular atrophy
Respiratory System Disorders	Dyspnea
Skin and Subcutaneous Disorders	Alopecia; urticaria; seborrhea; discoloured hair
Vascular Disorders	Decreased diastolic blood pressure; flushing; vasodilation

DRUG INTERACTIONS

Drug-Drug Interactions

Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose and therefore, may necessitate a decrease in the dose of anti-diabetic medication.

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 NATESTO.

Corticosteroids: The concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation; thus these drugs should be administered cautiously and require monitoring, 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.

Oxymetazoline: A 2.6% decrease in mean AUC(0-24) and 3.6% decrease in mean Cmax of total testosterone was observed in males with symptomatic seasonal rhinitis when treated with oxymetazoline 30 minutes prior to NATESTO compared to when left untreated. Oxymetazoline does not impact the absorption of testosterone when concomitantly administered with

NATESTO (see **ACTION AND CLINICAL PHARMACOLOGY – Drug Interactions**). Drug interaction potential with other nasally administered drugs other than oxymetazoline has not been studied. NATESTO is not recommended for use with nasally administered drugs other than sympathomimetic decongestants (e.g., oxymetazoline).

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

Prior to initiating NATESTO, confirm the diagnosis of hypogonadism by ensuring symptoms typical of hypogonadism and that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

Dosing Considerations
NATESTO is a testosterone nasal gel available in a dispenser with a metered dose pump. One pump actuation delivers 5.5 mg of testosterone per nostril. Each dose is applied as two actuations (one per nostril), for a total dose of 11.0 mg. NATESTO is dosed either two or three times daily.

Recommended Dose and Dosage Adjustment
The recommended starting dose of NATESTO (testosterone) is 11.0 mg of testosterone (1 actuation per nostril) administered intranasally twice daily for a total daily dose of 22.0 mg.

The NATESTO dose can be increased to a maximum recommended dose of 11.0 mg three times daily (33mg total daily dose) if either of the following conditions are met:

1) a serum total testosterone from a single blood draw sample taken 20 minutes to 2 hours after a morning application of NATESTO is less than 300 ng/dL.
2) if symptoms are not adequately treated within 90 days.

Serum total testosterone concentrations should be checked periodically:

- If the measured serum total testosterone concentration from the single morning blood draw is less than 300 ng/dL, the daily dose of NATESTO may be increased to 33.0 mg daily;

- For patients on the maximum recommended dose and whose serum total testosterone concentration from the single morning blood draw is consistently less than 300 ng/dL and a desired clinical response is not achieved, NATESTO should be discontinued and an alternative treatment should be considered.

If a post-dose morning total testosterone concentration consistently exceeds 1050 ng/dL, NATESTO should be discontinued.

Missed Dose
If a dose is missed, patients are instructed to skip the dose and take their next scheduled dose.

Administration

For twice daily, NATESTO is administered once in the morning and once in the evening (at least 6 hours from prior dose and at least 1 hour before laying down for bed), preferably at the same time each day. Patients should be instructed to completely depress the pump 1 time in each nostril to receive the total dose. For three times daily, NATESTO is administered intranasally once in the morning, once in the afternoon and once in the evening (approximately 6-8 hours apart and at least 1 hour before laying down for bed), preferably at the same time each day.

Do not administer NATESTO to other parts of the body including scrotum, penis, abdomen, shoulders, axilla, or upper arms.

Preparing the Pump

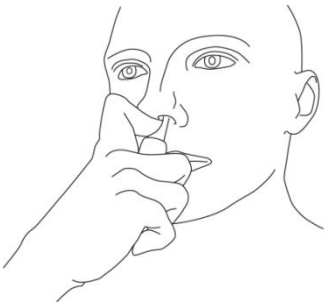
When using NATESTO for the first time, patients should be instructed to prime the pump by inverting the pump, depressing the pump 10 times, and discarding any small amount of product dispensed directly into a sink and then washing the gel away thoroughly with warm water. The tip should be wiped with a clean, dry tissue. If the patient gets gel on their hands, it is recommended that they wash their hands with warm water and soap. This priming should be done only prior to the first use of each dispenser.

