Cornerstones4Care™

your blood sugar diary

staying on track

Model is for illustrative purpose only.
This booklet belongs to:
Name
Address
City State ZIP
Phone E-mail

If this booklet is found, please contact the owner listed above. Thank you!

Quotes reflect the opinions of the people quoted and not necessarily those of Novo Nordisk. Novo Nordisk does not verify the information in the quotes. Individual results may vary.
Levemir® (insulin detemir [rDNA origin] injection)

**Indications and Usage:**
Levemir® (insulin detemir [rDNA origin] injection) is a man-made long-acting insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

**Important Safety Information:**
Do not take Levemir® if your blood sugar is too low (hypoglycemia) or if you are allergic to anything in Levemir®. If you take too much Levemir®, your blood sugar may fall too low.

NovoLog® (insulin aspart [rDNA origin] injection)

**Indications and Usage:**
NovoLog® (insulin aspart [rDNA origin] injection) is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

**Important Safety Information:**
Do not take NovoLog® if your blood sugar is too low (hypoglycemia) or if you are allergic to anything in NovoLog®. If you take too much NovoLog®, your blood sugar may fall too low.

NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

**Indications and Usage:**
NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]) is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus.

It is not known if NovoLog® Mix 70/30 is safe or effective in children.

**Important Safety Information:**
Do not take NovoLog® Mix 70/30 if your blood sugar is too low (hypoglycemia) or if you are allergic to any of the ingredients in NovoLog® Mix 70/30. If you take too much NovoLog® Mix 70/30, your blood sugar may fall too low (hypoglycemia).

For more information about Novo Nordisk products for diabetes care, please go to Cornerstones4Care.com and click on Diabetes Medicines.

Please see Important Safety Information on pages 36–39 and Prescribing Information on pages 43–98.
Make sure you’re on the right track

Keeping a close eye on your blood sugar levels can give you and your diabetes care team a good idea of how well your diabetes medicine is working. So it’s important to check your blood sugar as directed by your diabetes care team. Remember to write down the results and share this information with your diabetes care team at your next office visit.

Using the blood sugar diary and sharing the results with your diabetes care team can help you adjust your medicine as needed to help you reach your blood sugar goal.

To order a new blood sugar diary, please call 1-800-727-6500.

You can learn more about checking your blood sugar and staying on track at Cornerstones4Care.com. Plus, when you enroll in the Cornerstones4Care™ program, you will have access to online tools and resources and receive ongoing support.

For more information about Novo Nordisk products for diabetes care, please go to Cornerstones4Care.com and click on Diabetes Medicines.

Please see Important Safety Information on pages 36–39 and Prescribing Information on pages 43–98.

How to use your diary

The table below lists blood sugar goals for people with diabetes. You and your diabetes care team will set the goals that are right for you. Write your goals in the last column.

<table>
<thead>
<tr>
<th>Time</th>
<th>Goals for people with diabetes</th>
<th>Your goals</th>
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<tbody>
<tr>
<td>Before meals</td>
<td>70 to 130 mg/dL</td>
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<td>1 to 2 hours after the start of a meal</td>
<td>Less than 180 mg/dL</td>
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<td>A1C</td>
<td>Less than 7%</td>
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“Every part of my day gets put down in my journal. This helps me see patterns and talk to my doctor about them.”

– Thelma M, New Mexico

“Monitoring your blood sugar and eating habits truly makes each of us a winner in all aspects of our diabetes care. I have had diabetes for approximately 43 years and lead a ‘close-to-normal’ life.”

– Carolyn P, Arizona

If you check your blood sugar and it is too low, you should not take your insulin. Ask your diabetes care team how often you should check your blood sugar and what to do if it is high or low.
Here’s how to use the blood sugar diary:

1. Write down the date
2. Write the time you took your diabetes medicine
3. Write the type and amount of your diabetes medicine
4. Write the time and your blood sugar readings in the “before” and “after” spaces. After-meal readings are usually taken 1 to 2 hours after you start your meal

5. If your doctor suggests ketone testing, write your ketone test results here
6. If you are counting carbs, write how many grams of carbs you ate
7. Write how many minutes of physical activity you did
8. Write notes about anything that might have affected your blood sugar readings, such as the food you ate, any physical activity you did, or any stress you might be under

9. Use the last row to record your latest A1C levels, along with the date of the check

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Your blood sugar diary

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*You and your diabetes care team will decide the best times for you to check your blood sugar.

If you’d like to use an online blood sugar diary, you can find one at [Cornerstones4Care.com](https://www.cornerstones4care.com).
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*You and your diabetes care team will decide the best times for you to check your blood sugar.

If you’d like to use an online blood sugar diary, you can find one at Cornerstones4Care.com.
Your blood sugar diary

If you’d like to use an online blood sugar diary, you can find one at Cornerstones4Care.com.

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*You and your diabetes care team will decide the best times for you to check your blood sugar.
**Levemir®**

**Indications and Usage:**
Levemir® (insulin detemir [rDNA origin] injection) is a man-made long-acting insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

**Important Safety Information:**
Do not take Levemir® if your blood sugar is too low (hypoglycemia) or if you are allergic to anything in Levemir®. If you take too much Levemir®, your blood sugar may fall too low.

Check your blood sugar levels. Ask your health care provider what your blood sugars should be and when you should check your blood sugar levels. Alcohol, including beer and wine, may affect your blood sugar when you take Levemir®.

Do not change the type of insulin you use unless told to do so by your health care provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Never mix Levemir® with other insulin products or use in an insulin pump. Needles and Levemir® FlexPen® must not be shared.

Tell your health care provider about all medicines you take and all of your medical conditions, including if you are pregnant or breastfeeding. Your Levemir® dose may change if you take other medicines.

The most common side effect of Levemir® is low blood sugar (hypoglycemia). Other possible side effects include reactions at the injection site (like redness, swelling and itching), and allergic reactions. Get medical help right away if you experience signs of serious allergic reaction such as body rash, trouble with your breathing, fast heartbeat, or sweating. Ask your doctor or pharmacist for further information.

For more information about Novo Nordisk products for diabetes care, please go to Cornerstones4Care.com and click on Diabetes Medicines.

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**NovoLog®**

**Indications and Usage:**
NovoLog® (insulin aspart [rDNA origin] injection) is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

**Important Safety Information:**
Do not take NovoLog® if your blood sugar is too low (hypoglycemia) or if you are allergic to anything in NovoLog®. If you take too much NovoLog®, your blood sugar may fall too low.

NovoLog® is a fast-acting insulin. You should eat a meal within 5 to 10 minutes after using NovoLog® to avoid low blood sugar. Do not inject NovoLog® if you do not plan to eat right after using NovoLog®. Check your blood sugar levels. Ask your health care provider what your blood sugars should be and when you should check your blood sugar levels. Alcohol, including beer and wine, may affect your blood sugar when you take NovoLog®.

Do not change the type of insulin you use unless told to do so by your health care provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Do not mix NovoLog® with any other insulins when used in a pump or with any insulins other than NPH when used with injections by syringe. Needles and NovoLog® FlexPen® must not be shared.

Tell your health care provider about all medicines you take and all of your medical conditions, including if you are pregnant or breastfeeding. Your NovoLog® dose may change if you take other medicines.

NovoLog® has not been studied in children with type 2 diabetes or in children with type 1 diabetes under the age of two.

The most common side effect of NovoLog® is low blood sugar (hypoglycemia). Other possible side effects include reactions at the injection site (like redness, swelling and itching), and allergic reactions. Get medical help right away if you experience signs of serious allergic reaction such as body rash, trouble with your breathing, fast heartbeat, or sweating. Ask your doctor or pharmacist for further information.

*Please see Prescribing Information on pages 43–98.*
Indications and Usage:
NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]) is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus.

It is not known if NovoLog® Mix 70/30 is safe or effective in children.

Important Safety Information:
Do not take NovoLog® Mix 70/30 if your blood sugar is too low (hypoglycemia) or if you are allergic to any of the ingredients in NovoLog® Mix 70/30. If you take too much NovoLog® Mix 70/30, your blood sugar may fall too low (hypoglycemia).

NovoLog® Mix 70/30 starts acting fast. If you have Type 1 diabetes, inject it up to 15 minutes before you eat a meal. If you have Type 2 diabetes, you may inject NovoLog® Mix 70/30 up to 15 minutes before or after starting your meal.

Check your blood sugar levels regularly. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels. Do not make any changes to your dose or type of insulin unless your healthcare provider tells you to. Alcohol, including beer and wine, may affect your blood sugar when you take NovoLog® Mix 70/30.

Before using NovoLog® Mix 70/30, tell your health care provider about all medicines you take and all of your medical conditions, including if you have kidney or liver problems or if you are pregnant or breastfeeding. It is not known if NovoLog® Mix 70/30 will harm your unborn baby or pass into breast milk. Your NovoLog® Mix 70/30 dose may change if you take other medicines.

Do not inject NovoLog® Mix 70/30 with any other insulin products or use in an insulin pump.

Do not share needles, insulin pens or syringes with others.

The most common side effects of NovoLog® Mix 70/30 include skin thickening or pits at the injection site (lipodystrophy), weight gain, swelling of your hands and feet, and vision changes. Serious adverse events may include low blood sugar (hypoglycemia), low potassium in your blood (hypokalemia), local allergic reactions at the injection site (like redness, swelling, and itching), and whole body reactions. Get medical help right away if you have any of these symptoms of an allergic reaction: a rash over the whole body, have trouble breathing, fast heart rate, sweating or if you feel faint.

Ask your health care provider or pharmacist for more information.

For more information about Novo Nordisk products for diabetes care, please go to Cornerstones4Care.com and click on Diabetes Medicines.

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- **Levemir**, NovoLog®, and NovoLog® Mix 70/30 are prescription medications. Talk with your doctor about healthy eating and being active.
- You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088

Talk with your doctor or pharmacist to find out if FlexPen® is right for you. Be sure to consult your doctor regarding your individual treatment plan.

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Please see Prescribing Information on pages 43–98.
Insulin delivery that’s going places, just like you

Uses NovoTwist® 32G Tip needles, our thinnest needle available*

Prefilled, ready to use in just a few steps

Available in three different insulin analogs:
Levemir®, NovoLog®, or NovoLog® Mix 70/30

Large, clear scale
Accurate dose adjustment
Push-button injection

FlexPen®—a discreet, prefilled, dial-a-dose insulin pen.

Things to know about FlexPen®:

- **Discreet**—Fits neatly in your pocket or purse
- **Prefilled with insulin**—No need to draw from a vial
- **Accurate**—Dial the exact dose of insulin you need
- **Ready**—In just a few steps, FlexPen® is ready-to-use
- **On the go**—Take FlexPen® with you almost everywhere

Ask your doctor about FlexPen® today to see if it’s right for you.

Be sure to consult your doctor regarding your individual treatment plan.

To learn more about a money-saving offer for FlexPen®, please register at Cornerstones4care.com.†

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

If you need assistance with prescription drug costs, help may be available. Visit pparx.org or call 1-888-4PPA-NOW.

*Needles are sold separately and may require a prescription in some states.

†Restrictions may apply. See site for full details.

Please see Important Safety Information on pages 36–39 and Prescribing Information on pages 43–98.
Support online

Enjoy the benefits and support of the free Cornerstones4Care™ program. Simply enroll online at Cornerstones4Care.com. You’ll be able to take advantage of all sorts of tools for managing your diabetes, including an online blood sugar diary and a My Priorities tool to help you create a personalized action plan. Don’t miss this chance. Join today!

DESCRIPTION
LEVEMIR® (insulin detemir [rDNA origin] injection) is a sterile solution of insulin detemir for use as an injection. Insulin detemir is a long-acting basal insulin analog, with up to 24 hours duration of action, produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae followed by chemical modification.

Insulin detemir differs from human insulin in that the amino acid threonine in position B30 has been omitted, and a C14 fatty acid chain has been attached to the amino acid B29. Insulin detemir has a molecular formula of C267H402O76N64S6 and a molecular weight of 5916.9. It has the following structure:

![Structure of LEVEMIR](image)

LEVEMIR® is a clear, colorless, aqueous, neutral sterile solution. Each milliliter of LEVEMIR® contains 100 U (14.2 mg/mL) insulin detemir, 65.4 mcg zinc, 2.06 mg m-cresol, 16.0 mg glycerol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride, and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. LEVEMIR® has a pH of approximately 7.4.

CLINICAL PHARMACOLOGY
Mechanism of Action
The primary activity of insulin detemir is the regulation of glucose metabolism. Insulins, including insulin detemir, exert their specific action through binding to insulin receptors.

Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

Pharmacodynamics
Insulin detemir is a soluble, long-acting basal human insulin analog with a relatively flat action profile. The mean duration of action of insulin detemir ranged from 5.7 hours at the lowest dose to 23.2 hours at the highest dose (sampling period 24 hours).

The prolonged action of LEVEMIR® is mediated by the slow systemic absorption of insulin detemir molecules from the injection site due to strong self-association of the drug molecules and albumin binding. Insulin detemir is distributed more slowly to peripheral target tissues since insulin detemir in the bloodstream is highly bound to albumin.

Figure 1 shows glucose infusion rate results from a glucose clamp study in patients with type 1 diabetes.

Figure 1: Activity Profiles in Patients with Type 1 Diabetes in a 24-hour Glucose Clamp Study

<table>
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<tr>
<th>Pharmacodynamic Parameters for LEVEMIR® and NPH</th>
<th>LEVEMIR®</th>
<th>NPH</th>
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<tbody>
<tr>
<td>Dose (U/kg)</td>
<td>0.2 U/kg</td>
<td>0.4 U/kg</td>
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<tr>
<td>AUCcorr (mg·h/kg)</td>
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<td>GIIcorr (mg·h/kg/min)</td>
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Figure 2 shows glucose infusion rate results from a 16-hour glucose clamp study in patients with type 2 diabetes. The clamp study was terminated at 16 hours according to protocol.

**Figure 2: Activity Profiles in Patients with Type 2 Diabetes in a 16-hour Glucose Clamp Study**

For doses in the interval of 0.2 to 0.4 U/kg, LEVEMIR® exerts more than 50% of its maximum effect from 3 to 4 hours up to approximately 14 hours after dose administration.

In a glucose clamp study, the overall glucodynamic effect (AUCGIR 0-24h) [mean mg/kg ± SD (CV)] of four separate subcutaneous injections in the thigh was 1702.6 ± 489 mg/kg (29%) in the LEVEMIR® group and 1922.8 ± 765 mg/kg (46%) for NPH. The clinical significance of this difference has not been established.

**Pharmacokinetics**

Absorption

After subcutaneous injection of insulin detemir in healthy subjects and in patients with diabetes, insulin detemir serum concentrations indicated a slower, more prolonged absorption over 24 hours in comparison to NPH human insulin. Maximum serum concentration (C_max) is reached between 6 and 8 hours after administration. The absolute bioavailability of insulin detemir is approximately 60%.

Distribution and Elimination

More than 98% insulin detemir in the bloodstream is bound to albumin. LEVEMIR® has a small apparent volume of distribution of approximately 0.1 L/kg. LEVEMIR®, after subcutaneous administration, has a terminal half-life of 5 to 7 days (40%) for NPH. The clinical significance of this difference has not been established.

**Special Populations**

- **Children and Adolescents:** The pharmacokinetic properties of LEVEMIR® were investigated in children (6 to 12 years) and adolescents (13 to 17 years) and adults with type 1 diabetes. Similar to NPH human insulin, slightly higher plasma Area Under the Curve (AUC) and C_max were observed in children by 10% and 24%, respectively, compared to adolescents and adults. There was no difference in pharmacokinetics between adolescents and adults.

- **Geriatrics:** In a clinical trial investigating differences in pharmacokinetics of a single subcutaneous dose of LEVEMIR® in young (25 to 35 years) versus elderly (≥ 68 years) healthy subjects, higher insulin AUC levels (up to 30%) were found in elderly subjects due to a reduced clearance. As with other insulin preparations, LEVEMIR® should always be titrated according to individual requirements.

- **Gender:** In controlled clinical trials, no clinically relevant difference between genders is seen in pharmacokinetic parameters based on subgroup analyses.

- **Race:** In two trials in healthy Japanese and Caucasian subjects, there were no clinically relevant differences seen in pharmacokinetic parameters. Pharmacokinetics and pharmacodynamics of LEVEMIR® were investigated in a clamp trial comparing patients with type 2 diabetes of Caucasian, African-American, and Latino origin. Dose-response relationships were comparable for LEVEMIR® in these three populations.

- **Renal impairment:** Individuals with renal impairment showed no difference in pharmacokinetic parameters as compared to healthy volunteers. However, literature reports have shown that clearance of human insulin is decreased in renally impaired patients. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

- **Hepatic impairment:** Individuals with severe hepatic dysfunction, without diabetes, were observed to have lower AUCs as compared to healthy volunteers. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

**Table 1: Efficacy and Insulin Dosage in Type 1 Diabetes Mellitus - Adult**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Treatment in combination with</td>
<td>LEVEMIR®</td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>276</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.30</td>
</tr>
<tr>
<td>End of study adjusted mean</td>
<td>7.66</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-0.64</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>202.0</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>10.80</td>
</tr>
<tr>
<td>Daily Basal Insulin Dose (U/kg)</td>
<td>0.36</td>
</tr>
<tr>
<td>Presudy mean</td>
<td>0.39</td>
</tr>
<tr>
<td>End of study mean</td>
<td>0.40</td>
</tr>
<tr>
<td>Daily Bolus Insulin Dose (U/kg)</td>
<td>0.40</td>
</tr>
<tr>
<td>Presudy mean</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Baseline values were included as covariates in an ANCOVA analysis.

**CLINICAL STUDIES**

**Type 1 Diabetes – Adult**

In one non-blinded clinical study (Study A, n=409), adult patients with type 1 diabetes were randomized to treatment with either LEVEMIR® at 12-hour intervals, LEVEMIR® morning and bedtime or NPH human insulin morning and bedtime. Insulin aspart was also administered before each meal. At 16 weeks of treatment, the combined LEVEMIR®-treated patients had similar HbA1c and fasting plasma glucose (FGP) reductions to NPH-treated patients (Table 1). Differences in timing of LEVEMIR® administration (or flexible dosing) had no effect on HbA1c, FPG, body weight, or risk of having hypoglycemic episodes.

Overall glycemic control achieved with LEVEMIR® was compared to that achieved with insulin glargine in a randomized, non-blinded, clinical study (Study B, n=320) in which patients with type 1 diabetes were treated for 26 weeks with either twice-daily (morning and bedtime) LEVEMIR® or once-daily (bedtime) insulin glargine. Insulin aspart was administered before each meal. LEVEMIR®-treated patients had a decrease in HbA1c similar to that of insulin glargine-treated patients.

In a randomized, controlled clinical study (Study C, n=749), patients with type 1 diabetes were treated with once-daily (bedtime) LEVEMIR® or NPH human insulin, both in combination with human soluble insulin before each meal for 6 months. LEVEMIR® and NPH human insulin had a similar effect on HbA1c.

**Type 1 Diabetes – Pediatric**

In a non-blinded, randomized, controlled clinical study (Study D, n=347), pediatric patients (age range 6 to 17) with type 1 diabetes were treated for 26 weeks with a basal-bolus insulin regimen. LEVEMIR® and NPH human insulin were administered once- or twice-daily (bedtime or morning and bedtime) according to pretrial dose regimen. Bolus insulin aspart was administered before each meal. LEVEMIR®-treated patients had a decrease in HbA1c similar to that of NPH human insulin.

**Pregnancy:** The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LEVEMIR® has not been studied (see PRECAUTIONS, Pregnancy).

**Smoking:** The effect of smoking on the pharmacokinetics and pharmacodynamics of LEVEMIR® has not been studied.
In a 24-week, non-blinded, randomized, clinical study (Study F, n=476), LEVEMIR® administered twice-daily (before breakfast and evening) was compared to a similar regimen of NPH human insulin as part of a regimen of combination therapy with one or two of the following oral antidiabetes agents (metformin, insulin secretagogue, or alpha-glucosidase inhibitor). LEVEMIR® and NPH similarly lowered HbA1c from baseline (Table 3).

### Table 3: Efficacy and Insulin Dosage in Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment duration</th>
<th>Treatment in combination with</th>
<th>Number of subjects treated</th>
<th>LEVEMIR® Mean change from baseline</th>
<th>NPH Mean change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>24 weeks</td>
<td>OAD</td>
<td>237</td>
<td>-8.54</td>
<td>-8.21</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td>239</td>
<td>0.72</td>
<td>-0.90</td>
</tr>
</tbody>
</table>

In a 22-week, non-blinded, randomized, clinical study (Study F, n=395) in adults with Type 2 diabetes, LEVEMIR® and NPH human insulin were given once or twice-daily as part of a basal-bolus regimen. As measured by HbA1c or FPG, LEVEMIR® had efficacy similar to NPH human insulin.

### INDICATIONS AND USAGE

LEVEMIR® is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.

### CONTRAINDICATIONS

LEVEMIR® is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.
Systemic allergy: Generalized allergy to insulin, which is less common but potentially more serious, 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.

Intercurrent Conditions

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or other stresses.

Information for Patients

LEVEMIR® must only be used if the solution appears clear and colorless with no visible particles (see DOSAGE AND ADMINISTRATION, Preparation and Handling). Patients should be informed about potential risks and advantages of LEVEMIR® therapy, including the possible side effects. Patients should 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 dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LEVEMIR® “Patient Information” circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy (see PRECAUTIONS, Pregnancy).

Laboratory Tests

As with all insulin therapy, the therapeutic response to LEVEMIR® should be monitored by periodic blood glucose tests. Periodic measurement of HbA1c is recommended for the monitoring of long-term glycemic control.

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 reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

The following are examples of substances that may increase the blood-glucose-lowering effect of insulin and susceptibility to hypoglycemia: oral anti diabetic drugs, ACE inhibitors, diisopropyl, lactates, fluoxetine, MAO inhibitors, propoxyphene, sulfonamide antibiotics.

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 medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

The results of in-vitro and in-vivo protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs.

Mixing of Insulins

If LEVEMIR® is mixed with other insulin preparations, the profile of action of one or both individual components may change. Mixing LEVEMIR® with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in AUC(0-2h) and C max for insulin aspart compared to separate injections when the ratio of insulin aspart to LEVEMIR® was less than 50%.

LEVEMIR® should NOT be mixed or diluted with any other insulin preparations.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the in-vitro reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the in-vivo mouse micronucleus test.

Pregnancy: Teratogenic Effects: Pregnancy Category C

In a fertility and embryofetal development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder

Table 4: Safety Information on Clinical Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th># of subjects</th>
<th>Baseline</th>
<th>End of treatment</th>
<th>Major**</th>
<th>Minor***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study A</td>
<td>LEVEMIR®</td>
<td>115</td>
<td>70.0</td>
<td>0.045</td>
<td>2.184</td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td>115</td>
<td>70.1</td>
<td>0.035</td>
<td>3.063</td>
</tr>
<tr>
<td>Study C</td>
<td>LEVEMIR®</td>
<td>115</td>
<td>70.5</td>
<td>0.029</td>
<td>2.397</td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td>115</td>
<td>70.4</td>
<td>0.027</td>
<td>2.564</td>
</tr>
<tr>
<td>Study D</td>
<td>LEVEMIR®</td>
<td>323</td>
<td>N/A</td>
<td>0.076</td>
<td>2.677</td>
</tr>
<tr>
<td>Pediatric</td>
<td>NPH</td>
<td>115</td>
<td>N/A</td>
<td>0.053</td>
<td>3.203</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study E</td>
<td>LEVEMIR®</td>
<td>237</td>
<td>82.7</td>
<td>0.001</td>
<td>0.396</td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td>237</td>
<td>82.3</td>
<td>0.006</td>
<td>0.595</td>
</tr>
<tr>
<td>Study F</td>
<td>LEVEMIR®</td>
<td>195</td>
<td>81.8</td>
<td>0.003</td>
<td>0.193</td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td>200</td>
<td>82.0</td>
<td>0.006</td>
<td>0.235</td>
</tr>
</tbody>
</table>

* See CLINICAL STUDIES section for description of individual studies
** Major = requires assistance of another individual because of neurologic impairment
*** Minor = plasma glucose <56 mg/dl, subject able to deal with the episode himself/herself

Nursing mothers

It is unknown whether LEVEMIR® is excreted in significant amounts in human milk. For this reason, caution should be exercised when LEVEMIR® is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

Pediatric use

In a controlled clinical study, HbA1c concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR® and patients treated with NPH human insulin.

Geriatric use

Of the total number of subjects in intermediate and long-term clinical studies of LEVEMIR®, 85 (type 1 studies) and 363 (type 2 studies) were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

ADVERSE REACTIONS

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

Body as Whole: allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages: lipodystrophy, pruritus, rash. Mild injection site reactions occurred more frequently with LEVEMIR® than with NPH human insulin and usually resolved in a few hours to a few weeks (see PRECAUTIONS, Allergy).

Other:

Hypoglycemia: (see WARNINGS and PRECAUTIONS).

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, the incidence of severe hypoglycemia with LEVEMIR® was comparable to the incidence with NPH, and, as expected, greater overall in patients with type 1 diabetes (Table 4).

