

Medicare Ponders Medically 'Unbelievable' Edits

BY JOYCE FRIEDEN
Associate Editor, Practice Trends

WASHINGTON — If you don't like medically "unbelievable" edits, how about medically "unusual" ones?

Members of the Practicing Physicians Advisory Council (PPAC), which advises the Centers for Medicare and Medicaid Services (CMS) on issues of interest to physicians, were upset about the name of the proposed Medically Unbelievable Edits

program, which aims to find obvious errors in Medicare claims—for example, a claim for doing a hysterectomy on a male patient.

"'Unbelievable' is a value judgment," PPAC member Dr. Peter Grimm, a radiation oncologist from Seattle, said at a recent council meeting. "You're going to get immediate reaction from people, so changing that word to 'unusual' doesn't change your [acronym] and really accurately describes what you're trying to do."

Council member Dr. Carlos Hamilton,

an endocrinologist and executive vice president for clinical affairs at the University of Texas Health Science Center in Houston, said that "there is considerably more angst in the medical community about this issue than may immediately appear."

He noted that while the idea of using anatomical edits seems workable, there are often exceptions.

For example, one possible edit would return a claim if a surgeon took out two

spleens in the same patient on the same day. "I'm not a surgeon, but [I know that] there are some people who do have accessory spleens, and it is conceivable that you might have to take out a second spleen," he said. "I really think you need to come up with a modifier for situations that don't appear to be straightforward before you bring this [system] out."

PPAC member Dr. M. LeRoy Sprang, an Evanston, Ill., ob.gyn., had another idea. "How about 'medically unexpected?' It's a softer word, and it really covers what you want to do. It's just not as obnoxious as 'unbelievable.'"

The program in question is designed to detect implausible Medicare claims submissions and avert inappropriate claims payment, according to Lisa Zone, director of the program integrity group at the CMS Office of Financial Management.

"I realize that this is an unfortunate title," she said. "We are trying to install edits to detect true errors in the system."

A recent CMS report found that Medicare's national paid claims error rate was 5.1%, "and we know that 1.7% is related to improper coding or billing errors," Ms. Zone said. "When you look at the federal dollars expended in the coding error class, it's in the billions of dollars."

The comment period for the proposed program ended on June 19, and Ms. Zone noted that "given that we've [already] heard from various provider organizations about the MUEs out there today for comment, we are not going to be going forward with the MUEs as they are."

Instead, the office will look at the edits as a whole and make decisions on the best way to move forward. Initially, Ms. Zone's office will concentrate on developing edits to catch "anatomical" errors, such as procedures performed on the wrong body part. Then, they will address edits for typographical errors—someone bills for 500 units instead of 5, for example.

After those changes, the proposal will go out for more comments. The MUEs will not be implemented until at least January of next year, and there will be a "test period" beforehand, which will include an appeals process, she said.



Brief Summary (for full Prescribing Information and Patient Information, refer to package insert.)

INDICATIONS AND USAGE

AndroGel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

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

AndroGel has not been clinically evaluated in males under 18 years of age.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.

AndroGel is not indicated for use in women, has not been evaluated in women, and must not be used in women.

Pregnant women should avoid skin contact with AndroGel application sites in men. Testosterone may cause fetal harm. In the event that unwashed or undressed skin to which AndroGel has been applied does come in direct contact with the skin of a pregnant woman, the general area of contact on the woman should be washed with soap and water as soon as possible. *In vitro* studies show that residual testosterone is removed from the skin surface by washing with soap and water.

AndroGel should not be used in patients with known hypersensitivity to any of its ingredients, including testosterone USP that is chemically synthesized from soy.

WARNINGS

- 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.
- Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.
- 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. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men. Increases in serum PSA from baseline values were seen in approximately 18% of individuals in an open label study of 162 hypogonadal men treated with AndroGel for up to 42 months. Most of these increases were seen within the first year of therapy. (see **ADVERSE REACTIONS** and **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests**).
- Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.
- Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.
- The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.
- ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL HAS DRIED.**

PRECAUTIONS

Transfer of testosterone to another person can occur when vigorous skin-to-skin contact is made with the application site. The following precautions are recommended to minimize potential transfer of testosterone from AndroGel-treated skin to another person:

- Patients should wash their hands immediately with soap and water after application of AndroGel.
 - Patients should cover the application site(s) with clothing after the gel has dried (e.g., a shirt).
 - In the event that unwashed or undressed skin to which AndroGel has been applied 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 vitro* studies show that residual testosterone is removed from the skin surface by washing with soap and water.
- Changes in body hair distribution, significant increase in acne, or other signs of virilization of the female partner should be brought to the attention of a physician.

General

The physician should instruct patients to report any of the following:

- Too frequent or persistent erections of the penis.
- Any nausea, vomiting, changes in skin color, or ankle swelling.
- Breathing disturbances, including those associated with sleep.