Administering the Dose

To administer the dose, patients should be instructed to perform the following steps:

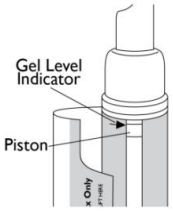
- Blow the nose.
- Remove the cap from the dispenser.
- Place the right index finger on the pump of the actuator and while in front of a mirror, slowly advance the tip of the actuator into the left nostril upwards until their finger on the pump reaches the base of the nose.

- Tilt the actuator so that the opening on the tip of the actuator is in contact with the lateral wall of the nostril to ensure that the gel is applied to the nasal wall.



- Slowly depress the pump until it stops.
- Remove the actuator from the nose while wiping the tip along the inside of the lateral nostril wall to fully transfer the gel.
- Using your left index finger, repeat the steps outlined in bullets 3 through 6 for the right nostril.
- Use a clean, dry tissue to wipe the tip of the actuator.
- Replace the cap on the dispenser.
- Press on the nostrils at a point just below the bridge of the nose and lightly massage.
- Refrain from blowing the nose or sniffing for 1 hour after administration.
- Refrain from laying down for 1 hour to avoid post-nasal drip.

The dispenser should be replaced when the top of the piston inside the dispenser reaches the arrow at the top of the inside label. The inside label may be found by unwrapping the outer flap from around the container.



Use with Nasally Administered Drugs Other than Sympathomimetic Decongestants
The drug interaction potential between NATESTO and nasally administered drugs other than sympathomimetic decongestants is unknown. Therefore, NATESTO is not recommended for use with nasally administered drugs other than sympathomimetic decongestants (e.g., oxymetazoline) (see **Drug Interactions** and **Actions and Clinical Pharmacology**).

Temporary Discontinuation of Use for Severe Rhinitis
If the patient experiences an episode of severe rhinitis, temporarily discontinue NATESTO therapy pending resolution of the severe rhinitis symptoms. If the severe rhinitis symptoms persist, an alternative testosterone replacement therapy is recommended.

OVERDOSAGE

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

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

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 (395nmol/l).

ACTION AND CLINICAL PHARMACOLOGY

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 the 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, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

Pharmacodynamics
No specific pharmacodynamic studies were conducted using NATESTO.

General Androgen Effects
Drugs in the androgen class also promote retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium.
Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein. Androgens have been reported to stimulate the production of red blood cells by enhancing erythropoietin production.

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

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

Pharmacokinetics

Table 3: Summary of NATESTO Pharmacokinetic Parameters for Serum Total Testosterone at Day 90 by Treatment (Intent-to-Treat Population – Treatment Period) in Hypogonadal Men.

