Could NATESTO®
BE RIGHT FOR ADAM?

Adam is a 39-year-old financial manager, 6-foot-2, 185 pounds. He is father to a 4-year-old and currently on a transdermal gel TTh following 2 morning testosterone evaluations earlier in the year.

Symptoms include:

- Low energy
- Depressed mood
- Decreased libido

Presenting concerns:

He and his spouse want to expand their family, while still holding on to his ability to produce his own endogenous testosterone. He also has concerns about TTh transference.

Actor portrayal.

See back to learn why Natesto can be
AN APPROPRIATE CHOICE FOR ADAM

TTh=testosterone therapy.

INDICATION

Natesto is indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

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

Limitations of use:

- Safety and efficacy of Natesto in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established
- Safety and efficacy of Natesto in males less than 18 years old have not been established

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Natesto is contraindicated in:

- Men with carcinoma of the breast, or known or suspected carcinoma of the prostate
- Women who are or who may become pregnant, or who are breastfeeding. 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

Please see additional Important Safety Information [inside] [throughout] and [accompanying] Full Prescribing Information.

natesto® (testosterone) nasal gel

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

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. Patients should be instructed to report any nasal symptoms or signs to their healthcare professional. In that circumstance, healthcare professionals should determine whether further evaluation 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 safety or efficacy, Natesto is not recommended for use in patients with a 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.

Worsening of Benign Prostatic Hyperplasia and Potential Risk of Prostate Cancer: Monitor patients with benign prostatic hyperplasia (BPH) treated with Natesto for worsening signs and symptoms of BPH. Patients treated with androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating treatment. It would be appropriate to re-evaluate patients 3 to 6 months after initiation of treatment and then in accordance with prostate cancer screening practices.

Polycythemia: Increases in hematocrit, reflective of increases in red blood cell mass, may require discontinuation of Natesto. Check hematocrit prior to initiation. 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.

Venous Thromboembolism: Postmarketing reports of venous thromboembolic events (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), have been reported in patients using testosterone products such as Natesto. Evaluate patients who report symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a VTE is suspected, discontinue treatment with Natesto and initiate appropriate workup and management.

Cardiovascular Risk: Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. Some studies, but not all, have reported an increased risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use Natesto.

Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations: Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions. If abuse is suspected, check testosterone levels to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

Use in Women: Due to lack of controlled studies in women and potential virilizing effects, Natesto is not indicated for use in women.

Potential for Adverse Effects on Spermatogenesis: At large doses of exogenous androgens, including Natesto, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) that could lead to adverse effects on semen parameters, including sperm count.

Hepatic Adverse Effects: Prolonged use of high doses of orally active androgens (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 has produced multiple hepatic adenomas. Natesto is not known to cause 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.

Edema: 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. In addition to discontinuation of the drug, diuretic therapy may be required.

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

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

Lipids: Changes in the serum lipid profile may occur. Monitor the lipid profile periodically, particularly after starting testosterone therapy. Changes in serum lipid profile may require discontinuation of testosterone therapy.

Hypercalcemia: 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 these patients.

Please see additional Important Safety Information [on back] [throughout] and [accompanying] Full Prescribing Information.

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IMPORTANT SAFETY INFORMATION (cont)

Decreased Thyroxine-binding Globulin: Androgens, including Natesto, may decrease concentrations of thyroxine-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

ADVERSE REACTIONS

Natesto was evaluated in a 90-day clinical study that included a 90-day extension period and a subsequent 180-day extension period. Among the 78 patients who received Natesto three times daily in the 90-day clinical study, 69 of those patients received Natesto treatment during the 90-day extension period. A total of 18 patients received Natesto treatment in all three treatment periods, including the 90-day clinical study, the first 90-day extension period, and the second 180-day extension period.

The most common adverse reactions (incidence ≥3%) in the 90-day clinical study were prostate-specific antigen (PSA) increased (5.1%), headache (3.8%), rhinorrhea (3.8%), epistaxis (3.8%), nasal discomfort (3.8%), nasopharyngitis (3.8%), bronchitis (3.8%), upper respiratory tract infection (3.8%), sinusitis (3.8%), and nasal scab (3.8%). Among the 69 patients who received Natesto during the 90-day extension period, the most common adverse reactions were: nasopharyngitis (8.7%), PSA increased (5.8%), parosmia (5.8%), nasal discomfort (5.8%), rhinorrhea (7.2%), and nasal scab (5.8%).

