

Rifaximin Approved for Hepatic Encephalopathy

BY ELIZABETH MEHCATIE

The Food and Drug Administration has approved the oral antibiotic rifaximin as a treatment to reduce the risk of developing episodes of overt hepatic encephalopathy in adults with chronic liver disease, making this the second drug approved for this indication.

Approved in 2004 for treating travelers' diarrhea caused by noninvasive strains of

Escherichia coli in people aged 12 and older, rifaximin is a poorly absorbed oral antibiotic derived from rifamycin, and has a broad spectrum of activity against gram-positive and gram-negative, aerobic and anaerobic enteric bacteria.

Rifaximin reduces levels of gut-derived neurotoxins such as ammonia, which is known to cause hepatic encephalopathy in patients with hepatic impairment, according to the manufac-

turer, Salix Pharmaceuticals, which markets the drug as Xifaxan.

The approval is for "reduction in risk of overt hepatic encephalopathy recurrence" in patients aged 18 and older. The approved dosage is one 550-mg tablet taken orally twice a day, with or without food.

Approval was based on a study comparing treatment with rifaximin to placebo in 299 patients with advanced liver

disease. The study was published on March 25, the same day that the FDA announced the approval (N. Engl. J. Med. 2010;362:1071-81).

During the 6-month study, 31 of 140 patients (22%) on rifaximin and 73 of 159 (46%) on placebo had a breakthrough episode, a significant difference that represented a nearly 60% reduction in risk. Secondary end points, including the risk of hepatic encephalopathy-related hospitalizations, also were significantly reduced among those on rifaximin.

Based on the findings, the FDA's Gastrointestinal Drugs Advisory Committee voted 14-4 in February that the risk-benefit profile of rifaximin supported its approval for this indication. The panelists supporting approval emphasized that the drug's labeling should clearly inform prescribers that most of the patients (91%) who participated in the study submitted for approval were also being treated with lactulose, a drug approved in the 1970s for the indication, and that most had Child-Pugh class A or B cirrhosis.

The safety of rifaximin was uncertain when used for more severe liver disease, as was its efficacy as a single agent.

During their meeting in Silver Spring, Md., panelists said that if the drug was approved, these questions would need to be addressed in postmarketing studies, which should evaluate the safety of the drug in patients with more severe disease, those with Child-Pugh class C cirrhosis or a model for end-stage liver disease (MELD) score above 25.

The safety of chronic treatment, including the effects of long-term use on the gut flora, also was unclear, and should be studied further if the drug was approved, panelists said. Also, the clinical trial conducted by the manufacturer for this indication was for 6 months, but treatment is expected to continue until the patient undergoes a liver transplant or dies. The longest follow-up that Salix has done is an average of 1 year in patients followed in an extension study.

These concerns were reflected in the revised label, which states in the warning and precautions section that the drug should be used "with caution" in patients with severe (Child-Pugh C) hepatic impairment. The label also says that *Clostridium difficile*-associated diarrhea should be considered if a patient develops diarrhea during treatment and it does not improve or gets worse.

In the randomized, controlled study of 299 patients with advanced liver disease, treatment with rifaximin at a dose of 550 mg twice a day was compared with placebo. In the study, conducted by Dr. Nathan M. Bass of the University of California, San Francisco, and his associates, most of the patients were white, and the average age was 56 years. Patients were treated at 70 medical centers in the United States, Russia, and Canada starting in 2005.

Participants had Conn scores of 0 (two-thirds of the patients) or 1. They had had at least two episodes of hepatic

Reference: 1. IMS Health Inc. National Sales Perspectives (12 months ending December 2008).

NovoLog® (insulin aspart [rDNA origin] injection)

Rx only

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

INDICATIONS AND USAGE: 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 hypersensitive 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.

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 [see *Clinical Pharmacology*]. 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 [see *Drug Interactions*]. 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 [see *Drug Interactions*]. 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 [see *Clinical Pharmacology*].

Hepatic Impairment: As with other insulins, the dose requirements for NovoLog® may be reduced in patients with hepatic impairment [see *Clinical Pharmacology*]. **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. **Subcutaneous continuous 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 *Dosage and Administration, Warnings and Precautions, How Supplied/Storage and Handling, and Patient Counseling Information*]. NovoLog® is recommended for use in pump systems suitable for insulin infusion as listed below. **Pumps:** MiniMed 500 series and other equivalent pumps. **Reservoirs and infusion sets:** NovoLog® is recommended for use in reservoir and infusion sets that are compatible with insulin and the specific pump. In-vitro studies

have shown that pump malfunction, loss of metacresol, and insulin degradation, may occur when NovoLog® is maintained in a pump system for longer than 48 hours. Reservoirs and infusion sets should be changed at least every 48 hours. 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 *Dosage and Administration, Warnings and Precautions and How Supplied/Storage and Handling, Patient Counseling Information*].