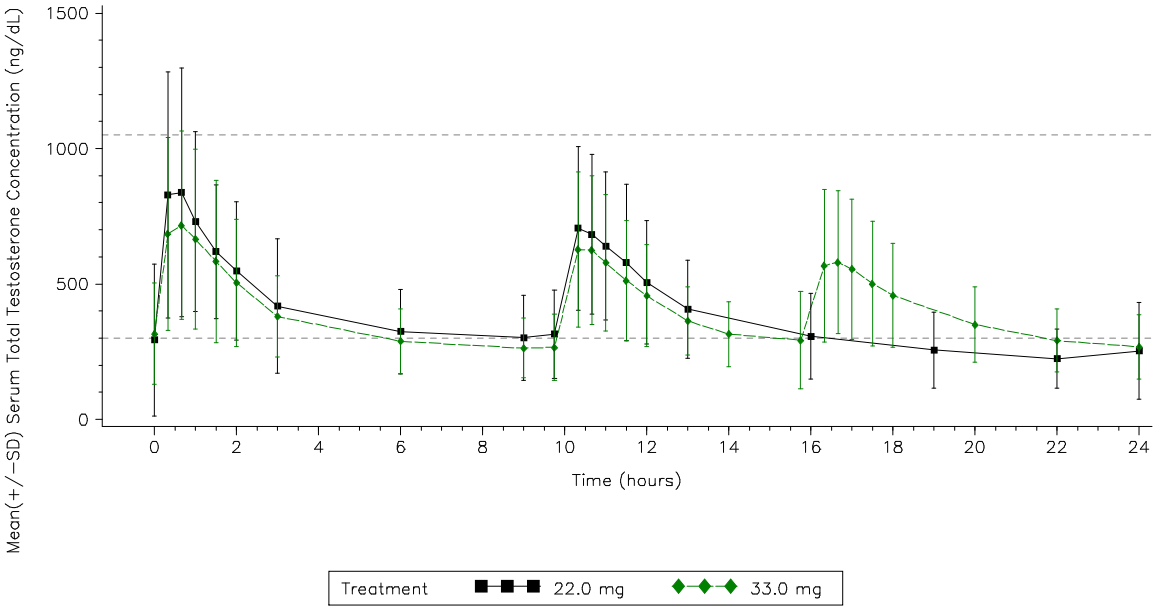
Treatment Statistic	**AUC_{0-24}** **(ng·hr/dL)**	**C_{avg}** **(ng/dL)**	**C_{min}** **(ng/dL)**	**C_{max}** **(ng/dL)**	**T_{max}** **(hr)**
NATESTO 22.0 mg (N=141)					
n	122	122	122	122	122
Mean (SD)	9007.51 (3092.53)	375.31 (128.86)	186.31 (92.63)	1045.72 (467.06)	1.35 (2.48)
CV%	34.3	34.3	49.7	44.7	183.8
Geometric mean	8590.17	357.92	166.79	958.04	0.74
Median	8412.15	350.51	164.00	987.50	0.67
Min, Max	4527.5, 26345.1	188.6, 1097.7	50.2, 556.0	262.0, 3570.0	0.2, 14.0
Combined NATESTO 33.0mg (N=162)					
n	151	151	151	151	151
Mean (SD)	9285.28 (2684.86)	386.89 (111.87)	200.94 (72.73)	934.93 (381.24)	0.96 (0.98)
CV%	28.9	28.9	36.2	40.8	0.70

Treatment Statistic	**AUC_{0-24}** **(ng·hr/dL)**	**C_{avg}** **(ng/dL)**	**C_{min}** **(ng/dL)**	**C_{max}** **(ng/dL)**	**T_{max}** **(hr)**
Geometric mean	8918.64	371.61	187.64	861.69	0.70
Median	9068.02	377.83	192.00	884.00	0.67
Min, Max	3960.1, 18339.3	165.0, 764.1	57.9, 416.0	304.0, 2260.0	0.3, 6.1

AUC_{0-24} =area under the plasma concentration-time curve from time zero to 24 hours post-dose; Cavg = average concentration; Cmin = minimum concentration' Cmax=maximum concentration; CV%=percent coefficient of variation; Min=minimum; Max=maximum; SD=standard deviation; Tmax=time to maximum concentration

Absorption:
NATESTO delivers physiologic circulating testosterone that restores testosterone levels following intranasal administration to the normal concentration range seen in healthy men. In the nasal cavity, the small amount of gel administered spreads thinly across the nasal mucosa. The bioadhesive characteristics of the gel ensure that it does not run or drip out of the nasal cavity. The maximum concentration for NATESTO is achieved within 45 minutes of administration and has a half-life ranging from 10 to 100 minutes.

Figure 1: Mean Serum Total Testosterone Concentrations on Day 90 in Patients Following NATESTO 22.0 mg Daily Administered at 9 p.m. and 7 a.m. (N=122) and 33.0 mg Daily Administered at 9 p.m., 7 a.m. and 1 p.m. (N=151)



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 loosely bound to albumin and other proteins.

Metabolism:
There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes.

Testosterone is metabolized to various 17-keto steroids through 2 different pathways. The major active metabolites of testosterone are estradiol and DHT.

DHT concentrations increased in parallel with testosterone concentrations during testosterone treatment. After 90 days of treatment, mean DHT/testosterone ratio was 0.09 which was within the normal range.

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.

Drug Interactions

Use in patients with allergic rhinitis and oxymetazoline: The effects of allergic rhinitis and the use of oxymetazoline on the absorption of testosterone were investigated in a 3-way cross-over clinical study. Eighteen males who suffered from seasonal allergic rhinitis received 3 doses of 11 mg of testosterone intranasally (testosterone dose of 33 mg/day) while they were in the asymptomatic, symptomatic, and symptomatic but treated (with oxymetazoline) states using an environmental challenge chamber model.

