

Lack of Antidiscrimination Law Hobbles Genomics

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Contributing Writer

WASHINGTON — Genomic science is advancing rapidly on many fronts, but without solid federal policy to prevent genetic discrimination, it will be very difficult for physicians and patients to harvest the fruits of researchers’ labors, said Dr. Francis S. Collins, director of the National Human Genomic Research Institute, National Institutes of Health.

“All of the original goals of the Human Genome Project have been achieved,” the nation’s gene dean said at the World Health Care Congress, a health policy conference sponsored by the Wall Street Journal. Genomic researchers are making significant, clinically relevant, and potentially cost-saving discoveries in early disease detection, pharmacogenomics, nutrigenomics, and rational gene-based drug design. But widespread clinical application of these advances will remain a dream with-

out adequate antidiscrimination safeguards. “We really need this kind of protection to forward genomic medicine. The single greatest inhibition that people have about genomic medicine is the fear that the genetic information will be used against them. We’ve known about this hang-up for 10 years now,” Dr. Collins said. He and other leaders in the genomics field have repeatedly pushed for federal legislation that would guarantee nondiscrimination in

employment or health insurance coverage decisions. Though such a bill has repeatedly been introduced, Congress has failed to come through. One particular bill (S. 1053) died in the last Congress and was reintroduced in the current Congress as S. 306 and HR. 1227, Dr. Collins said. Though it is technically still alive, he expressed doubt that either branch of Congress will move on it this year. The hang-up? Dr. Collins said that many in the business community are concerned that this type of legislation would provide further chum for already voracious antidiscrimination attorneys, leading to an avalanche of spurious genetic discrimination lawsuits that could paralyze corporate America. “Some of us are concerned that if someone doesn’t start to move this soon, nothing will happen,” Dr. Collins said. Dr. Elias Zerhouni, director of the National Institutes of Health, agreed. In a separate address at the conference, he said he shares Dr. Collins’ concern. “We really

need antidiscrimination legislation.” Stasis on the policy front would be a tragedy, he continued, because genomic researchers are “coming up with some pretty nifty clinical stuff these days.”

Among the new advances

Dr. Zerhouni and Dr. Collins cited is the evolution of the Hereditary Non-Polyposis Colon Cancer (HNPCC) screening panel that allows clinicians to predict the risk of colon cancer in families that have members with this type of colon cancer. According to a cost-analysis published in 2001, HNPCC screening of individuals with the cancer costs roughly \$42,000 per life-year gained. Not exactly a bargain, Dr. Collins admitted.

“But remember that each patient has relatives, and each first-degree relative has a 50% risk of developing the cancer,” he added. If you look at screening of parents, siblings, and children of index cases, the cost drops dramatically to \$7,556 per life-year gained (Ann. Intern. Med. 2001;135: 577). “This is much more cost effective, and it should be reimbursed.”

A multigene assay for predicting risk of recurrence in women with node-negative, tamoxifen-treated breast cancer is another bright light on the clinical genomics horizon. This assay can accurately identify which women are most and least likely to have positive long-term recurrence-free responses to tamoxifen chemotherapy (N. Engl. J. Med. 2004;351:2817-26). Its main virtue is that it allows patients who are unlikely to respond to tamoxifen to avoid undergoing the often unpleasant chemotherapy regimen.

The assay “has been widely adopted by many oncologists, and it has a big patient

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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:

1. 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.
2. 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 unclothed 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

1. 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.
2. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.
3. 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**).
4. 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.
5. Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.
6. 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.
7. 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 unclothed 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

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

TABLE 1. Adverse Events Possibly, Probably or Definitely Related to Use of AndroGel in the 180-Day Controlled Clinical Trial

Adverse Event	Dose of AndroGel		
	5 g n = 77	7.5 g n = 40	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, discolored hair, dizziness, dry skin, hirsutism, hostility, impaired urination, parasthesia, 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 prostate 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.

OVERDOSSAGE

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.