Information for Patients

Advise patients to carefully read the information brochure that accompanies each carton of AndroGel single-use packets or 75 g AndroGel Pump.

Advise patients of the following:

- AndroGel should not be applied to the scrotum.
- AndroGel should be applied once daily to clean dry skin.
- After application of AndroGel, it is currently unknown for how long showering or swimming should be delayed. 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.
- SINCE ALCOHOL BASED GELS ARE FLAMMABLE, AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL HAS DRIED.**

Laboratory Tests

- Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long-term androgen therapy.
- Liver function, prostatic specific antigen, cholesterol, and high-density lipoprotein should be checked periodically.
- To ensure proper dosing, serum testosterone concentrations should be measured (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

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.

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

Drug/Laboratory Test 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Human Data: There are rare reports of hepatocellular carcinoma in patients receiving long-term oral therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

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.

In men receiving testosterone replacement therapy, screening for prostate cancer should be consistent with current practices for eugonadal men. Increases in serum PSA from baseline values were reported in approximately 18% of individual patients treated for up to 42 months in an open-label safety study (see **ADVERSE REACTIONS**).

Pregnancy Category X (see **CONTRAINDICATIONS**) – Teratogenic Effects: AndroGel is not indicated for women and must not be used in women.

Nursing Mothers: AndroGel is not indicated for women and must not be used in women.

Pediatric Use: Safety and efficacy of AndroGel in pediatric patients have not been established.

ADVERSE REACTIONS
In a controlled clinical study, 154 patients were treated with AndroGel for up to 6 months. Adverse Events possibly, probably or definitely related to the use of AndroGel and reported by ≥1% of the patients are listed in Table 1.

Adverse Event	Dose of AndroGel*		
	5 g n = 77	7.5 g n = 39	10 g n = 78
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 Disorder**	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 results.

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

The following adverse events possibly related to the use of AndroGel occurred in fewer than 1% of patients: amnesia, anxiety, discolorated 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 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. Among 17 patients in foreign clinical studies there was one instance each of acne, erythema and benign prostatic adenoma associated with a 2.5% testosterone gel formulation applied dermally.

One hundred sixty-two (162) patients 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.

TABLE 2. Incidence of Adverse Events Possibly, Probably or Definitely Related to the Use of AndroGel in the 3 Year Open-Label Extension Clinical Trial

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

* 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.

Increases in Serum PSA

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 was no statistically significant increase 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 ≥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.

DRUG ABUSE AND DEPENDENCE

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

Oral ingestion of AndroGel will not result in clinically significant serum testosterone concentrations due to extensive first-pass metabolism.

OVERDOSAGE

No reports of AndroGel overdose have been received. However, there is one report of acute overdose by injection of testosterone enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

DOSAGE AND ADMINISTRATION

The recommended starting dose of AndroGel is 5 g delivering 5 mg of testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Serum testosterone levels should be measured approximately 14 days after initiation of therapy to ensure proper dosing. If the serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved, the daily AndroGel dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g as instructed by the physician.

AndroGel is available in either unit-dose packets or multiple-dose pumps. The metered-dose pump delivers 1.25 g of product when the pump mechanism is fully depressed once.

AndroGel must not be applied to the genitals.

If using the multi-dose AndroGel Pump, patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times and discard this portion of the product to assure precise dose delivery. After the priming procedure, patients should completely depress the pump one time (actuation) for every 1.25 g of product required to achieve the daily prescribed dosage. The product may be delivered directly into the palm of the hand and then applied to the desired application sites, either one pump actuation at a time or upon completion of all pump 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. Please refer to the chart below for specific dosing guidelines when the AndroGel Pump is used.

Prescribed Daily Dose	Number of Pump Actuations
5 g	4 (once daily)
7.5 g	6 (once daily)
10 g	8 (once daily)

If using the packets, the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. Alternately, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied.

Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after AndroGel has been applied.

HOW SUPPLIED

AndroGel is supplied in non-aerosol, metered-dose pumps. The pump is composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each individual packaged AndroGel Pump is capable of dispensing 75 g or 60 metered 1.25 g doses.

AndroGel is also supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively.

NDC Number	Package Size
0051-8488-88	2 x 75 g pumps (each pump dispenses 60 metered 1.25 g doses)
0051-8425-30	30 packets (2.5 g per packet)
0051-8450-30	30 packets (5 g per packet)

Keep AndroGel out of the reach of children.

Manufactured by:

Unimed Pharmaceuticals, Inc.
A Solvay Pharmaceuticals, Inc. Company
Montrouge, France

For:

Unimed Pharmaceuticals, Inc.
A Solvay Pharmaceuticals, Inc. Company
Marietta, GA 30062-2224, USA

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