Serum total testosterone concentrations were decreased by 21 to 24% in males with symptomatic allergic rhinitis. A 2.6% decrease in mean $AUC_{(0-24)}$ and 3.6% decrease in mean C_{max} of total testosterone was observed in males with symptomatic seasonal rhinitis when treated with oxymetazoline 30 minutes prior to NATESTO compared to when left untreated. Oxymetazoline does not impact the absorption of testosterone when concomitantly administered with NATESTO. Drug interaction potential with nasally administered drugs other than ozymetazoline has not been studied.

Special Populations and Conditions

Renal and Hepatic Impairment: No studies were conducted in patients with renal or hepatic impairment.

Use in Men with Body Mass Index greater than 35 kg/m^2: Safety and efficacy of NATESTO in males with body mass index greater than 35 kg/m2 has not been established.

Allergic Rhinitis: Serum total testosterone concentrations were decreased by 21 to 24% in males with symptomatic allergic rhinitis, whether treated with nasal decongestants such as oxymetazoline, or left untreated [see **Clinical Pharmacology**].

STORAGE AND STABILITY

Store at room temperature (15 to 30˚C). Keep in a safe place out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

Used NATESTO dispensers should be discarded in household trash in a manner that prevents accidental exposure by household members, especially nursing/pregnant women and children. Alternatively empty dispensers may be returned to the pharmacy for disposal.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NATESTO (testosterone nasal gel, 4.5% w/w) is available as a metered dose pump containing 11.0 g of gel dispensed as 60 metered pump actuations. One pump actuation delivers 5.5 mg of testosterone in 122.5 mg of gel.

Active Ingredient: testosterone

Non-medicinal ingredients: castor oil, colloidal silicon dioxide oleoyl polyoxylglycerides

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

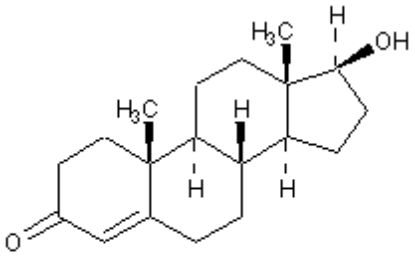
Drug Substance

Proper name: Testosterone USP

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

Molecular formula and molecular mass: $C_{19}H_{28}O_2$, 288.42

Structural formula:



Testosterone

Physicochemical properties:

Description:	White to practically white crystalline powder
Solubility:	Soluble in acetone, dioxane and vegetable oils
- water:	practically insoluble
- dehydrated alcohol:	1 in 6 of dehydrated alcohol
- chloroform:	1 in 2 of chloroform
- ether:	1 in 100 of ether

CAS Registry No: 58-22-0
Melting point: 153°- 157°C

CLINICAL TRIALS

Study Demographics and Trial Design

Table 4: Summary of Patient Demographics in the Phase 3 Pivotal Trial

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
TBS-1-2011-03	Phase 3, open-label, randomized, 2-arm, parallel design	11.0 mg twice daily (22.0mg) 11.0 mg thrice daily (33.0mg); 90 days (all; efficacy) 180 days (all) 360 days (subset of 75 patients)	142[a] 164[a]	54.4 (18-80)	Male

[a] Patients were randomized 3:1 to the 22.0 and 33.0mg treatment arms. A total of 228 patients were randomized to 22.0mg treatment and 78 to 33.0mg treatment; 86 patients from 22.0mg treatment were titrated up to 33.0mg treatment on Day 45; 122 patients completed 90 days of 22.0mg treatment and 152 patients completed 90 days of 33.0mg treatment.

Clinical Studies in Hypogonadal Men

A total of 430 men with hypogonadism and 45 healthy men received at least one dose of NATESTO in clinical trials. 4.5% NATESTO was evaluated in a multicentre, open label, 90-day treatment period followed by 2 sequential safety extension periods of 90 and 180 days that enrolled 306 men. Patients were instructed to self-administer NATESTO (11 mg of testosterone) intranasally. During the initial treatment period (Days 1 – 30) 228 patents were treated with 22.0 mg of testosterone daily and 78 patients were treated with 33.0 mg of testosterone daily. On Day 45 of the trial, patients were maintained at the same dose or were titrated to three times a day, based on an assessment of 24-hour average serum testosterone concentration. The primary endpoint was the percentage of patients with an average serum total testosterone concentration (Cavg) within the normal range (300 to 1050 ng/dL) on Day 90.