DOSE 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:
Laboratoires Besins International
Montrouge, France

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

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Rev Aug 2005

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satisfaction benefit," Dr. Collins said. But he acknowledged that the test is marginally cost efficient.

Another example from Dr. Collins: The emergence of assays to evaluate warfarin metabolism based on genetic variations in the function of the hepatic cytochrome P-450 (CYP-450) enzyme system has tremendous everyday potential for routine clinical practice. Assessment of the gene coding for CYP 2C9 can help physicians tailor warfarin doses to prevent bleeding episodes in patients with genetic propensities for higher-than-average responsiveness to the drug.

The test costs roughly \$135 per patient and can prevent one major bleeding



NATIONAL HUMAN GENOME RESEARCH INSTITUTE/ERNI BRANSON, NIH

"If something doesn't start to move soon, nothing will happen," Dr. Collins said.

episode for every 44 patients on warfarin (Am. J. Man. Care. 2003;9:493-500). Prevention of a single severe hemorrhage using the genetic test would cost roughly \$6,000, the approximate cost of managing a bleeding episode. So this test, by itself, is cost neutral, "but it is a major improvement in terms of patient outcomes," said Dr. Collins, who called for a prospective trial on the subject.

According to Dr. Zerhouni, early detection of disease susceptibility years, if not decades, before symptoms emerge and genomically guided drug therapy are the future of American medicine. "DNA sequencing costs are plummeting. This is opening up a new vista regarding our ability to understand disease."

He said he believes genomic medicine is at a critical inflection point. "We have a lot of information. We need to exploit it to intervene, not at the most costly advanced stages of symptoms, but at early pre-symptomatic stages where we can truly prevent diseases from manifesting."

Dr. Reed Tuckson, senior vice president for consumer health and medical care advancement at UnitedHealth Group, said there's a lot of public and physician education work that needs to be done before anyone will be able to make good on Dr. Zerhouni's vision.

"Physicians do not have time for abstract theoretical discourses on the genomics revolution. They want practical answers on how it applies to patient care and how it pertains to their daily practices. The learning systems need to meet these

needs," Dr. Tuckson said. He added that by and large, physicians and the health care system are not prepared to deal with the challenges of genomics.

"What if a doctor detects a breast cancer susceptibility gene in a patient? Does he then try to track down the patient's daughters or her sisters? This brings up some very real patient-doctor communications issues."

The public is even further behind in terms of understanding the implications and value of genomic medicine. Dr. Tuckson called for intensive public education efforts, pointing out that the science curricula in many school systems are being

decimated, leaving young people at a significant disadvantage in their ability to understand genetics. He also said that integration of genomic developments into routine practice requires many more qualified genetics counselors than are now available.

Then there's the matter of reimbursement. Dr. Tuckson noted that health plans have been slow to cover genetic testing on a wider basis because administrators have yet to be convinced that the tests, and the courses of action after testing, are ultimately cost effective.

"We need to make sure that the tests work, and then get them covered. But we

really need predictive tests, not just diagnostic tests. We need a robust database to answer the question of whether this adds value, because we really need supplantive technology, not just additive technology," Dr. Tuckson said.

The future of genomic medicine hinges on further research and development, and that requires funding. "You need to fight like hell to increase the budgets for the National Institutes of Health, the Agency for Healthcare Research and Quality, the Centers for Disease Control, the FDA, and other agencies. If we don't get the research, we can't make the choices," Dr. Tuckson added. ■

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NovoLog® Mix 70/30

70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin)

Mealtime and in-between time

BRIEF SUMMARY. PLEASE CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

NovoLog Mix 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

CONTRAINDICATIONS

NovoLog Mix 70/30 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog Mix 70/30 or one of its excipients.

WARNINGS

Because NovoLog Mix 70/30 has peak pharmacodynamic activity one hour after injection, it should be administered with meals.

NovoLog Mix 70/30 should not be administered intravenously.

NovoLog Mix 70/30 is not to be used in insulin infusion pumps.

NovoLog Mix 70/30 should not be mixed with any other insulin product.

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog Mix 70/30. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog Mix 70/30 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level).