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 lipoatrophy (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. See *Clinical Studies* for the incidence of serious hypoglycemia in the individual clinical trials.

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. See *Clinical Studies* for the incidence of serious hypoglycemia in the individual clinical trials.

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 [see *Patient Counseling Information*].

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

Manufactured for Novo Nordisk Inc., Princeton, New Jersey 08540

www.novonordisk-us.com

NovoLog® is a registered trademark of Novo Nordisk A/S.

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

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NovoLog®
insulin aspart (rDNA origin) injection

Continued on following page

Continued from previous page

encephalopathy, defined as a Conn score of at least 2, in the previous 6 months.

The 5-point Conn grading system is based on a clinician's subjective assessment, a concern raised by FDA reviewers. A score of 0 indicates that no abnormality was detected, whereas a score of 1 indicates trivial lack of awareness, shortened attention span, impaired addition or subtraction, euphoria, or anxiety. A score of 2 is used to indicate lethargy or apathy, disorientation to time, obvious personality change, and/or inappropriate behavior, and a score of 4 indicates coma (unable to test mental state).

Neurologic impairment was also evaluated with the Asterix score, which ranges from grade 0 (no tremors) and grade 1 (rare flapping motions) to grade 2 (occasional, irregular flaps), grade 3 (frequent flaps), and grade 4 (almost continuous flapping motions).

The primary end point was the time

to first breakthrough overt hepatic encephalopathy episode, defined as an increase of the Conn score to a 2 or higher, or an increase in the Conn score and Asterix grade of 1 each among those with a baseline Conn score of 0.

The active drug also reduced the relative risk for hospitalization by 50%. Hospitalization involving hepatic encephalopathy was reported for 13.6% of patients on rifaximin and 22.6% of those on placebo.

Mortality was 6% (9 of 140) with rifaximin and 7% (11 of 159) with placebo; deaths were due mostly to worsen-

ing hepatic function and progression of the underlying disease.

Since the drug was approved more than 5 years ago for traveler's diarrhea, there have been five postmarketing reports of *C. difficile* colitis associated with rifaximin treatment, including one death, according to the FDA.

In addition, anaphylaxis has been identified as a notable adverse effect in postmarketing reports, and this risk is now included in the drug's label.

"These data suggest that four patients would need to be treated with rifaximin for 6 months to prevent one episode of

overt hepatic encephalopathy," Dr. Bass and his colleagues said. First approved in Italy in 1985, rifaximin is now approved in 33 countries for various GI uses, including hepatic encephalopathy and adjunctive treatment of hyperammonemia, according to the manufacturer. ■

Disclosures: The study was supported by Salix Pharmaceuticals. Dr. Bass reported receiving consulting, advisory, and lecture fees from Salix. Members of FDA advisory panels have been cleared for potential conflicts of interest related to the topic under review prior to the meeting.

Try Lactulose, Then Rifaximin

Hepatic encephalopathy, a frequent complication for patients with cirrhosis, results in disability that is generally recognized as episodes of overt confusion. Minimal hepatic encephalopathy from cirrhosis may be more difficult to recognize, because it produces less-overt complications such as impaired driving and automobile accidents.



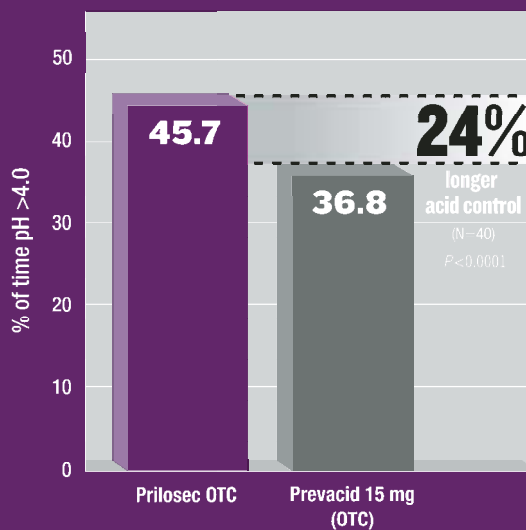
Lactulose, a nonabsorbable disaccharide that alters colonic pH and bowel frequency, has been the mainstay of therapy for hepatic encephalopathy, although the laxative effect of lactulose can be a problem for some patients. Rifaximin, an antibiotic with limited absorption, reduces the frequency of episodes of hepatic encephalopathy in patients with cirrhosis and thus offers another therapeutic option.

Given the associated cost savings, I typically use lactulose as first-line therapy for most patients with hepatic encephalopathy, and reserve rifaximin for those who are poorly controlled or who develop significant GI side effects from lactulose.

ROWEN K. ZETTERMAN, M.D., a gastroenterologist, is dean of the school of medicine at Creighton University, Omaha, Neb. He reported no relevant conflicts of interest.

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For more information, visit www.prilosecOTC-hcp.com.

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