At the end of the treatment period (Day 90), 122 patients were receiving 22.0 mg of testosterone daily and 152 patients were receiving 33.0 mg of testosterone daily. Among these patients, 71% who received 22.0 mg of testosterone daily and 76% who received 33.0 mg of testosterone daily had C_{avg} within the normal range at Day 90.

Of the 273 patients who completed the 90-day treatment, 237 patients did so with no deviation from the protocol.

For this population, 75% who received 22.0 mg of testosterone daily and 77% who received

33.0 mg of testosterone daily had C_{avg} within the normal range at Day 90.

Table 5 summarizes the testosterone concentration data in the patients after 90 days of treatment.

Table 5: Baseline Unadjusted Arithmetic Mean (±SD) Steady-State Serum Testosterone Concentration and Percentage of Patients in the Normal Range on Day 90 in Patients Who Completed 90 days of Each Treatment (ITT population)

Daily Dose of NATESTO	N	C_{avg} (ng/dL)	% of Patients with C_{avg} in the Normal Range
22.0 mg	122	375	71%
33.0 mg	151	387	76%

Secondary endpoints included assessments of sexual function and mood. Treatment with NATESTO produced significant improvements from baseline in multiple sexual function parameters as measured by patient responses to a questionnaire completed prior to commencing treatment and after 90 days of treatment. These parameters included erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction.

In addition, the overall mean summary scores showed a significant increase in positive mood and a significant decrease in negative mood after 90 days of treatment compared to baseline.

Effect of Allergic Rhinitis and Oxymetazoline

The interaction of allergic rhinitis and oxymetazoline was evaluated in a clinical study with NATESTO. Eighteen healthy men who suffered from allergic rhinitis were treated with NATESTO in asymptomatic, symptomatic and untreated, and symptomatic and treated with oxymetazoline nasal spray. The symptomatic state was induced by exposure to *Dactylis glomerata* pollen in an environmental challenge chamber (ECC). The symptomatic state was defined by a positive case history, a positive skin prick and/or intradermal test for *Dactylis glomerata* pollen allergen, a Total Nasal Symptom Score (TNSS) of ≥6/12, and a congestion score of ≥ 2/3. A series of blood samples were collected over a 24 hour period.

A reliable increase in serum testosterone was observed in patients with allergic rhinitis in untreated subjects and in subjects treated with a commonly used decongestant; however bioequivalence was not observed. A 21% decrease in testosterone levels observed in men with allergic rhinitis, was neither ameliorated nor aggravated by the administration of the nasal decongestant, oxymetazoline.

TOXICOLOGY

Single-dose toxicity
Testosterone was administered to Swiss Webster mice in a single 5000 mg/kg dose oral toxicity study using testosterone gel. All 10 animals showed some instances of lethargy during the first four hours following dosing. No other signs of toxicity or deaths occurred during the 14-day post dosing observation period. The LD_{50} was greater than 5000 mg/kg.

Repeat dose toxicity
A 90 day repeat dose study was undertaken to evaluate the effects of NATESTO in male rabbits. No evidence of systemic drug-related toxicity was observed in rabbits after repeated twice daily administration of NATESTO over a 90-day period up to a dose level of 6-fold the maximum clinical daily dose.

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

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

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

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

Effects on the Prostate
An induction of prostate adenocarcinomas in male rats following the chronic administration of testosterone has been reported. Testosterone was given chronically by subcutaneous administration in pellets (1-3 pellets, each containing 10 mg testosterone propionate) to Noble

(Nb) strain rats. A 20% incidence of prostate carcinoma in rats whose mean exposure to testosterone was 64 weeks was seen. When the treatment regimen included estrogen and testosterone, the incidence of prostate adenocarcinoma was not significantly different from the group receiving testosterone alone. The latency period for the appearance of this tumour type was reduced.