Weight gain:

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, LEVEMIR® was associated with somewhat less weight gain than NPH (Table 4). Whether these observed differences represent true differences in the effects of LEVEMIR® and NPH insulin is not known, since these trials were not blinded and the protocols (e.g., diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences has not been established.
**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. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

**DOSAGE AND ADMINISTRATION**

LEVEMIR® can be administered once- or twice-daily. The dose of LEVEMIR® should be adjusted according to blood glucose measurements. The dosage of LEVEMIR® should be individualized based on the patient’s advice, in accordance with the needs of the patient.

- For patients treated with LEVEMIR® once-daily, the dose should be administered with the evening meal or at bedtime.
- For patients who require twice-daily dosing for effective blood glucose control, the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose.

LEVEMIR® should be administered by subcutaneous injection in the thigh, abdominal wall, or upper arm. Injection sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

**Dose Determination for LEVEMIR®**

- For patients with type 1 or type 2 diabetes on basal-bolus treatment, changing the basal insulin to LEVEMIR® can be done on a unit-to-unit basis. The dose of LEVEMIR® should then be adjusted to achieve glycemic targets. In some patients with type 2 diabetes, more LEVEMIR® may be required than NPH insulin. In a clinical study, the mean dose at end of treatment was 0.77 U/kg for LEVEMIR® and 0.52 U/kg for NPH human insulin (see Table 3).
- For patients currently receiving only basal insulin, changing the basal insulin to LEVEMIR® can be done on a unit-to-unit basis.
- For insulin-naïve patients with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs, LEVEMIR® should be started at a dose of 0.1 to 0.2 U/kg once-daily in the evening or 10 units once- or twice-daily, and the dose adjusted to achieve glycemic targets.
- As with all insulins, close glucose monitoring is recommended during the transition and in the initial weeks thereafter. Dose and timing of concurrent short-acting insulins or other concomitant antidiabetic treatment may need to be adjusted.

**Preparation and Handling**

LEVEMIR® should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

LEVEMIR® should not be mixed or diluted with any other insulin preparations.

After each injection, patients must remove the needle without recapping and dispose of it in a puncture-resistant container. Used syringes, needles, or lancets should be placed in “sharps” containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

**HOW SUPPLIED**

LEVEMIR® is available in the following package sizes: each presentation containing 100 Units of insulin detemir per mL (U-100).

- 10 mL vial
  - NDC 0169-3687-12
- 3 mL PenFill® cartridges
  - NDC 0169-3305-11
- 3 mL InnoLet®
  - NDC 0169-2312-11
- 3 mL FlexPen®
  - NDC 0169-6439-10

*LEVEMIR® PenFill® cartridges are for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles.

**RECOMMENDED STORAGE**

Unused LEVEMIR® should be stored between 2° and 8°C (36°F to 46°F). Do not freeze. Do not use LEVEMIR® if it has been frozen.

**Vials:**

After initial use, vials should be stored in a refrigerator, never in a freezer. If refrigeration is not possible, the in-use vial can be kept unrefrigerated at room temperature, below 30°C (86°F), for up to 42 days, as long as it is kept as cool as possible and away from direct heat and light.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

**PenFill® cartridges, FlexPen® or InnoLet®:**

After initial use, a cartridge (PenFill®) or a prefilled syringe (including FlexPen® or InnoLet®) may be used for up to 42 days if it is kept at room temperature, below 30°C (86°F). In-use cartridges and prefilled syringes in-use must NOT be stored in a refrigerator and must NOT be stored with the needle in place. Keep all cartridges and prefilled syringes away from direct heat and sunlight.

Not in-use (unopened) LEVEMIR® PenFill®, FlexPen® or InnoLet® can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused cartridges and prefilled syringes in the carton so they will stay clean and protected from light.

The storage conditions are summarized in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Not in-use (unopened)</th>
<th>Not in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room Temperature</td>
<td>Refrigerated</td>
<td>Room Temperature</td>
</tr>
<tr>
<td></td>
<td>(below 30°C)</td>
<td></td>
<td>(below 30°C)</td>
</tr>
<tr>
<td>10 mL vial</td>
<td>42 days</td>
<td>Until expiration date</td>
<td>42 days refrigerated/room temperature</td>
</tr>
<tr>
<td>3 mL PenFill® cartridges</td>
<td>42 days</td>
<td>Until expiration date</td>
<td>(Do not refrigerate)</td>
</tr>
<tr>
<td>3 mL InnoLet®</td>
<td>42 days</td>
<td>Until expiration date</td>
<td>(Do not refrigerate)</td>
</tr>
<tr>
<td>3 mL FlexPen®</td>
<td>42 days</td>
<td>Until expiration date</td>
<td>(Do not refrigerate)</td>
</tr>
</tbody>
</table>

**Rx Only**

Date of Issue: July 15, 2009

Version: 5

Novo Nordisk®, Levemir®, NovoLog®, FlexPen®, InnoLet®, PenFill®, and NovoFine® are registered trademarks owned by Novo Nordisk A/S.

Levemir® is covered by US Patent Nos. 5,750,497; 5,866,538; 6,011,007; 6,869,930 and other patents pending.

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

Manufactured for:

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143844 January 2011
LEVEMIR® (insulin detemir [rDNA origin] injection)

Patient Information

Levemir® (LEV–uh-mere)
(insulin detemir [rDNA origin] injection)

Important:

Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Make sure you know the type and strength of insulin prescribed for you.

Read the Patient Information that comes with Levemir® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment. Make sure that you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is Levemir®?

Levemir® is a man-made long-acting insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not use Levemir®?

Do not take Levemir® if:

• Your blood sugar is too low (hypoglycemia).
• You are allergic to anything in Levemir®. See the end of this leaflet for a complete list of ingredients in Levemir®. Check with your healthcare provider if you are not sure.

Tell your healthcare provider:

• about all of your medical conditions. Medical conditions can affect your insulin needs and your dose of Levemir®.
• if you are pregnant or breast-feeding. You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. Levemir® has not been studied in pregnant or nursing women.
• about all medicines you take, including prescriptions and non-prescription medicines, vitamins and herbal supplements. Your Levemir® dose may change if you take other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider when you get a new medicine.

How should I take Levemir®?

Inject Levemir® into the skin of your stomach area, upper arms, or thighs
• Never inject Levemir® into a vein
• Never inject Levemir® into a muscle.
• Change (rotate) your injection site within the chosen area (for example, stomach or upper arm) with each dose. Do not inject into the exact same spot for each injection.
• If you take too much Levemir®, your blood sugar may fall low (hypoglycemia). You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it can get worse and you could pass out (become unconscious).

What should I avoid while using Levemir®?

Never mix Levemir® with other insulin products.

Never use Levemir® in an insulin pump.

Your insulin dosage may need to change because of:

• illness
• other medicines you take
• change in physical activity or exercise

What should I avoid while using Levemir®?

• Alcohol. Alcohol, including beer and wine, may affect your blood sugar when you take Levemir®.
• Driving and operating machinery. You may have difficulty concentrating or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright to drive if you often have:
• low blood sugar
• decreased or no warning signs of low blood sugar

What are the possible side effects of Levemir®?

• Low blood sugar (hypoglycemia). Symptoms of low blood sugar may include:
• sweating
• shakiness
• fast heart beat
• trouble concentrating or confusion
• slurred speech
• headache
• frequent urination
• loss of appetite
• change in diet

Severe low blood sugar can cause unconsciousness (passing out), seizures, and death. Know your symptoms of low blood sugar. Follow your healthcare provider’s instructions for treating low blood sugar. Talk to your healthcare provider if low blood sugar is a problem for you.

• Serious allergic reaction (whole body reaction). Get medical help right away, if you develop a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.
• Reactions at the injection site (local allergic reaction). You may get redness, swelling, and itching at the injection site. If you keep having skin reactions or they are serious, talk to your healthcare provider. You may need to stop using Levemir® and use a different insulin. Do not inject insulin into skin that is red, swollen, or itchy.
• Skin thickens or pits at the injection site (lipodystrophy). Change (rotate) where you inject your insulin to help to prevent these skin changes from happening. Do not inject insulin into this type of skin.
• Swelling of your hands and feet
• Vision changes
• Low potassium in your blood (hypokalemia)

These are not all of the possible side effects from Levemir®. Ask your healthcare provider or pharmacist for more information. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How should I store Levemir®?

All Unopened Levemir®:
- Keep all unopened Levemir® in the refrigerator between 36° to 46°F (2° to 8°C).
- Do not freeze. Do not use Levemir® if it has been frozen.
- Keep unopened Levemir® in the carton to protect from light.

Levemir® in use:
- Vials
  - Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 42 days.
  - Keep vials away from direct heat or light.
  - Throw away an opened vial after 42 days of use, even if there is insulin left in the vial.
  - Unopened vials can be used until the expiration date on the Levemir® label, if the medicine has been stored in a refrigerator.
- Levemir® FlexPen®
  - Keep at room temperature below 86°F (30°C) for up to 42 days.
  - Do not store a Levemir® FlexPen® that you are using in the refrigerator.
  - Keep Levemir® FlexPen® away from direct heat or light.
  - Throw away a used Levemir® FlexPen® after 42 days, even if there is insulin left in the syringe.

General advice about Levemir®

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use Levemir® for a condition for which it was not prescribed. Do not give Levemir® to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Levemir®. If you would like more information about Levemir® or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Levemir® that is written for healthcare professionals. Call 1-800-727-6500 or visit www.novonordisk-us.com for more information.

Helpful information for people with diabetes is published by the American Diabetes Association, 1701 N Beauregard Street, Alexandria, VA 22311 and on www.diabetes.org.

Levemir® ingredients include:
- Insulin detemir
- Phenol
- Zinc
- Sodium chloride
- Hydrochloric acid or sodium hydroxide
- Glycerol
- Metacresol
- Sodium chloride
- Disodium hydrogen phosphate dihydrate
- Water for injection

All Levemir® vials and Levemir® FlexPen® are latex free.

Date of Issue: May 22, 2009
Version: 4

Levemir®, PenFill®, FlexPen®, InnoLet®, NovoPen®, NovoFine®, and PenMate® are trademarks of Novo Nordisk A/S.

Levemir® is covered by US Patent Nos. 5,750,497; 5,866,538; 6,011,007; 6,869,930, and other patents pending.

PenFill® is covered by US Patent Nos. 6,126,646; 5,693,027; DES 347894, and other patents pending.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
For information about Levemir®, contact:
Novo Nordisk Inc.
100 College Road West
Princeton, New Jersey 08540
http://www.novonordisk-us.com
1-800-727-6500
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H. Turn the dose selector to the number of units you need to inject. The pointer should line up with your dose. The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer (see diagram H). When turning the dose selector, be careful not to press the push-button as insulin will come out. You cannot select a dose larger than the number of units left in the cartridge. You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear. Do not use the cartridge scale printed on the cartridge to measure your dose of insulin.

Giving the injection
Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting.

I. Insert the needle into your skin.
   - Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see diagram I). Be careful only to push the button when injecting. Turning the dose selector will not inject insulin.

J. Keep the needle in the skin for at least 6 seconds, and keep the push-button pressed all the way in until the needle has been pulled out of the skin (see diagram J). This will make sure that the full dose has been given. You may see a drop of Levemir® at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. Do not rub the area.

After the injection
Do not recap the needle. Recapping can lead to a needle stick injury. Remove the needle from the Levemir® FlexPen® after each injection. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

The Levemir® FlexPen® prevents the cartridge from being completely emptied. It is designed to deliver 300 units.

K. Put the pen cap on the Levemir® FlexPen® and store the Levemir® FlexPen® without the needle attached (see diagram K).

Function Check
If your Levemir® FlexPen® is not working the right way, follow the steps below:

L. Screw on a new NovoFine® needle.
   - Remove the big outer needle cap and the inner needle cap.
   - Do an airshot as described in “Giving the airshot before each injection”.
   - Put the big outer needle cap onto the needle. Do not put on the inner needle cap.
   - Turn the dose selector so the dose indicator window shows 20 units.
   - Hold the Levemir® FlexPen® so the needle is pointing down.
   - Press the push-button all the way in.

The insulin should fill the lower part of the big outer needle cap (see diagram L). If Levemir® FlexPen® has released too much or too little insulin, do the function check again. If the same problem happens again, do not use your Levemir® FlexPen® and contact Novo Nordisk at 1-800-727-6500.
NovoLog® (insulin aspart [rDNA origin] injection)

——— DRUG INTERACTIONS ———

- The following may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrate, fluoxetine, monoamine oxidase inhibitors, propoxyphene, salicylates, somatostatin analogs, sulfonamide antibiotics (7).
- The following 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 (7).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin (7).
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia (7).
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine (7).