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.

DRUG INTERACTIONS

Insulin: Natesto can cause changes in insulin sensitivity or glycemic control. In diabetic patients, androgens may decrease blood glucose and may necessitate a decrease in the dose of anti-diabetic medication.

Oral Anticoagulants: Anticoagulant activity may be affected by androgens. More frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy.

Corticosteroids: Use of testosterone and corticosteroids concurrently may increase fluid retention and requires careful monitoring, particularly in patients with cardiac, renal, or hepatic disease.

Oxymetazoline: A 2.6% decrease in mean 24-hour bioavailability of testosterone and 3.6% decrease in mean maximum observed concentration 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 other nasally administered drugs other than oxymetazoline has not been studied.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category X – Natesto is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Nursing Mothers: 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 mothers.

Pediatric Use: Safety and efficacy of Natesto has not been established in pediatric patients less than 18 years of age. Improper use may result in acceleration of bone age and premature closure of epiphyses.

Geriatric Use: There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing Natesto to determine whether efficacy in those over 65 years of age differs from younger subjects. There is insufficient long-term safety data in geriatric patients using Natesto to assess the potentially increased risk of cardiovascular disease and prostate cancer.

Renal Impairment: No studies were conducted in patients with renal impairment.

Hepatic Impairment: No studies were conducted in patients with 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/m^2 has not been established.

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

DRUG ABUSE AND DEPENDENCE

Natesto contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids, may be abused by athletes and bodybuilders.

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids, and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility, and aggression.

The following adverse reactions have been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

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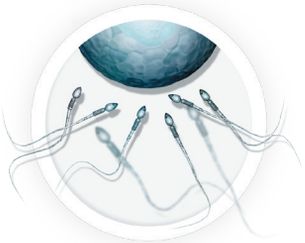
Natesto could be THE RIGHT CHOICE FOR ADAM

Demonstrated improvements in symptoms and restored T levels to therapeutic range[1-3]

90% OF MEN
WITHIN THERAPEUTIC RANGE
(300-1050 ng/dL) ON DAY 90[1*]



HPG AXIS REMAINS ACTIVE

with no significant change in sperm count, motility, and total motile sperm count.[4†‡]

NO-TOUCH INTRANASAL ADMINISTRATION

minimizes transference risk, eliminating time before contact with loved ones.[1,5]

*Primary endpoint from a phase 3, 90-day, open-label, multicenter, pivotal study (N=306).[1]

†Natesto is indicated only for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, not for other health conditions.[1]

‡Results from a phase 4, 6-month, single-center, open label, single-arm trial that studied the effect of Natesto (11 mg, TID) on reproductive hormones, semen parameters, and hypogonadal symptoms (N=60).[4]

HPG=hypothalamic pituitary gonadal; TID=3 times per day.

Please see the Important Safety Information and Full Prescribing Information for a complete list of side effects associated with Natesto, including potential effects on spermatogenesis.

IMPORTANT SAFETY INFORMATION (cont)

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Withdrawal symptoms can be experienced upon abrupt discontinuation in patients with addiction. Withdrawal symptoms include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido, and hypogonadotropic hypogonadism. Drug dependence in individuals using approved doses for approved indications have not been documented.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For more information, visit Natestohcp.com, or call 1-833-698-3786.

Please see [accompanying] Full Prescribing Information.

References: 1. Natesto (Prescribing Information). Mississauga, Ontario: Acerus Pharmaceuticals Corporation; 2016. **2.** Clinical Study Report TBS-1-2011-03. A 90-day, randomized, dose-ranging study, including potential dose titration, evaluating the efficacy and safety of intranasal TBS-1 in the treatment of male hypogonadism with sequential safety extension periods of 90 and 180 days. Trimel Biopharma SRL. May 28, 2013 (Final 2.0). **3.** Lipshultz L, Westfield G, Guidry M, Bryson N, Khera M. Clinical improvements in erectile function and mood in hypogonadal men treated with 4.5% nasal testosterone gel. *J Urol.* 2017;197(4S, suppl):e1346-e1347. **4.** Ramasamy R, Masterson TA, Best JC, et al. Effect of Natesto on reproductive hormones, semen parameters and hypogonadal symptoms: a single center, open label, single arm trial. *J Urol.* 2020;240(3):557-563. **5.** Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

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ACERUS PHARMA

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