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

Reproductive and Developmental Toxicity

Effects on exogenously dosed male animals

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

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

The relationship between testosterone induced decreased spermatogenic activity and fertility, pregnancy outcome and offspring was reported by Robaire *et al.* In this study, groups of six male rats received testosterone by subdermal implants at one of the following doses: 0, 15, 30, 60, 90, 120 or 240 μg/day. Testosterone administration to male rats produced biphasic effects.

Low doses produced decreases in spermatogenesis due to suppression of gonadotrophins and subsequent decreases in intra-testicular testosterone, whereas higher doses of testosterone have been shown to maintain spermatogenesis by presenting high serum levels of the hormone. Serum testosterone levels were not significantly different among treatment and control groups; however, reported levels were highest among the group receiving 240 μg/day (4.1 ng/ml vs. 2.5 ng/ml). Testosterone is also capable of maintaining spermatogenesis in the hypophysectomized animal. Testes weights were significantly reduced in groups receiving 90, 120 or 240 μg/day testosterone. Decreased spermatozoa reserves of less than five million were shown to be infertile in individual animals. It was further demonstrated in rats that a decrease in epididymal spermatozoal reserves mediated by testosterone did not cause an observed increase in teratogenic incidences in their progeny as compared with that of controls.

Local Tolerance

Local tolerance studies in rat and rabbit following single dose and repeated dose administrations showed that testosterone nasal gel was well tolerated. Testosterone nasal gel was classified as a nonirritant in the Hen's Egg Test Chorioallantoic Membrane test.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

NATESTO®
Testosterone nasal gel 4.5% w/w

Read this carefully before you start taking **NATESTO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NATESTO**.

What is NATESTO used for?

- Testosterone replacement therapy in adult males for conditions where your body is not making enough or any testosterone.

It is not known if NATESTO is safe or effective to treat you if you have low testosterone due to aging alone.

How does NATESTO work?

NATESTO contains testosterone. NATESTO delivers testosterone into your bloodstream through your nose. NATESTO helps raise your testosterone to normal levels. Your healthcare professional will test the testosterone level in your blood before you start and while you are using NATESTO.

What are the ingredients in NATESTO?

Medicinal ingredient: Testosterone.
Non-medicinal ingredients: Castor oil, colloidal silicon dioxide, oleoyl polyoxylglycerides.

NATESTO comes in the following dosage form:

Nasal gel, 4.5% w/w (5.5 mg of testosterone per actuation).

Do not use NATESTO if you:

- have or it is suspected that you have prostate or breast cancer;
- have a known allergy to any of the ingredients in NATESTO including the medicinal; ingredient testosterone, which is made from soy;
- **are a woman**. Pregnant and breast feeding women are especially at risk. Testosterone may cause harm to an unborn baby. Testosterone exposure during pregnancy has been associated with birth defects.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NATESTO. Talk about any health conditions or problems you may have, including 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 any type of cancer, especially cancer that has spread to the bones;
- have liver, kidney or heart problems;
- have high blood pressure;
- have diabetes;
- have breathing problems during sleep (sleep apnea);
- have heart or blood vessel problems or a history of these problems such as heart attack, stroke, or blood clot in the lungs or legs;
- have or have had nose (nasal) or sinus problems or nasal or sinus surgery;
- have had a broken nose (fracture) within the past 6 months;
- have or have had a fracture of your nose that caused the inside of your nose to be crooked (deviated anterior nasal septum);
- have or have had problems with swelling of the lining of your nose (mucosal inflammatory disorder).

Other warnings you should know about:

- Children and women should avoid contact with NATESTO.
    - 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.

- NATESTO must not be used by children under the age of 18. Improper use of NATESTO may affect bone growth in children.

- There is very little information from clinical trials with testosterone in the older male (> 65 years of age) to support safe use of NATESTO 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.

- NATESTO contains testosterone, which is a controlled substance under Schedule G of the Food and Drugs Act. Keep your NATESTO in a safe place to protect it. Never give your NATESTO to anyone else, even if they have the same symptoms you have.