——— USE IN SPECIFIC POPULATIONS ———

- Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <2 years of age (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 10/2010
NovoLog® (insulin aspart [rDNA origin] injection)

<table>
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14.1 Subcutaneous Daily Injections
14.2 Continuous Subcutaneous Insulin Infusion (CSII) by External Pump
14.3 Intravenous Administration of NovoLog®

16 HOW SUPPLIED/STORAGE AND HANDLING
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17 PATIENT COUNSELING INFORMATION
17.1 Physician Instructions
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17.3 FDA-Approved Patient Labeling

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
1.1 Treatment of Diabetes Mellitus

NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION
2.1 Dosing

NovoLog® is an insulin analog with an earlier onset of action than regular human insulin. The dosage of NovoLog® must be individualized. NovoLog® given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin.[See Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)]. The total daily insulin requirement may vary and is usually between 0.5 to 1.0 units/kg/day. When used in a meal-related subcutaneous injection treatment regimen, 30 to 70% of total insulin requirements may be provided by NovoLog® and the remainder provided by an intermediate-acting or long-acting insulin. Because of NovoLog®'s comparatively rapid onset and short duration of glucose lowering activity, some patients may require more basal insulin and more total insulin to prevent pre-meal hypoglycemia when using NovoLog® than when using human regular insulin.

Do not use NovoLog® that is viscous (thickened) or cloudy; use only if it is clear and colorless. NovoLog® should not be used after the printed expiration date.

2.2 Subcutaneous Injection

NovoLog® should be administered by subcutaneous injection in the abdominal region, buttocks, thigh, or upper arm. Because NovoLog® has a more rapid onset and a shorter duration of activity than human regular insulin, it should be injected immediately (within 5-10 minutes) before a meal. Injection sites should be rotated within the same region to reduce the risk of lipodystrophy. As with all insulins, the duration of action of NovoLog® will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

NovoLog® may be diluted with Insulin Diluting Medium for NovoLog® for subcutaneous injection. Diluting one part NovoLog® to nine parts diluent will yield a concentration one-tenth that of NovoLog® (equivalent to U-10). Diluting one part NovoLog® to one part diluent will yield a concentration one-half that of NovoLog® (equivalent to U-50).

2.3 Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

NovoLog® can also be infused subcutaneously by an external insulin pump.[See Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2)]. Diluted insulin should not be used in external insulin pumps. Because NovoLog® has a more rapid onset and a shorter duration of activity than human regular insulin, it should be infused immediately (within 5-10 minutes) before a meal. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy. The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is usually given as meal-related boluses of NovoLog® and the remainder is given as a basal infusion. Change the NovoLog® in the reservoir at least every 6 days, change the infusion sets and the infusion set insertion site at least every 3 days.

The following insulin pumps have been used in NovoLog® clinical or in vitro studies conducted by Novo Nordisk, the manufacturer of NovoLog®:

- Medtronic Paradigm® 512 and 712
- MiniMed 508
- Disetronic® D-TROND® and H-TROND®

Before using a different insulin pump with NovoLog®, read the pump label to make sure the pump has been evaluated with NovoLog®.

NovoLog® can be administered intravenously under medical supervision for glycemic control with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia.[See Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)]. For intravenous use, NovoLog® should be used at concentrations from 0.06 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog® has been shown to be stable in infusion fluids such as 0.9% sodium chloride.

Inspect NovoLog® for particulate matter and discoloration prior to parenteral administration.

3 DOSAGE FORMS AND STRENGTHS

NovoLog® is available in the following package sizes: each presentation contains 100 units of insulin aspart per mL (U-100).

- 10 mL vials
- 3 mL PenFill cartridges for the 3 mL PenFill® cartridge delivery device (with or without the addition of a NovoPen® 3 PenMate™) with NovoMix® or NovoFine® disposable needles
- 3 mL NovoLog® FlexPen®

4 CONTRAINDICATIONS

NovoLog® is contraindicated

- during episodes of hypoglycemia
- in patients with hypersensitivity to NovoLog® or one of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 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.

1 Needles and NovoLog® FlexPen® must not be shared.

5.2 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 (12)]. 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 (7)]. 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 long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.[See Drug Interactions (7)]. 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.

5.3 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).
NovoLog® (insulin aspart [rDNA origin] injection)

5.4 Renal Impairment
As with other insulins, the dose requirements for NovoLog® may be reduced in patients with renal impairment [see Clinical Pharmacology (12.3)].

5.5 Hepatic Impairment
As with other insulins, the dose requirements for NovoLog® may be reduced in patients with hepatic impairment [see Clinical Pharmacology (12.3)].

5.6 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.

5.7 Antibody Production
Increases in anti-insulin antibody titer 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.

5.8 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.

5.9 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 insulin may be required [see Dosage and Administration (2.3), Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2) and Patient Counseling Information (17.2)].

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 (2.3), Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17.2)].

6 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 (5)].

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**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)**

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

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms. See Section 14 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)**

<table>
<thead>
<tr>
<th></th>
<th>NovoLog® + NPH N=91</th>
<th>Human Regular Insulin + NPH N=91</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td>25 27%</td>
<td>33 36%</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>10 11%</td>
<td>6 7%</td>
</tr>
<tr>
<td>Ophthalmopathy</td>
<td>9 10%</td>
<td>5 5%</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>8 9%</td>
<td>6 7%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 8%</td>
<td>6 7%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 5%</td>
<td>3 3%</td>
</tr>
<tr>
<td>Headache</td>
<td>5 5%</td>
<td>3 3%</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>5 5%</td>
<td>2 2%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 5%</td>
<td>1 1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5 5%</td>
<td>1 1%</td>
</tr>
</tbody>
</table>

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms. See Section 14 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 (17)].
NovoLog® (insulin aspart [rDNA origin] injection) 64

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-glucose-lowering effect and susceptibility to hypoglycemia:
  - Oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, furosamide, fluoxetine, monamine oxidase (MAO) inhibitors, propranolol, 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, progesterones (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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking NovoLog®.

An open-label, randomized study compared the safety and efficacy of NovoLog® (n=157) versus regular human insulin (n=165) in 322 pregnant women with type 1 diabetes. Two-thirds of the enrolled patients were already pregnant when they entered the study. Because only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Both groups achieved a mean HbA1c of ~6% during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

Subcutaneous reproduction and teratology studies have been performed with NovoLog® 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 in 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.

8.3 Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk. Use of NovoLog® is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

NovoLog® is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. NovoLog® has not been studied in pediatric patients younger than 2 years of age. NovoLog® has not been used in pediatric patients with type 2 diabetes. Please see Section 14 CLINICAL STUDIES for summaries of clinical studies.

8.5 Geriatric Use

Of the total number of patients (n=1,375) treated with NovoLog® in 3 controlled clinical studies, 2.6% (n=36) were 65 years of age or over. One-half of these patients had type 1 diabetes (n=1285) and the other half had type 2 diabetes (n=90). The HbA1c response to NovoLog®, as compared to human insulin, did not differ by age, particularly in patients with type 2 diabetes. Additional studies in larger populations of patients 65 years of age or over are needed to permit conclusions regarding the safety of NovoLog® in elderly compared to younger patients. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of NovoLog® action have not been performed.

10 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.

NovoLog® (insulin aspart [rDNA origin] injection) 65

11 DESCRIPTION

NovoLog® (insulin aspart [rDNA origin] injection) is a rapid-acting human insulin analog used to lower blood glucose. NovoLog® is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing Saccharomyces cerevisiae (baker’s yeast). Insulin aspart has the empirical formula C_{265}H_{381}N_{65}O_{79}S_{6} and a molecular weight of 5825.8.

Figure 1. Structural formula of insulin aspart.

NovoLog® is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart 100 Units/mL, glicentin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 mg/mL, disodium hydrogen phosphate dodehydrate 1.25 mg/mL, sodium chloride 0.58 mg/mL, and water for injection. NovoLog® has a pH of 7.2-7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of NovoLog® is the regulation of glucose metabolism. Insulins, including NovoLog®, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose and simultaneously inhibiting the output of glucose from the liver.

12.2 Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that subcutaneous administration of NovoLog® 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® occurred between 1 and 3 hours after subcutaneous injection (see Figure 2). The duration of action for NovoLog® is 3 to 5 hours. The time course of action of insulin and insulin analogs such as NovoLog® may vary considerably in different individuals or within the same individual. The parameters of NovoLog® 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 (5.7)).

Figure 2. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog® (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

A double-blind, randomized, two-way cross-over study in 16 patients with type 1 diabetes demonstrated that intravenous infusion of NovoLog® resulted in a blood glucose profile that was similar to that after intravenous infusion with regular human insulin. NovoLog® or human insulin was infused until the patient’s blood glucose decreased to 36 mg/dL, or until the patient demonstrated signs of hypoglycemia (rise in heart rate and onset of sweating), defined as the time of autonomic reaction (R) (see Figure 3).
NovoLog® (insulin aspart [rDNA origin] injection)

12.3 Pharmacokinetics

The single substitution of the amino acid proline with aspartic acid at position B28 in NovoLog® reduces the molecule’s tendency to form hexamers as observed with regular human insulin. NovoLog® is, therefore, more rapidly absorbed after subcutaneous injection compared to regular human insulin.

In a randomized, double-blind, crossover study 17 healthy Caucasian male subjects between 18 and 40 years of age received an intravenous infusion of either NovoLog® or regular human insulin at 1.5 mL/kg/min for 120 minutes. The mean insulin clearance was similar for the two groups with mean values of 1.2 l/h/kg for the NovoLog® group and 1.2 l/h/kg for the regular human insulin group.

Bioavailability and Absorption - NovoLog® has a faster absorption, a faster onset of action, and a shorter duration of action than regular human insulin after subcutaneous injection (see Figure 2 and Figure 4). The relative bioavailability of NovoLog® compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

Figure 3. Mean blood glucose profiles following intravenous infusion of NovoLog® (hatched curve) and regular human insulin (solid curve) in 16 patients with type 1 diabetes. R represents the time of autonomic reaction.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog®. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog® 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, at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), no direct adverse effects on male or female fertility, or general reproductive performance of animals was observed.

13.2 Animal Toxicology and/or Pharmacology

In standard biological assays in mice and rabbits, one unit of NovoLog® has the same glucose-lowering effect as one unit of regular human insulin. In humans, the effect of NovoLog® is more rapid in onset and of shorter duration, compared to regular human insulin, due to its faster absorption after subcutaneous injection (see Section 12 CLINICAL PHARMACOLOGY Figure 2 and Figure 4).

14 CLINICAL STUDIES

14.1 Subcutaneous Daily Injections

Two six-month, open-label, active-controlled studies were conducted to compare the safety and efficacy of NovoLog® to Novolin® R in adult patients with type 1 diabetes. Because the two study designs and results were similar, data are shown for only one study (see Table 3). NovoLog® was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA1c and the incidence rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens in this study (Table 3) as well as in the other clinical studies that are cited in this section. Diabetic ketoacidosis was not reported in any of the adult studies in either treatment group.

Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog® (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

In studies in healthy volunteers (total n=107) and patients with type 1 diabetes (total n=40), NovoLog® consistently reached peak serum concentrations approximately twice as fast as regular human insulin. The median time to maximum concentration in these trials was 40 to 50 minutes for NovoLog® versus 80 to 120 minutes for regular human insulin. In a clinical trial in patients with type 1 diabetes, NovoLog® and regular human insulin, both administered subcutaneously at a dose of 0.15 U/kg body weight, reached mean maximum concentrations of 82 and 36 mU/L, respectively. Pharmacokinetic/pharmacodynamic characteristics of insulin aspart have not been established in patients with type 2 diabetes.

The intra-individual variability in time to maximum serum insulin concentration for healthy male volunteers was significantly less for NovoLog® than for regular human insulin. The clinical significance of this observation has not been established.

In a clinical study in healthy non-obese subjects, the pharmacokinetic differences between NovoLog® and regular human insulin described above, were observed independent of the site of injection (abdomen, thigh, or upper arm).
NovoLog® (insulin aspart [rDNA origin] injection) subcutaneous multiple-dose treatment regimens: NovoLog® (n = 187) or Novolin® R (n = 96). NPH insulin was administered as the basal insulin. NovoLog® achieved glycemic control comparable to Novolin® R, as measured by change in HbA1c (Table 4) and both treatment groups had a comparable incidence of hypoglycemia. Subcutaneous administration of NovoLog® and regular human insulin have also been compared in children with type 1 diabetes (n=29) aged 2 to 6 years with similar effects on HbA1c and hypoglycemia.

