

Micronized Progesterone Subdues Hot Flashes

BY DOUG BRUNK

FROM THE ANNUAL MEETING OF THE ENDOCRINE SOCIETY

SAN DIEGO — Postmenopausal women who took oral micronized progesterone for 12 weeks had significant improvements in vasomotor symptom scores as well as significant reductions in the number of daily vasomotor symptoms, results from a randomized, placebo-controlled trial showed.

"If we know that progestin works, why would we investigate oral micronized progesterone?" mused Dr.

Jerilynn C. Prior of the Centre for Menstrual Cycle and Ovulation Research at the University of British Columbia, Vancouver, at the meeting. Firstly, "it's molecularly identical to what our own bodies make, so we can make clear inferences about the metabolism of this hormone in our bodies." Also, it's approved by the Food and Drug Administration, and it has been shown in randomized controlled trials to improve sleep and cause no problems with cognition.

During June 2003 through October 2009, she and Christine Hitchcock, Ph.D., recruited 133 healthy postmenopausal women seeking hormone therapy for hot flashes and night sweats and randomized them to receive three 100-mg capsules of oral micronized progesterone (Prometrium) or placebo at bedtime



Micronized progesterone is 'molecularly identical to what our own bodies make.'

DR. PRIOR

nightly for 12 weeks. The time since their last menstrual flow was 1-10 years.

Study participants were asked to record the intensity and number of vasomotor symptoms in a daily diary, and the researchers calculated their average daily vasomotor symptom score during the last 28 days of therapy, as well as the average number of vasomotor symptoms they experienced per day.

Women who had been on any kind of hormonal therapy within the previous 6 months were excluded from the trial, as were those with cardiovascular disease at baseline, and those who had difficulty completing the Daily Menopause Diary.

At baseline, the mean age of the 127 women with complete data was 55, their mean body mass index was 25 kg/m², and 91% were white. Their average vasomotor symptom score was 17, and they had an average of 6.8 vasomotor symptoms per day.

At the end of 12 weeks, women in the oral micronized progesterone group had a 56% improvement in vasomotor symptom scores and a 48% reduction in the number of vasomotor symptoms per day, while those in the placebo group had a 28% improvement in vasomotor symptom scores and a 22% reduction in the number of vasomotor symptoms per day.

"Oral micronized progesterone is highly effective therapy for hot flashes and night sweats," Dr. Prior concluded. "We saw no serious side effects in this trial, and there were numerically more dropouts in the placebo arm than in the treatment arm." The investigators are evaluating several other measures collected during the trial, "including what happens when women stop oral micronized progesterone, since we know that some women experience a rebound greater increase when they stop estrogen."

VITALS

Major Finding: Postmenopausal women who took oral micronized progesterone for 12 weeks had a 56% decrease in vasomotor symptoms from baseline, compared with 28% who took placebo.

Data Source: Randomized, placebo-controlled study of 133 postmenopausal women seeking hormonal therapy for hot flashes and night sweats.

Disclosures: The trial was funded by the Centre for Menstrual Cycle and Ovulation Research. Besins Healthcare and Schering Canada donated the progesterone and placebo used in the study.

NovoLog® (insulin aspart [rDNA origin] injection)

Rx only

BRIEF SUMMARY. Please consult package insert for full prescribing information.

INDICATIONS AND USAGE: Treatment of Diabetes Mellitus: NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CONTRAINDICATIONS: NovoLog® is contraindicated during episodes of hypoglycemia and in patients with hypersensitivity to NovoLog® or one of its excipients.