Tell your healthcare professional about all the medicines you take, including any drugs,

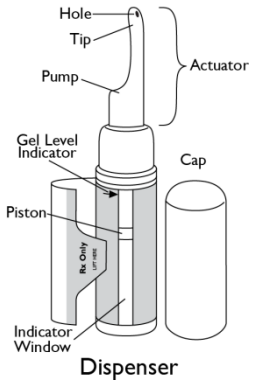
vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NATESTO:
- insulin used to treat diabetes;
- corticosteroids used to treat joint pain and swelling;
- propranolol used to treat heart problems such as chest pain and high blood pressure;
- medication used to prevent clotting such as warfarin;
- St. John's Wort an herbal product used to treat depression.

How to take NATESTO:
- It is important that you apply NATESTO exactly as your healthcare professional tells you to.
- Your healthcare professional will tell you how much NATESTO to apply and when to apply it.
- NATESTO is to be applied into the nose (intranasally) only. Do not apply NATESTO to any other parts of your body such as your scrotum, penis, abdomen, shoulders, axilla, or upper arms.
- NATESTO can be used with nasal spray decongestants such as oxymetazoline. NATESTO should not be used with any other nasal sprays.

Supplies needed to give your NATESTO dose:
- 1 NATESTO dispenser;
- 2 clean, dry tissues;
- A clean and flat surface, like a table;
- A mirror.

Parts of your NATESTO dispenser (See Figure A):



(Figure A)

How to prime your NATESTO pump:
- Before you use NATESTO for the first time, you will need to prime your NATESTO pump.
- Hold your NATESTO dispenser over a sink, turn it upside down and slowly press and release the pump 10 times (See Figure B).

(Figure B)

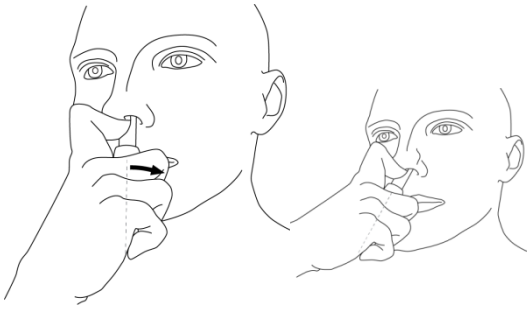
- Any gel that comes out when you prime your pump should be rinsed down the sink with warm water.
- If there is any gel on the tip of your actuator after priming, wipe the tip with a clean, dry tissue.
- If any gel gets on your hands, wash your hands with warm water and soap.

How to administer NATESTO:

- Blow your nose.
- Remove the cap from the dispenser.
- While looking in the mirror, place the right index finger on the pump of your NATESTO actuator and slowly slide the tip of the actuator into the left nostril until the finger on the pump touches the bottom of your nose (See Figure C).

(Figure C)

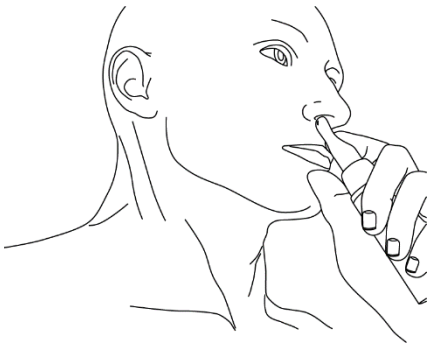
- Slightly tilt the actuator so that the opening in the tip touches the inside wall of your nostril to ensure that the gel is applied in the correct place (See Figure D).



(Figure D)

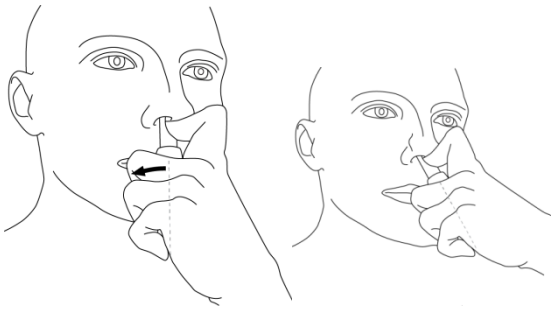
- With the actuator in place, slowly push down on the pump until it stops.

- Remove the actuator from your nose while wiping the tip along the inside wall, to make sure all the gel stays in the nose.
- While looking in the mirror, put your left index finger on the pump of your NATESTO actuator and slowly slide the tip of the actuator into the right nostril until the finger on the pump touches the bottom of the your nose (See Figure E).