Table 4. Pediatric Subcutaneous Administration of NovoLog® in Type 1 Diabetes (24 weeks; n=283)

<table>
<thead>
<tr>
<th>N</th>
<th>NovoLog® + NPH</th>
<th>Novolin® R + NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>187</td>
<td>96</td>
</tr>
<tr>
<td>Baseline HbA1c (%)*</td>
<td>8.3 ± 1.2</td>
<td>8.3 ± 1.3</td>
</tr>
<tr>
<td>Change from Baseline HbA1c (%)</td>
<td>0.1 ± 1.0</td>
<td>0.1 ± 1.1</td>
</tr>
<tr>
<td>Treatment Difference in HbA1c, Mean (95% confidence interval)</td>
<td>0.2 (-0.1, 0.4)</td>
<td></td>
</tr>
<tr>
<td>Baseline insulin dose (IU/kg/24 hours)*</td>
<td>0.4 ± 0.2</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>End-of-Study insulin dose (IU/kg/24 hours)*</td>
<td>0.4 ± 0.2</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>Patients with severe hypoglycemia (n, %)**</td>
<td>11 (5%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis (n, %)</td>
<td>10 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Baseline body weight (kg)*</td>
<td>50.6 ± 19.6</td>
<td>48.7 ± 15.8</td>
</tr>
<tr>
<td>Weight Change from baseline (kg)*</td>
<td>2.7 ± 3.5</td>
<td>2.4 ± 2.6</td>
</tr>
</tbody>
</table>

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A 24-week, parallel-group study of children and adolescents with type 1 diabetes (n = 283) aged 6 to 18 years compared two subcutaneous multiple-dose treatment regimens: NovoLog® (n = 187) or Novolin® R (n = 96). NPH insulin was administered as the basal insulin. NovoLog® achieved glycemic control comparable to Novolin® R, as measured by change in HbA1c (Table 4) and both treatment groups had a comparable incidence of hypoglycemia. Subcutaneous administration of NovoLog® and regular human insulin have also been compared in children with type 1 diabetes (n=29) aged 2 to 6 years with similar effects on HbA1c and hypoglycemia.

Table 5. Subcutaneous NovoLog® Administration in Type 2 Diabetes (6 months; n=176)

<table>
<thead>
<tr>
<th>N</th>
<th>NovoLog® + NPH</th>
<th>Novolin® R + NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>Baseline HbA1c (%)*</td>
<td>8.1 ± 1.2</td>
<td>7.8 ± 1.1</td>
</tr>
<tr>
<td>Change from Baseline HbA1c (%)</td>
<td>-0.3 ± 1.0</td>
<td>-0.1 ± 0.8</td>
</tr>
<tr>
<td>Treatment Difference in HbA1c, Mean (95% confidence interval)</td>
<td>-0.1 (-0.4, -0.1)</td>
<td></td>
</tr>
<tr>
<td>Baseline insulin dose (IU/kg/24 hours)*</td>
<td>0.6 ± 0.3</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>End-of-Study insulin dose (IU/kg/24 hours)*</td>
<td>0.7 ± 0.3</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>Patients with severe hypoglycemia (n, %)**</td>
<td>9 (10%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Baseline body weight (kg)*</td>
<td>88.4 ± 13.3</td>
<td>85.8 ± 14.8</td>
</tr>
<tr>
<td>Weight Change from baseline (kg)*</td>
<td>1.2 ± 3.0</td>
<td>0.4 ± 3.1</td>
</tr>
</tbody>
</table>

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

NovoLog® (insulin aspart [rDNA origin] injection) Continuous Subcutaneous Insulin Infusion (CSI) by External Pump

Two open-label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog® to buffered regular human insulin (Velosulin®) in adults with type 1 diabetes receiving a subcutaneous infusion with an external insulin pump. The two treatment regimens had comparable changes in HbA1c and rates of severe hypoglycemia.

Table 6. Adult Insulin Pump Study in Type 1 Diabetes (16 weeks; n=118)

<table>
<thead>
<tr>
<th>N</th>
<th>NovoLog®</th>
<th>Buffered human insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Baseline HbA1c (%)*</td>
<td>7.3 ± 0.7</td>
<td>7.5 ± 0.8</td>
</tr>
<tr>
<td>Change from Baseline HbA1c (%)</td>
<td>0.0 ± 0.5</td>
<td>0.2 ± 0.6</td>
</tr>
<tr>
<td>Treatment Difference in HbA1c, Mean (95% confidence interval)</td>
<td>0.3 (-0.1, 0.4)</td>
<td></td>
</tr>
<tr>
<td>Baseline insulin dose (IU/kg/24 hours)*</td>
<td>0.7 ± 0.7</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>End-of-Study insulin dose (IU/kg/24 hours)*</td>
<td>0.7 ± 0.7</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>Patients with severe hypoglycemia (n, %)**</td>
<td>1.2 (1%)</td>
<td>2.3 (1%)</td>
</tr>
<tr>
<td>Baseline body weight (kg)*</td>
<td>77.4 ± 16.1</td>
<td>74.8 ± 13.8</td>
</tr>
<tr>
<td>Weight Change from baseline (kg)*</td>
<td>0.1 ± 3.5</td>
<td>-0.0 ± 1.7</td>
</tr>
</tbody>
</table>

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes (n=298) aged 4-18 years compared two subcutaneous infusion regimens administered via an external insulin pump: NovoLog® (n=138) or insulin lispro (n=100). These two treatments resulted in comparable changes from baseline in HbA1c and comparable rates of hypoglycemia after 16 weeks of treatment (see Table 7).

Table 7. Pediatric Insulin Pump Study in Type 1 Diabetes (16 weeks; n=298)

<table>
<thead>
<tr>
<th>N</th>
<th>NovoLog®</th>
<th>Lispro</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>138</td>
<td>100</td>
</tr>
<tr>
<td>Baseline HbA1c (%)*</td>
<td>8.0 ± 0.9</td>
<td>8.2 ± 0.8</td>
</tr>
<tr>
<td>Change from Baseline HbA1c (%)</td>
<td>-0.1 ± 0.8</td>
<td>-0.1 ± 0.7</td>
</tr>
<tr>
<td>Treatment Difference in HbA1c, Mean (95% confidence interval)</td>
<td>-0.1 (-0.3, 0.1)</td>
<td></td>
</tr>
<tr>
<td>Baseline insulin dose (IU/kg/24 hours)*</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>End-of-Study insulin dose (IU/kg/24 hours)*</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Patients with severe hypoglycemia (n, %)**</td>
<td>19 (10%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis (n, %)</td>
<td>1 (0%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Baseline body weight (kg)*</td>
<td>54.1 ± 19.7</td>
<td>55.5 ± 19.0</td>
</tr>
<tr>
<td>Weight Change from baseline (kg)*</td>
<td>1.8 ± 2.1</td>
<td>1.6 ± 2.1</td>
</tr>
</tbody>
</table>

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

One six-month, open-label, active-controlled study was conducted to compare the safety and efficacy of NovoLog® to Novolin® R in patients with type 2 diabetes (Table 5). NovoLog® was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA1c and the rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens.

Table 8. Pump Therapy in Type 2 Diabetes (16 weeks; n=127)

<table>
<thead>
<tr>
<th>N</th>
<th>NovoLog® pump</th>
<th>NovoLog® + NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td>Baseline HbA1c (%)*</td>
<td>8.2 ± 1.4</td>
<td>8.0 ± 1.1</td>
</tr>
<tr>
<td>Change from Baseline HbA1c (%)</td>
<td>-0.6 ± 1.1</td>
<td>-0.5 ± 0.9</td>
</tr>
<tr>
<td>Treatment Difference in HbA1c, Mean (95% confidence interval)</td>
<td>0.1 (-0.4, 0.3)</td>
<td></td>
</tr>
<tr>
<td>Baseline insulin dose (IU/kg/24 hours)*</td>
<td>0.7 ± 0.3</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td>End-of-Study insulin dose (IU/kg/24 hours)*</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.5</td>
</tr>
<tr>
<td>Baseline body weight (kg)*</td>
<td>96.4 ± 17.0</td>
<td>98.9 ± 17.9</td>
</tr>
<tr>
<td>Weight Change from baseline (kg)*</td>
<td>1.7 ± 3.7</td>
<td>0.7 ± 4.1</td>
</tr>
</tbody>
</table>

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization. An open-label, 16-week parallel design trial compared pre-prandial NovoLog® injection in conjunction with NPH injections to NovoLog® administered by continuous subcutaneous infusion in 127 adults with type 2 diabetes. The two treatment groups had similar reductions in HbA1c and rates of severe hypoglycemia (Table 8) (see Indications and Usage (1), Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)).
14.3 Intravenous Administration of NovoLog®
See Section 12.2 CLINICAL PHARMACOLOGY/Pharmacodynamics.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
NovoLog® is available in the following package sizes: each presentation containing 100 Units of insulin aspart per mL (U-100).

- 10 mL vials NDC 0169-7501-11
- 3 mL PenFill® cartridges* NDC 0169-3303-12
- 3 mL NovoLog® FlexPen® NDC 0169-6339-10

*NovoLog® FlexPen® cartridges are designed for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices (with or without the addition of a NovoPen® 3 PenMate®) with NovoTwist® or NovoFine® disposable needles.

16.2 Recommended Storage
Unused NovoLog® should be stored in a refrigerator between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze NovoLog® and do not use NovoLog® if it has been frozen. NovoLog® should not be drawn into a syringe and stored for later use.

Vials: After initial use a vial may be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Opened vials may be refrigerated.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

PenFill® cartridges or NovoLog® FlexPen®:

Once a cartridge or a NovoLog® FlexPen® is punctured, it should be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. A NovoLog® FlexPen® or cartridge in use must NOT be stored in the refrigerator. Keep the NovoLog® FlexPen® and all PenFill® cartridges away from direct heat and sunlight. Unpunctured NovoLog® FlexPen® and PenFill® cartridges can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused NovoLog® FlexPen® and PenFill® cartridges in the carton so they will stay clean and protected from light.

Always remove the needle after each injection and store the 3 mL PenFill® cartridge delivery device or NovoLog® FlexPen® without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

Pump:
NovoLog® in the pump reservoir should be discarded after at least every 6 days of use or after exposure to temperatures that exceed 37°C (98.6°F). The infusion set and the infusion set insertion site should be changed at least every 3 days.

Summary of Storage Conditions:
The storage conditions are summarized in the following table:

<table>
<thead>
<tr>
<th>NovoLog® presentation</th>
<th>Not in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room Temperature (below 30°C)</td>
<td>Room Temperature (below 30°C)</td>
<td></td>
</tr>
<tr>
<td>Not in-use (unopened) Regulated</td>
<td>Not in-use (unopened) Regulated</td>
<td></td>
</tr>
<tr>
<td>10 mL vial</td>
<td>28 days</td>
<td>Until expiration date 28 days (refrigerated/room temperature)</td>
</tr>
<tr>
<td>3 mL PenFill® cartridges</td>
<td>28 days</td>
<td>Until expiration date 28 days (Do not refrigerate)</td>
</tr>
<tr>
<td>3 mL NovoLog® FlexPen®</td>
<td>28 days</td>
<td>Until expiration date 28 days (Do not refrigerate)</td>
</tr>
</tbody>
</table>

Storage of Diluted NovoLog®
NovoLog® diluted with Insulin Diluting Medium for NovoLog® to a concentration equivalent to U-10 or equivalent to U-50 may remain in patient use at temperatures below 30°C (86°F) for 28 days.

Storage of NovoLog® in Infusion Fluids
Infusion bags prepared as indicated under Dosage and Administration (2) are stable at room temperature for 24 hours. Some insulin will be initially adsorbed to the material of the infusion bag.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.3)]

17.1 Physician Instructions
Maintenance of normal or near-normal glucose control is a treatment goal in diabetes mellitus and has been associated with a reduction in diabetic complications. Patients should be informed about potential risks and benefits of NovoLog® therapy including the possible adverse reactions. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycoated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction in the use of injection or subcutaneous infusion devices, and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia.

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. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental substitutions between NovoLog® and other insulin products have been reported. Patients should be instructed to always carefully check that they are administering the appropriate insulin to avoid medication errors between NovoLog® and any other insulin. The written prescription for NovoLog® should be written clearly, to avoid confusion with other insulin products, for example, NovoLog® Mix 70/30.

17.2 Patients Using Pumps
Patients using external pump infusion therapy should be trained in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.

The following insulin pumps† have been used in NovoLog® clinical or in vitro studies conducted by Novo Nordisk, the manufacturer of NovoLog®:

- Medtronic Paradigm® 512 and 712
- MiniMed 508
- D Insulet® D-TRON® and H-TRON®

Before using another insulin pump with NovoLog®, read the pump label to make sure the pump has been evaluated with NovoLog®.

NovoLog® is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. Please see recommended reservoir and infusion sets in the pump manual.