Fixed ratio insulins are typically dosed on a twice daily basis, i.e., before breakfast and supper, with each dose intended to cover two meals or a meal and snack. The dose of insulin required to provide adequate glycemic control for one of the meals may result in hyper- or hypoglycemia for the other meal. The pharmacodynamic profile may also be inadequate for patients (e.g., pregnant women) who require more frequent meals.

Adjustments in insulin dose or insulin type may be needed during illness, emotional stress, and other physiologic stress in addition to changes in meals and exercise.

The pharmacokinetic and pharmacodynamic profiles of all insulins may be altered by the site used for injection and the degree of vascularization of the site. Smoking, temperature, and exercise contribute to variations in blood flow and insulin absorption. These and other factors contribute to inter- and intra-patient variability.

Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

Hypoglycemia - As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog Mix 70/30. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment - Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of renal impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with renal impairment.

Hepatic Impairment - Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of hepatic impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with hepatic impairment.

Allergy - Local Reactions - Erythema, swelling, and pruritus at the injection site have been observed with NovoLog Mix 70/30 as with other insulin therapy. Reactions may be related to the insulin molecule, other components in the insulin preparation including protamine and cresol, components in skin cleansing agents, or injection techniques.

Systemic Reactions - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Antibody production - Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3-month, open-label comparator trial as well as in a long-term extension trial. Changes in cross-reactive antibodies were more common after NovoLog Mix 70/30 than with Novolin® 70/30 but these changes did not correlate with change in HbA1c or increase in insulin dose. The clinical significance of these antibodies has not been established. Antibodies did not increase further after long-term exposure (>6 months) to NovoLog Mix 70/30.

Information for patients - Patients should be informed about potential risks and advantages of NovoLog Mix 70/30 therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction for use of injection devices, and proper storage of insulin.

Female patients should be advised to discuss with their physician if they intend to, or if they become, pregnant because information is not available on the use of NovoLog Mix 70/30 during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

Laboratory Tests - The therapeutic response to NovoLog Mix 70/30 should be assessed by measurement of serum or blood glucose and glycosylated hemoglobin.

Drug Interactions - A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin.

Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medical products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

Mixing of Insulins

NovoLog Mix 70/30 should not be mixed with any other insulin product.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog Mix 70/30. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog®, the rapid-acting component of NovoLog Mix 70/30, at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in ex vivo UDS test in rat liver hepatocytes. In fertility studies in male and female rats, NovoLog at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area) had no direct adverse effects on male and female fertility, or on general reproductive performance of animals.

Pregnancy-Teratogenic Effects—Pregnancy Category C

Animal reproduction studies have not been conducted with NovoLog Mix 70/30. However, reproductive toxicology and teratology studies have been performed with NovoLog (the rapid-acting component of NovoLog Mix 70/30) and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog did not differ from those observed

with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32-times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area), and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits based on U/body surface area.

It is not known whether NovoLog Mix 70/30 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in pregnant women. NovoLog Mix 70/30 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - It is unknown whether NovoLog Mix 70/30 is excreted in human milk as is human insulin. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in lactating women.

Pediatric Use - Safety and effectiveness of NovoLog Mix 70/30 in children have not been established.

Geriatric Use - Clinical studies of NovoLog Mix 70/30 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

ADVERSE REACTIONS

Clinical trials comparing NovoLog Mix 70/30 with Novolin 70/30 did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as whole: Allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages: Local injection site reactions or rash or pruritus, as with other insulin therapies, occurred in 7% of all patients on NovoLog Mix 70/30 and 5% on Novolin 70/30. Rash led to withdrawal of therapy in <1% of patients on either drug (see PRECAUTIONS, Allergy).

Hypoglycemia: see WARNINGS and PRECAUTIONS.

Other: Small elevations in alkaline phosphatase were observed in patients treated in NovoLog controlled clinical trials. There have been no clinical consequences of these laboratory findings.

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

More detailed information is available on request.

Rx Only

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Date of issue:
November 21, 2005 126208R