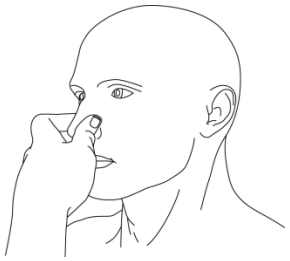
(Figure E)

- Slightly tilt the actuator so that the opening in the tip touches the inside wall of your nostril to ensure that the gel is applied in the correct place (See Figure F).



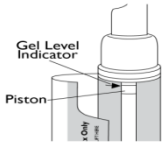
(Figure F)

- With the actuator in place, slowly push down on the pump until it stops.
- Remove the actuator from your nose while wiping the tip along the inside wall to make sure all the gel stays in the nose.
- Wipe the tip of the actuator with a clean, dry tissue.
- Replace the cap.
- Press your nostrils together just below the middle of your nose (bridge) and lightly rub them together (See Figure G).
- Do not blow your nose or sniff for 1 hour after using NATESTO
- Do not lay down for 1 hour to avoid post-nasal drip.



(Figure G)

When to replace NATESTO:
Replace your NATESTO dispenser when the top of the piston inside the dispenser reaches the arrow at the tip of the inside label. The inside label may be found by unwrapping the outer flap from around the container (See Figure H).



(Figure H)

Adult dose:
The recommended starting therapy is two doses (1 dose = 1 actuation per nostril) per day for a total of 22 mg. Each actuation contains 5.5 mg of testosterone.
Your dose may be increased by your healthcare professional to 33 mg/day applied in three doses (1 dose = 1 actuation per nostril).
Doses must be at least 6 hours apart. The night dose should be taken at least 1 hour before laying down for bed.

Daily Prescribed Dose	Each dose requires one actuation per nostril
22mg	Apply NATESTO to each nostril once in the morning and once in the evening, at the same time each day.
33mg	Apply NATESTO to each nostril once in the morning once in the afternoon and once in the evening, at the same time each day.

Overdose:

If you think you have taken too much NATESTO, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you missed a dose of NATESTO, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using NATESTO?

These are not all the possible side effects you may feel when taking NATESTO. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- acne;
- metallic and/or unpleasant taste;
- cough;
- muscle pain;
- sleep disturbances caused by breathing problems;
- loss of hair and baldness;
- weight gain;
- headache, dizziness;
- lowered sperm count;
- nose problems:
  - abnormal or unpleasant odour;
  - constant runny nose, congestion, sneezing;
  - nose bleed;
  - discomfort in the nose, scabbing, dryness.

NATESTO can increase your risk for prostate cancer. Your healthcare professional should check your prostate before you start taking NATESTO and regularly during your treatment.

NATESTO can cause abnormal blood test results, including an increase in prostatic specific antigen (PSA). Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Benign prostatic hyperplasia (BPH):** urinary symptoms such as change in frequency/ colour, dribbling, pain on urination straining, weak stream, small amounts		✓	
Gynecomastia: breast enlargement or breast pain		✓	
UNCOMMON **Edema:** swelling of ankles and legs		✓	
Priapism: unwanted erections that are too frequent or continue for too long		✓	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
Abnormal Heart Rhythm: fast or irregular heart beat		✓	
High Blood Pressure: headaches, shortness of breath, vision problems		✓	
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Changes in Mood: sad mood (depression), aggression, anger, hostility		✓	
Blood Clot in the Lung: sharp chest pain, coughing up blood, shortness of breath			✓
Blood Clot in the Leg: pain, redness, swelling and tenderness in the leg			✓
Heart attack: crushing chest pain, tightness, pressure or squeezing, pain in the arm, jaw			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
or back, trouble breathing, anxiety, sweating			
Stroke: a sudden severe headache, vomiting, dizziness, fainting, problems with your vision or speech, weakness, or numbness in the face, arm or leg			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (www.heathcanada.gc.ca/medeffect)
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store NATESTO at room temperature (15°C-30°C). Keep out of reach and sight of children and pets.

If you want more information about NATESTO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.aceruspharma.com, or by contacting Acerus Pharmaceuticals Corporation at 1-844-850-1642 or at AcerusPV@innomar-strategies.com.

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This leaflet was prepared by Acerus Pharmaceuticals Corporation.

Last Revised April 4, 2019