To avoid insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), insulin in the reservoir should be replaced at least every 6 days; infusion sets and infusion set insertion sites should be changed at least every 3 days.

Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing, or sport case is exposed to sunlight or radiant heat. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected because continued infusion may increase the skin reaction and/or the absorption of NovoLog®. Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time. Insulin in a small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences are particularly relevant when patients are switched from multiple injection therapy. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their physician [see Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)].

17.3 FDA Approved Patient Labeling
See separate leaflet.

Rx only
Date of Issue: October 2010
Version: 18
Novo Nordisk®, NovoLog®, NovoPen®, PenFill®, Novolin®, FlexPen®, PenMate®, NovoTwist® and NovoFine® are registered trademarks of Novo Nordisk A/S.
NovoLog® is covered by US Patent Nos. 6,582,404, 5,666,538, and other patents pending. FlexPen® is covered by US Patent Nos. 6,188,913, 6,582,404, 6,004,297, 235,004, and other patents pending. PenFill® is covered by US Patent No. 5,693,027.
†The brands listed are the registered trademarks of their respective owners and are not trademarks of Novo Nordisk A/S.
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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143756 January 2011

NovoLog® (insulin aspart [rDNA origin] injection)
NovoLog® (insulin aspart [rDNA origin] injection)

Patient Information

NovoLog® (N-o-v-o-log)
(insulin aspart [rDNA origin] injection)

Important:

Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Make sure you know the type and strength of insulin prescribed for you.

Read the Patient Information that comes with NovoLog® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment. Make sure you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is NovoLog®?

NovoLog® is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not use NovoLog®?

Do not take NovoLog® if:

• Your blood sugar is too low (hypoglycemia).
• You are allergic to anything in NovoLog®, See the end of this leaflet for a complete list of ingredients in NovoLog®. Check with your healthcare provider if you are not sure.

Tell your healthcare provider:

• about all of your medical conditions. Medical conditions can affect your insulin needs and your dose of NovoLog®.
• if you are pregnant or breastfeeding. You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. NovoLog® has not been studied in nursing women.

• about all medicines you take, including prescriptions and non-prescription medicines, vitamins and herbal supplements. Your NovoLog® dose may change if you take other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers when you get a new medicine.

How should I take NovoLog®?

Only use NovoLog® if it appears clear and colorless. There may be air bubbles. This is normal. If it looks cloudy, thickened, or colored, or if it contains solid particles do not use it and call Novo Nordisk at 1-800-727-6500.

NovoLog® comes in:

• 10 mL vials (small bottles) for use with syringe
• 3 mL PenFill® cartridges for use with the Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoTwist® or NovoFine® disposable needles. The cartridge delivery device can be used with a NovoPen® 3 PenMate®
• 3 mL NovoLog® FlexPen®

Read the instructions for use that come with your NovoLog® product. Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject NovoLog® before you start taking it.

Take NovoLog® exactly as prescribed. You should eat a meal within 5 to 10 minutes after using NovoLog® to avoid low blood sugar.

NovoLog® is a fast-acting insulin. The effects of NovoLog® start working 10 to 20 minutes after injection or bolus pump infusion.

Do not inject NovoLog® if you do not plan to eat right after your injection or bolus pump infusion.

• The greatest blood sugar lowering effect is between 1 and 3 hours after the injection or infusion. This blood sugar lowering lasts for 3 to 5 hours.
• While using NovoLog® you may have to change your total dose of insulin, your dose of longer-acting insulin, or the number of injections of longer-acting insulin you use. Pump users given NovoLog® may need to change the amount of total insulin given as a basal infusion.
• Do not mix NovoLog®:
  • with any other insulins when used in a pump
  • with any insulins other than NPH when used with injections by syringe

If your healthcare provider recommends diluting NovoLog®, follow your healthcare provider’s instructions exactly so that you know:

• How to make NovoLog® more dilute (that is, a smaller number of units of NovoLog® for a given amount of liquid) and
• How to use this more dilute form of NovoLog®. Do not use dilute insulin in a pump.

NovoLog® (insulin aspart [rDNA origin] injection)

• Inject NovoLog® into the skin of your stomach area, upper arms, buttocks or upper legs. NovoLog® may affect your blood sugar levels sooner if you inject it into the skin of your stomach area. Never inject NovoLog® into a vein or into a muscle.

• Change (rotate) your injection site within the chosen area (for example, stomach or upper arm) with each dose. Do not inject into the exact same spot for each injection.

• If you take too much NovoLog®, your blood sugar may fall low (hypoglycemia). You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and you could pass out (become unconscious). If you pass out you will need help from another person or emergency medical services right away, and will need treatment with a glucagon injection or treatment at a hospital. See “What are the possible side effects of NovoLog®?” for more information on low blood sugar (hypoglycemia).

• If you forget to take your dose of NovoLog®, your blood sugar may go too high (hyperglycemia). If high blood sugar (hyperglycemia) is not treated it can lead to serious problems, like loss of consciousness (passing out), coma or even death. Follow your healthcare provider’s instructions for treating high blood sugar. Know your symptoms of high blood sugar which may include:

  • increased thirst
  • fruity smell on the breath
  • frequent urination
  • drowsiness
  • loss of appetite
  • a hard time breathing
  • high amounts of sugar and ketones in your urine
  • nausea, vomiting (throwing up) or stomach pain

• Check your blood sugar levels. Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.

Your insulin dosage may need to change because of:

• illness
• change in diet
• stress
• other medicines you take
• change in physical activity or exercise

What should I avoid while using NovoLog®?

• Alcohol. Alcohol, including beer and wine, may affect your blood sugar when you take NovoLog®.

• Driving and operating machinery. You may have difficulty concentrating or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright to drive if you often have:

  • low blood sugar
  • decreased or no warning signs of low blood sugar

What are the possible side effects of NovoLog®?

• Low blood sugar (hypoglycemia). Symptoms of low blood sugar may include:

  • sweating
  • blurred vision
  • trouble concentrating or confusion
  • dizziness or lightheadedness
  • hunger
  • Shakiness
  • slurred speech
  • fast heart beat
  • tingling of lips and tongue
  • anxiety, irritability or mood changes
  • headache

Severe low blood sugar can cause unconsciousness (passing out), seizures, and death. Know your symptoms of low blood sugar. Follow your healthcare provider’s instructions for treating low blood sugar. Talk to your healthcare provider if low blood sugar is a problem for you.

• Serious allergic reaction (whole body reaction). Get medical help right away, if you develop a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.

• Reactions at the injection site (local allergic reaction). You may get redness, swelling, and itching at the injection site. If you keep having skin reactions or they are serious talk to your healthcare provider. You may need to stop using NovoLog® and use a different insulin. Do not inject insulin into skin that is red, swollen, or itchy.

• Skin thickens or pits at the injection site (lipodystrophy). Change (rotate) where you inject your insulin to help to prevent these skin changes from happening. Do not inject insulin into this type of skin.

• Swelling of your hands and feet

• Vision changes

• Low potassium in your blood (hypokalemia)

• Weight gain

These are not all of the possible side effects from NovoLog®. Ask your healthcare provider or pharmacist for more information. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How should I store NovoLog®?

All Unopened NovoLog®:
- Keep all unopened NovoLog® in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze. Do not use NovoLog® if it has been frozen.
- Keep unopened NovoLog® in the carton to protect from light.

NovoLog® in use:
- Vials
  - Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28 days.
  - Keep vials away from direct heat or light.
  - Throw away an opened vial after 28 days of use, even if there is insulin left in the vial.
  - Do not draw up NovoLog® into a syringe and store for later use.
- Unopened vials can be used until the expiration date on the NovoLog® label, if the medicine has been stored in a refrigerator.

PenFill® Cartridges or NovoLog® FlexPen®
- Keep at room temperature below 86°F (30°C) for up to 28 days.
- Do not store a PenFill® cartridge or NovoLog® FlexPen® that you are using in the refrigerator.
- Keep PenFill® cartridges and NovoLog® FlexPen® away from direct heat or light.
- Throw away a used PenFill® cartridge or NovoLog® FlexPen® after 28 days, even if there is insulin left in the cartridge or syringe.

NovoLog® in the pump reservoir and the complete external pump infusion set
- The infusion set and the infusion site should be changed at least every 3 days. The insulin in the reservoir should be changed at least every 6 days even if you have not used all of the insulin. Change the infusion set and the infusion site more often than every 3 days if you have high blood sugar (hyperglycemia), the pump alarm sounds, or the insulin flow is blocked (occlusion).

General advice about NovoLog®

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use NovoLog® for a condition for which it was not prescribed. Do not give NovoLog® to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about NovoLog®. If you would like more information about NovoLog® or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NovoLog® that is written for healthcare professionals. Call 1-800-727-6500 or visit www.novonordisk-us.com for more information.

Helpful information for people with diabetes is published by the American Diabetes Association, 1701 N Beauregard Street, Alexandria, VA 22311 and on www.diabetes.org.

NovoLog® ingredients include:
- insulin aspart
- zinc
- glycerin
- phenol
- metacresol
- sodium chloride
- disodium hydrogen phosphate dihydrate
- water for injection

All NovoLog® vials, PenFill® cartridges and NovoLog® FlexPen® are latex free.

Date of Issue: October 2010
Version: 10

Novo Nordisk®, NovoLog®, PenFill®, FlexPen®, NovoPen®, NovoTwist®, NovoFine®, and PenMate® are registered trademarks of Novo Nordisk A/S.

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.

PenFill® is covered by US Patent No. 5,693,027.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
For information about NovoLog® contact:
Novo Nordisk Inc.
100 College Road West
Princeton, New Jersey 08540
© 2002-2011 Novo Nordisk A/S
143756 January 2011
You cannot select a dose larger than the number of units left in the cartridge. You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

Do not use the cartridge scale printed on the cartridge to measure your dose of insulin.

**Function Check**

Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting.

1. Insert the needle into your skin.
   - Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see diagram I). Be careful only to push the button when injecting.
   - Turning the dose selector will not inject insulin.
2. Keep the needle in the skin for at least 6 seconds, and keep the push-button pressed all the way in until the needle has been pulled out from the skin (see diagram J). This will make sure that the full dose has been given.
   - You may see a drop of NovoLog® at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. Do not rub the area.

**After the injection**

Do not recap the needle. Recapping can lead to a needle stick injury. Remove the needle from the NovoLog® FlexPen® after each injection. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

- Put the needle and any empty NovoLog® FlexPen® or any used NovoLog® FlexPen® still containing insulin in a sharps container or same type of hard plastic or metal container with a screw top such as a detergent bottle or empty coffee can. These containers should be sealed and thrown away the right way. Check with your healthcare provider about the right way to throw away used syringes and needles. There may be local or state laws about how to throw away used needles and syringes. Do not throw away used needles and syringes in household trash or recycling bins.
- The NovoLog® FlexPen® prevents the cartridge from being completely emptied. It is designed to deliver 300 units.

- Put the pen cap on the NovoLog® FlexPen® and store the NovoLog® FlexPen® without the needle attached (see diagram K).

**Function Check**

- If your NovoLog® FlexPen® is not working the right way, follow the steps below:
  - Screw on a new NovoFine® needle.
  - Remove the big outer needle cap and the inner needle cap.
  - Do an airshot as described in “Giving the airshot before each injection”.
  - Put the big outer needle cap onto the needle. Do not put on the inner needle cap.
  - Turn the dose selector so the dose indicator window shows 20 units.
  - Hold the NovoLog® FlexPen® so the needle is pointing down.
  - Press the push-button all the way in.

The insulin should fill the lower part of the big outer needle cap (see diagram L). If the NovoLog® FlexPen® has released too much or too little insulin, do the function check again. If the same problem happens again, do not use your NovoLog® FlexPen® and contact Novo Nordisk at 1-800-727-6500.

**Maintenance**

Your FlexPen® is designed to work accurately and safely. It must be handled with care. Avoid dropping your FlexPen® as it may damage it. If you are concerned that your FlexPen® is damaged, use a new one. You can clean the outside of your FlexPen® by wiping it with a damp cloth. Do not soak or wash your FlexPen® as it may damage it. Do not refill your FlexPen®.

- Remove the needle from the NovoLog® FlexPen® after each injection. This helps to ensure sterility, prevent leakage of insulin, and will help to make sure you inject the right dose of insulin for future injections.
- Be careful when handling used needles to avoid needle sticks and transfer of infectious diseases.
- Keep your NovoLog® FlexPen® and needles out of the reach of children.
- Use NovoLog® FlexPen® as directed to treat your diabetes.
- Needles and NovoLog® FlexPen® must not be shared. Always use a new needle for each injection.

Novo Nordisk is not responsible for harm due to using this insulin pen with products not recommended by Novo Nordisk.

