# **Clinical Pharmacology Review**

# Memo to File

NDA:	20-986 (S047)
Drug:	Novolog (Insulin aspart [rDNA origin] injection) solution for subcutaneous use
Sponsor:	Novo Nordisk
Submission Date:	5/11/2007
Indication:	To improve glycemic control in adults and children with diabetes mellitus
<b>Reviewer:</b>	Jayabharathi Vaidyanathan, Ph.D
Team Leader:	Sally Choe, Ph.D

**Recommendations:** The information in NDA 20-986/S047 (Novolog) was reviewed by the Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2). The following labeling comments were sent to the sponsor.

(Strikeout text should be removed from labeling and <u>underlined text</u> should be added to labeling.)

### 7 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-glucoselowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, 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), atypical antipsychotics.
- 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.
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine

## 12 CLINICAL PHARMACOLOGY

### 12.1 Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that subcutaneous administration of NovoLog<sup>®</sup> has a more rapid onset of action than regular human insulin.

In a study in patients with type 1 diabetes (n=22), the maximum glucose-lowering effect of NovoLog<sup>®</sup> occurred between 1 and 3 hours after subcutaneous injection (see Figure 2). The duration of action for NovoLog<sup>®</sup> is 3 to 5 hours <del>compared to 5 to 8 hours for regular human insulin</del>. The time course of action of insulin and insulin analogs such as NovoLog<sup>®</sup> may vary considerably in different individuals or within the same individual. The parameters of NovoLog<sup>®</sup> activity (time of onset, peak time and duration) as designated in Figure 2 should be considered only as general guidelines. The rate of insulin absorption and onset of activity is affected by the site of injection, exercise, and other variables [*see Warnings and Precautions (5.1)*].

### **Specific Populations**

*Obesity* - <u>A single subcutaneous dose of 0.10 U/kg NovoLog<sup>®</sup> was administered in a study</u> In a study of 23 patients with type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m<sup>2</sup>). <u>Thethe</u> pharmacokinetic parameters, AUC and Cmax, of NovoLog<sup>®</sup> were generally unaffected by BMI in the different groups – BMI 19-23 kg/m<sup>2</sup> (N=4); BMI 23-27 kg/m<sup>2</sup> (N=7); BMI 27-32 kg/m<sup>2</sup> (N=6) and BMI >32 kg/m<sup>2</sup> (N=6). Clearance of NovoLog<sup>®</sup> was reduced by 28% in patients with BMI >32 kg/m<sup>2</sup> compared to patients with BMI <23 kg/m<sup>2</sup>

**Renal Impairment** - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of 0.08 U/kg NovoLog<sup>®</sup> was administered in a study to subjects with either normal (N=6) creatinine clearance (CLcr) (> 80 ml/min) or mild (N=7; CLcr = 50-80 ml/min), moderate (N=3; CLcr = 30-50 ml/min) severe (N=2; CLcr = <30 ml/min) renal impairment. of 18 patients with creatinine clearance values ranging from normal to <30 mL/min and not requiring hemodialysis. No apparent effect of creatinine clearance values on AUC and Cmax of NovoLog<sup>®</sup> was found. However, only 2 patients with severe renal impairment were studied (<30 mL/min). Careful glucose monitoring and dose adjustments of insulin, including NovoLog<sup>®</sup>, may be necessary in patients with renal dysfunction [see Warnings and Precautions (5.5)].

*Hepatic Impairment* - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. <u>A single subcutaneous dose of 0.06 U/kg NovoLog<sup>®</sup> was administered in</u> an open-label, single-dose study of 24 patients subjects (N=6/group) with different degree of hepatic impairment (mild, moderate and severe) having Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment). <u>No no</u> correlation was found between the degree of hepatic failure and any NovoLog<sup>®</sup> pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoLog<sup>®</sup>, may be necessary in patients with hepatic dysfunction [*see Warnings and Precautions (5.6)*].

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/s/ Jayabharathi Vaidyanathan 3/17/2008 02:01:48 PM BIOPHARMACEUTICS

Sally Choe 3/25/2008 10:44:17 AM BIOPHARMACEUTICS