WARNINGS AND PRECAUTIONS: Administration: NovoLog® has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog® should immediately be followed by a meal within 5-10 minutes. Because of NovoLog®'s short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy. Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. As with all insulin preparations, the time course of NovoLog® action may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure. **Needles and NovoLog® FlexPen® must not be shared.** **Hypoglycemia:** Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., patients who are fasting or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Rapid changes in serum glucose levels 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 longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycemia. **Hypokalemia:** All insulin products, including NovoLog®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin). **Renal Impairment:** As with other insulins, the dose requirements for NovoLog® may be reduced in patients with renal impairment. **Hepatic Impairment:** As with other insulins, the dose requirements for NovoLog® may be reduced in patients with hepatic impairment. **Hypersensitivity and Allergic Reactions: Local Reactions -** As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog® injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog®. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog®. **Systemic Reactions -** Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog®. Anaphylactic reactions with NovoLog® have been reported post-approval. Generalized allergy to insulin may also cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. In controlled clinical trials, allergic reactions were reported in 3 of 735 patients (0.4%) treated with regular human insulin and 10 of 1394 patients (0.7%) treated with NovoLog®. In controlled and uncontrolled clinical trials, 3 of 2341 (0.1%) NovoLog®-treated patients discontinued due to allergic reactions. **Antibody Production:** Increases in anti-insulin antibody titers that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog®. Increases in anti-insulin antibodies are observed more frequently with NovoLog® than with regular human insulin. Data from a 12-month controlled trial in patients with type 1 diabetes suggest that the increase in these antibodies is transient, and the differences in antibody levels between the regular human insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose. **Mixing of Insulins:** Mixing NovoLog® with NPH human insulin immediately before injection attenuates the peak concentration of NovoLog®, without significantly affecting the time to peak concentration or total bioavailability of NovoLog®. If NovoLog® is mixed with NPH human insulin, NovoLog® should be drawn into the syringe first, and the mixture should be injected immediately after mixing. The efficacy and safety of mixing NovoLog® with insulin preparations produced by other manufacturers have not been studied. Insulin mixtures should not be administered intravenously. **Continuous Subcutaneous Insulin Infusion by External Pump: When used in an external subcutaneous insulin infusion pump, NovoLog® should not be mixed with any other insulin or diluent.** When using NovoLog® in an external insulin pump, the NovoLog®-specific information should be followed (e.g., in-use time, frequency of changing infusion sets) because NovoLog®-specific information may differ from general pump manual instructions. Pump or infusion set malfunctions or insulin degradation can lead to a rapid onset of hyperglycemia and ketosis because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly

absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required [see Warnings and Precautions]. NovoLog® should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog® that will be used in a pump should not be mixed with other insulin or with a diluent [see Warnings and Precautions].**

ADVERSE REACTIONS: Clinical Trial Experience: Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. **Hypoglycemia:** Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog® [see Warnings and Precautions]. **Insulin initiation and glucose control intensification:** Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy. **Lipodystrophy:** Long-term use of insulin, including NovoLog®, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. **Weight gain:** Weight gain can occur with some insulin therapies, including NovoLog®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. **Peripheral Edema:** Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. **Frequencies of adverse drug reactions:** The frequencies of adverse drug reactions during NovoLog® clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (Adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

Preferred Term	NovoLog® + NPH N= 596		Human Regular Insulin + NPH N= 286	
	N	(%)	N	(%)
Hypoglycemia*	448	75%	205	72%
Headache	70	12%	28	10%
Injury accidental	65	11%	29	10%
Nausea	43	7%	13	5%
Diarrhea	28	5%	9	3%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL with or without symptoms.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

	NovoLog® + NPH N= 91		Human Regular Insulin + NPH N= 91	
	N	(%)	N	(%)
Hypoglycemia*	25	27%	33	36%
Hyporeflexia	10	11%	6	7%
Onychomycosis	9	10%	5	5%
Sensory disturbance	8	9%	6	7%
Urinary tract infection	7	8%	6	7%
Chest pain	5	5%	3	3%
Headache	5	5%	3	3%
Skin disorder	5	5%	2	2%
Abdominal pain	5	5%	1	1%
Sinusitis	5	5%	1	1%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms.

Postmarketing Data: The following additional adverse reactions have been identified during postapproval use of NovoLog®. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog® have been identified during postapproval use.

OVERDOSAGE: Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. 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. Hypokalemia must be corrected appropriately.

More detailed information is available on request.

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Manufactured by Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

For information about NovoLog® contact: Novo Nordisk Inc., Princeton, New Jersey 08540 1-800-727-6500 www.novonordisk-us.com

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NovoLog® is covered by US Patent Nos. 5,618,913, 5,866,538, and other patents pending.

FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,004, and other patents pending.

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