As a precautionary measure, always carry a spare insulin delivery device in case your NovoLog® FlexPen® is lost or damaged.

Remember to keep the disposable NovoLog® FlexPen® with you. Do not leave it in a car or other location where it can get too hot or too cold.
NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

**INDICATIONS AND USAGE**

NovoLog® Mix 70/30 is an insulin analog indicated to improve glycemic control in patients with diabetes mellitus. Important Limitations of Use: In premix insulins, such as NovoLog® Mix 70/30, the proportions of rapid acting and long acting insulins are fixed and do not allow for basal versus prandial dose adjustments (1).

**DOSAGE AND ADMINISTRATION**

- Only for subcutaneous injection (2.1)
  - Type 1 DM: dose within 15 minutes before meal initiation.
  - Type 2 DM: dose within 15 minutes before or after starting a meal.
- Do not administer intravenously (2.1).
- Do not use in insulin infusion pumps (2.1).
- Must be resuspended immediately before use (2.2).

**DOSAGE FORMS AND STRENGTHS**

Each presentation contains 100 Units of insulin aspart per mL (U-100) (3)
- 10 mL vials
- 3 mL NovoLog® Mix 70/30 FlexPen®

**CONTRAINDICATIONS**

- Do not use during episodes of hypoglycemia (4).
- Do not use in patients with hypersensitivity to NovoLog® Mix 70/30 or one of its excipients (4).

**WARNINGS AND PRECAUTIONS**

- NovoLog® Mix 70/30 should not be mixed with any other insulin product (5.1).
- Hypoglycemia is the most common adverse effect of insulin therapy. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision (5.1, 5.2).
- Insulin, particularly when given in settings of poor glycemic control, can cause hypokalemia. Use caution in patients predisposed to hypokalemia (5.3).
- Like all insulins, NovoLog® Mix 70/30 requirements may be reduced in patients with renal impairment or hepatic impairment (5.4, 5.5).

**ADVERSE REACTIONS**

Adverse reactions observed with insulin therapy include hypoglycemia, allergic reactions, local injection site reactions, lipodystrophy, rash and pruritus (6).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- The following may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g. octreotide), sulfonamide antibiotics (7).
- The following 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 (7).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin (7).
- Pentamidine may cause hypoglycemia, which may be followed by hyperglycemia (7).
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 5/2010
NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

8.5 Geriatric Use

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NovoLog® Mix 70/30 is an insulin analog indicated to improve glycemic control in patients with diabetes mellitus.

Important Limitations of Use:

In premix insulins, such as NovoLog® Mix 70/30, the proportions of rapid acting and long acting insulins are fixed and do not allow for basal versus prandial dose adjustments.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

NovoLog® Mix 70/30 is an insulin analog with an earlier onset and intermediate duration of action in comparison to the basal human insulin premix. The addition of protamine to the rapid-acting aspart insulin analog (NovoLog®) results in insulin activity that is 30% short-acting and 70% long-acting. NovoLog® Mix 70/30 is typically dosed on a twice-daily basis (with each dose intended to cover 2 meals or a meal and a snack). The dose of NovoLog® Mix 70/30 must be individualized. The written prescription for NovoLog® Mix 70/30 should include the full name, to avoid confusion with NovoLog® (insulin aspart) and Novolin® 70/30 (human premix).

NovoLog® Mix 70/30 should appear uniformly white and cloudy. Do not use it if it looks clear or if it contains solid particles. NovoLog® Mix 70/30 should not be used after the printed expiration date.

NovoLog® Mix 70/30 should be administered by subcutaneous injection in the abdominal region, buttoks, thigh, or upper arm. NovoLog® Mix 70/30 has a faster onset of action than human insulin premix 70/30 and should be dosed within 15 minutes before meal initiation for patients with type 1 diabetes. For patients with type 2 diabetes, dosing should occur within 15 minutes before or after meal initiation. Injection sites should be rotated within the same region to reduce the risk of lipodystrophy. As with all insulins, the duration of action may vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

NovoLog® Mix 70/30 should not be administered intravenously or used in insulin infusion pumps. Dose regimens of NovoLog® Mix 70/30 will vary among patients and should be determined by the health care professional familiar with the patient's recommended glucose treatment goals, metabolic needs, eating habits, and other lifestyle variables.

2.2 Resuspension

NovoLog® Mix 70/30 is a suspension that must be visually inspected and resuspended immediately before use. The NovoLog® Mix 70/30 vial should be rolled gently in your hands in a horizontal position 10 times to mix it. The rolling procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately. Resuspension is easier when the insulin has reached room temperature.

The NovoLog® Mix 70/30 FlexPen® should be rolled 10 times gently between your hands in a horizontal position. Thereafter, turn the NovoLog® Mix 70/30 FlexPen® upside down so that the glass ball moves from one end of the reservoir to the other. Do this at least 10 times. The rolling and turning procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately. Before each subsequent injection, turn the disposable NovoLog® Mix 70/30 FlexPen® upside down so that the glass ball moves from one end of the reservoir to the other at least 10 times and until the suspension appears uniformly white and cloudy. Inject immediately.

3 DOSAGE FORMS AND STRENGTHS

NovoLog® Mix 70/30 is available in the following package sizes: each presentation contains 100 units of insulin aspart per mL (U-100).

- 10 mL vials
- 3 mL NovoLog® Mix 70/30 FlexPen®

4 CONTRAINDICATIONS

NovoLog® Mix 70/30 is contraindicated

- during episodes of hypoglycemia
- in patients with hypersensitivity to NovoLog® Mix 70/30 or one of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Administration

The short and long-acting components of insulin mixes, including NovoLog® Mix 70/30, cannot be titrated independently. Because NovoLog® Mix 70/30 has peak pharmacodynamic activity between 1-4 hours after injection, it should be administered within 15 minutes of meal initiation [see Clinical Pharmacology (12)]. 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 who require more frequent meals.

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

NovoLog® Mix 70/30 should not be used intravenously.

NovoLog® Mix 70/30 should not be used in insulin infusion pumps.

Glucose monitoring is recommended for all patients with diabetes. 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. Changes may also be necessary 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.

Needles and NovoLog® Mix 70/30 FlexPen® must not be shared.

5.2 Hypoglycemia

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog® Mix 70/30. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even 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® Mix 70/30.

The timing of hypoglycemia may reflect the time-action profile of the insulin formulation [see Clinical Pharmacology (12)]. Other factors, such as changes in dietary 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 (7)]. 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 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 long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control [see Drug Interactions (7)].

5.3 Hypokalemia

All insulin products, including NovoLog® Mix 70/30, 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 or patients taking medications sensitive to potassium concentrations).

5.4 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 [see Clinical Pharmacology (12.3)].

5.5 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 [see Clinical Pharmacology (12.3)].

5.6 Hypersensitivity and Allergic Reactions

Local Reactions - As with other insulin therapy, patients may experience reactions such as erythema, edema or pruritus at the site of NovoLog® Mix 70/30 injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog® Mix 70/30. In some instances, these reactions may be related to the insulin molecule, other components in the insulin preparation including protamine and cressel, components in skin cleansing agents, or injection techniques. Localized reactions and generalized myalgias have been reported with the use of cressel as an injectable excipient.

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.

5.7 Antibody Production

Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in a 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.

6 ADVERSE REACTIONS

Clinical Trial Experience

Clinical trials are conducted under widely varying designs, therefore, the adverse reaction rates reported in one clinical trial may not be easily compared to those 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® Mix 70/30 [see Warnings and Precautions (5.2)]. NovoLog® Mix 70/30 should not be used during episodes of hypoglycemia [see Contraindications (4) and Warnings and Precautions (5)].

- **Insulin initiation and glucose control intensification**

Intensification or rapid improvement in glucose control has been associated with transitory, reversible ophthalmologic refractive 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® Mix 70/30, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohyper trophy (thickening of adipose tissue) and lipatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy.

- **Weight gain**

Weight gain can occur with some insulin therapies, including NovoLog® Mix 70/30, and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

- **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 a clinical trial with NovoLog® Mix 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below. The trial was a three-month, open-label trial in patients with Type 1 or Type 2 diabetes who were treated twice daily (before breakfast and before supper) with NovoLog® Mix 70/30.

<table>
<thead>
<tr>
<th>Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 diabetes mellitus (Adverse events with frequency ≥ 5% are included.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
</tr>
<tr>
<td>Diastolic dyspnea</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Skeletal pain</td>
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<tr>
<td>Upper respiratory tract infection</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 diabetes mellitus (Adverse events with frequency ≥ 5% are included.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
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<td>Hypoglycemia</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Headache</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Neuropathy</td>
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<tr>
<td>Pharyngitis</td>
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<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
</tbody>
</table>

**Postmarketing Data**

Additional adverse reactions have been identified during post-approval use of NovoLog® Mix 70/30. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. They include medication errors in which other insulins have been accidentally substituted for NovoLog® Mix 70/30 [see Patient Counseling Information (17)].

7 **DRUG INTERACTIONS**

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.
NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

- The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, propramidone, bile salts, etc.
- The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, etc.
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

An open-label, randomized study compared the safety and efficacy of NovoLog® (the rapid-acting component of NovoLog® Mix 70/30) versus human insulin in the treatment of pregnant women with Type 1 diabetes (322 exposed pregnancies [NovoLog®: 157, human insulin: 165]). Two-thirds of the enrolled patients were already pregnant when they entered the study. Since only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Mean HbA1C of ~6% was observed in both groups during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

Animal reproduction studies have not been conducted with NovoLog® Mix 70/30. However, subcutaneous and intramuscular injection studies have been performed with NovoLog® (the rapid-acting component of NovoLog® Mix 70/30) in 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-partum rise in plasma glucose levels and increased plasma glucose levels 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 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.

Female patients should be advised to discuss with their physician if they intend to, or if they become pregnant. There are no adequate and well-controlled studies of the use of NovoLog® Mix 70/30 in pregnant women.

8.3 Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk as occurs with human insulin. There are no adequate and well-controlled studies of the use of NovoLog® Mix 70/30 or NovoLog® in lactating women. Women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

Safety and effectiveness of NovoLog® Mix 70/30 have not been established in pediatric patients.

8.5 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.
Figure 2. Pharmacodynamic Activity Profile of NovoLog® Mix 70/30 and Novolin® 70/30 in healthy subjects.

12.3 Pharmacokinetics

The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart (NovoLog®) reduces the molecule's tendency to form hexamers as observed with regular human insulin. The rapid absorption characteristics of NovoLog® are maintained by NovoLog® Mix 70/30. The insulin aspart in the soluble component of NovoLog® Mix 70/30 is absorbed more rapidly from the subcutaneous layer than regular human insulin. The remaining 70% is in crystalline form as insulin aspart protamine which has a prolonged absorption profile after subcutaneous injection.

Bioavailability and Absorption - The relative bioavailability of NovoLog® Mix 70/30 compared to NovoLog® and Novolin® 70/30 indicates that the insulins are absorbed to similar extent. In euglycemic clamp studies in healthy volunteers (n=23) after dosing with NovoLog® Mix 70/30 (0.2 U/kg), a mean maximum serum concentration (Cmax) of 23.4 ± 5.3 mU/L was reached after 60 minutes. The mean half-life (t1/2) of NovoLog® Mix 70/30 was about 8 to 9 hours. Serum insulin levels returned to baseline 15 to 18 hours after a subcutaneous dose of NovoLog® Mix 70/30. Similar data were seen in a separate euglycemic clamp study in healthy volunteers (n=24) after dosing with NovoLog® Mix 70/30 (0.3 U/kg). A Cmax of 61.3 ± 20.1 mU/L was reached after 65 minutes. Serum insulin levels returned to baseline 12 hours after a subcutaneous dose.

The Cmax and the area under the insulin concentration-time curve (AUC) after administration of NovoLog® Mix 70/30 was approximately 20% greater than those after administration of Novolin® 70/30, (see Fig. 3 for pharmacokinetic profiles).

Figure 3. Pharmacokinetic Profiles of NovoLog® Mix 70/30 and Novolin® 70/30

Distribution and Elimination - NovoLog® has a low binding to plasma proteins, 0 to 9%, similar to regular human insulin. After subcutaneous administration in normal male volunteers (n=24), NovoLog® was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

The effect of sex, age, obesity, ethnic origin, renal and hepatic impairment, pregnancy, or smoking, on the pharmacodynamics and pharmacokinetics of NovoLog® Mix 70/30 has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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 found with NovoLog® was not significantly different from that found with 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 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.

13.2 Animal Toxicology and/or Pharmacology

In standard biological assays in mice and rats, one unit of NovoLog® has the same glucose-lowering effect as one unit of regular human insulin. However, the effect of NovoLog® Mix 70/30 is more rapid in onset compared to Novolin® (human insulin) 70/30 due to its faster absorption after subcutaneous injection.

14 CLINICAL STUDIES

14.1 NovoLog® Mix 70/30 versus Novolin® 70/30

In a three-month, open-label trial, patients with Type 1 (n=104) or Type 2 (n=187) diabetes were treated twice daily (before breakfast and before supper) with NovoLog® Mix 70/30 or Novolin® 70/30. Patients had received insulin for at least 24 months before the study. Oral hypoglycemic agents were not allowed within 1 month prior to the study or during the study. The small changes in HbA1c were comparable across the treatment groups (see Table 3).

Table 3: Glycemic Parameters at the End of Treatment [Mean ± SD (N subjects)]

<table>
<thead>
<tr>
<th>Type 1, N=104</th>
<th>NovoLog® Mix 70/30</th>
<th>Novolin® 70/30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Blood Glucose (mg/dL)</td>
<td>174 ± 64 (48)</td>
<td>142 ± 59 (44)</td>
</tr>
<tr>
<td>1.5 Hour Post Breakfast (mg/dL)</td>
<td>187 ± 82 (48)</td>
<td>200 ± 82 (42)</td>
</tr>
<tr>
<td>1.5 Hour Post Dinner (mg/dL)</td>
<td>162 ± 77 (47)</td>
<td>171 ± 66 (41)</td>
</tr>
<tr>
<td>HbA1c (%) Baseline</td>
<td>8.4 ± 1.2 (51)</td>
<td>8.5 ± 1.1 (46)</td>
</tr>
<tr>
<td>HbA1c (%) Week 12</td>
<td>8.4 ± 1.1 (51)</td>
<td>8.3 ± 1.0 (47)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 2, N=187</th>
<th>NovoLog® Mix 70/30</th>
<th>Novolin® 70/30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Blood Glucose (mg/dL)</td>
<td>153 ± 40 (76)</td>
<td>152 ± 69 (93)</td>
</tr>
<tr>
<td>1.5 Hour Post Breakfast (mg/dL)</td>
<td>182 ± 65 (75)</td>
<td>200 ± 80 (92)</td>
</tr>
<tr>
<td>1.5 Hour Post Dinner (mg/dL)</td>
<td>168 ± 51 (75)</td>
<td>191 ± 65 (93)</td>
</tr>
<tr>
<td>HbA1c (%) Baseline</td>
<td>8.1 ± 1.2 (82)</td>
<td>8.2 ± 1.3 (98)</td>
</tr>
<tr>
<td>HbA1c (%) Week 12</td>
<td>7.9 ± 1.0 (81)</td>
<td>8.1 ± 1.1 (96)</td>
</tr>
</tbody>
</table>

The significance, with respect to the long-term clinical sequelae of diabetes, of the differences in postprandial hyperglycemia between treatment groups has not been established.

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.

14.2 Combination Therapy: Insulin and Oral Agents in Patients with Type 2 Diabetes

Trial 1:

In a 34-week, open-label trial, insulin-naïve patients with type 2 diabetes currently treated with 2 oral antidiabetic agents were switched to treatment with metformin and pioglitazone. During an 8-week optimization period metformin and pioglitazone were increased to 2500 mg per day and 30 or 45 mg per day, respectively. After the optimization period, subjects were randomized to receive either NovoLog® Mix 70/30 twice daily added on to the metformin and pioglitazone regimen or continue the current optimized metformin and pioglitazone therapy. NovoLog® Mix 70/30 was started at a dose of 6 IU twice daily (before breakfast and before supper). Insulin doses were titrated to a pre-meal glucose goal of 80-110 mg/dL. The total daily insulin dose at the end of the study was 56.9 ± 30.5 IU.
Table 4: Combination Therapy with Oral Agents and Insulin in Patients with Type 2 Diabetes Mellitus [Mean (SD)]

<table>
<thead>
<tr>
<th>Treatment duration 24-weeks</th>
<th>NovoLog® Mix 70/30 + Metformin + Pioglitazone</th>
<th>Metformin + Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c Baseline mean ± SD (n)</td>
<td>8.1 ± 1.0 (102)</td>
<td>8.1 ± 1.0 (98)</td>
</tr>
<tr>
<td>End-of-study mean ± SD (n) - LOCF</td>
<td>6.6 ± 1.0 (93)</td>
<td>7.8 ± 1.2 (87)</td>
</tr>
<tr>
<td>Adjusted Mean change from baseline ± SE (n)*</td>
<td>-1.6 ± 0.1 (93)</td>
<td>-0.3 ± 0.1 (87)</td>
</tr>
<tr>
<td>Treatment difference mean ± SE* 95% CI</td>
<td>-1.3 ± 0.1 (-1.6, -1.0)</td>
<td></td>
</tr>
<tr>
<td>Percentage of subjects reaching HbA1c &lt;7.0%</td>
<td>76%</td>
<td>24%</td>
</tr>
<tr>
<td>Percentage of subjects reaching HbA1c &lt;6.5%</td>
<td>59%</td>
<td>12%</td>
</tr>
<tr>
<td>Fasting Blood Glucose (mg/dL) Baseline Mean ± SD (n)</td>
<td>173 ± 39.8 (93)</td>
<td>163 ± 35.4 (88)</td>
</tr>
<tr>
<td>End of Study Mean ± SD (n) - LOCF</td>
<td>130 ± 50.0 (90)</td>
<td>162 ± 40.8 (84)</td>
</tr>
<tr>
<td>Adjusted Mean change from baseline ± SE (n)*</td>
<td>-43.0 ± 5.3 (90)</td>
<td>-3.9 ± 5.3 (84)</td>
</tr>
<tr>
<td>End of Study Blood Glucose (Plasma) (mg/dL) 2 Hour Post Breakfast</td>
<td>138 ± 42.8 (86)</td>
<td>188 ± 57.7 (74)</td>
</tr>
<tr>
<td>2 Hour Post Lunch</td>
<td>150 ± 41.5 (86)</td>
<td>176 ± 56.5 (74)</td>
</tr>
<tr>
<td>2 Hour Post Dinner</td>
<td>141 ± 57.8 (86)</td>
<td>196 ± 60.1 (74)</td>
</tr>
<tr>
<td>% of patients with severe hypoglycemia**</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>% of patients with minor hypoglycemia**</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>Weight gain at end of study (kg)**</td>
<td>4.6 ± 4.3 (92)</td>
<td>0.8 ± 3.2 (86)</td>
</tr>
</tbody>
</table>

*Adjusted mean per group, treatment difference, and 95% CI were obtained based on an ANCOVA model with treatment, FPG stratum, and secretagogue stratum as fixed factors and baseline HbA1c as the covariate.

**If metabolic control is improved by intensified insulin therapy, an increased risk of hypoglycemia and weight gain may occur.

Trial 2:
In a 26-week, open-label trial, insulin-naïve patients with type 2 diabetes with fasting plasma glucose above 140 mg/dL currently treated with metformin ± thiazolidinedione therapy were randomized to receive either NovoLog® Mix 70/30 twice daily (before breakfast and before supper) or insulin glargine once daily (see Table 5). NovoLog® Mix 70/30 was started at an average dose of 5-6 IU (0.07 ± 0.03 IU/kg) twice daily (before breakfast and before supper), and bedtime insulin glargine was started at 10-12 IU (0.13 ± 0.03 IU/kg). Insulin doses were titrated weekly by decrements or increments of -2 to +6 units per injection to a pre-meal glucose goal of 80-110 mg/dL. The metformin dose was adjusted to 2550 mg/day. Approximately one-third of the patients in each group were also treated with pioglitazone (30 mg/day). Insulin secretagogues were discontinued in order to reduce the risk of hypoglycemia. Most patients were Caucasian (53%), and the mean initial weight was 90 kg.

Table 5: Combination Therapy with Oral Agents and Two Types of Insulin in Patients with Type 2 Diabetes Mellitus [Mean (SD)]

<table>
<thead>
<tr>
<th>Treatment duration 28-weeks</th>
<th>NovoLog® Mix 70/30 + Metformin + Pioglitazone</th>
<th>Insulin Glargine + Metformin + Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>117</td>
<td>116</td>
</tr>
<tr>
<td>HbA1c Baseline (%)</td>
<td>9.7 ± 1.5 (117)</td>
<td>9.8 ± 1.4 (114)</td>
</tr>
<tr>
<td>End-of-study mean ± SD (108)</td>
<td>6.9 ± 1.2</td>
<td>7.4 ± 1.2 (114)</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-2.7 ± 1.6 (108)</td>
<td>-2.4 ± 1.5 (114)</td>
</tr>
<tr>
<td>Percentage of subjects reaching HbA1c ≥7.0%</td>
<td>66%</td>
<td>40%</td>
</tr>
<tr>
<td>Total Daily Insulin Dose at end of study (IU)</td>
<td>78 ± 40 (117)</td>
<td>51 ± 27 (116)</td>
</tr>
<tr>
<td>% of patients with severe hypoglycemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>% of minor hypoglycemia</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>Weight gain at end of study</td>
<td>5.4 ± 4.8 (117)</td>
<td>3.5 ± 4.5 (116)</td>
</tr>
</tbody>
</table>

*adjusted mean per group, treatment difference, and 95% CI were obtained based on an ANCOVA model with treatment, FPG stratum, and secretagogue stratum as fixed factors and baseline HbA1c as the covariate.

**If metabolic control is improved by intensified insulin therapy, an increased risk of hypoglycemia and weight gain may occur.

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
NovoLog® Mix 70/30 is available in the following package sizes: each presentation contains 100 Units of insulin aspart per mL (U-100).

10 mL vials NDC 0169-3685-12
3 mL NovoLog® Mix 70/30 FlexPen® NDC 0169-3696-19

NovoLog® Mix 70/30 vials and NovoLog® Mix 70/30 FlexPen® are latex free.

16.2 Recommended Storage
Unused NovoLog® Mix 70/30 should be stored in a refrigerator between 2°C and 8°C (36°F to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze NovoLog® Mix 70/30 or use NovoLog® Mix 70/30 if it has been frozen.

Vials: After initial use, a vial may be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Open vials may be refrigerated. Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

NovoLog® Mix 70/30 FlexPen®: Once a NovoLog® Mix 70/30 FlexPen® is punctured, it should be kept at temperatures below 30°C (86°F) for up to 14 days, but should not be exposed to excessive heat or sunlight. A NovoLog® Mix 70/30 FlexPen® use must NOT be stored in the refrigerator. Keep the disposable NovoLog® Mix 70/30 FlexPen® away from direct heat and sunlight. An unpunctured NovoLog® Mix 70/30 FlexPen® can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep any unused NovoLog® Mix 70/30 FlexPen® in the carton so it will stay clean and protected from light.

These storage conditions are summarized in the following table:

<table>
<thead>
<tr>
<th>Storage Condition</th>
<th>Not in-use (unopened)</th>
<th>Not in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room Temperature</td>
<td>Refrigetared</td>
<td>Room Temperature</td>
</tr>
<tr>
<td></td>
<td>(below 30°C[86°F])</td>
<td>(2°C - 8°C [36°F - 46°F])</td>
<td>(below 30°C[86°F])</td>
</tr>
<tr>
<td>10 mL vial</td>
<td>28 days</td>
<td>Until expiration date</td>
<td>28 days (refrigerated/room temperature)</td>
</tr>
<tr>
<td>3 mL NovoLog® Mix 70/30 FlexPen®</td>
<td>14 days</td>
<td>Until expiration date</td>
<td>14 days (Do not refrigerate)</td>
</tr>
</tbody>
</table>

17 PATIENT COUNSELING INFORMATION
[see FDA-Approved Patient Labeling]

17.1 Physician Instructions
Maintenance of normal or near-normal glucose control is a treatment goal in diabetes mellitus and has been associated with a reduction in diabetic complications. Patients should be informed about potential risks and advantages of NovoLog® Mix 70/30 therapy including the possible adverse reactions. 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. See Patient Information supplied with the product. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia, and diabetic ketoacidosis. 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. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental substitutions between NovoLog® Mix 70/30 and other insulin products have been reported. Patients should be instructed to always carefully check that they are administering the appropriate insulin to avoid medication errors between...
NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

NovoLog® Mix 70/30 and any other insulin. The prescription for NovoLog® Mix 70/30 should be written clearly in order to avoid confusion with other insulin products, for example, NovoLog® or Novolin® 70/30. In addition, the written prescription should clearly indicate the presentation, for example FlexPen® or vial.

Rx only

Date of Issue: May 7, 2010

Version: 9

Novo Nordisk®, NovoLog®, FlexPen®, and Novolin® are registered trademarks of Novo Nordisk® A/S.

NovoLog® Mix 70/30 is covered by US Patent Nos. 5,547,930; 5,618,913; 5,834,422; 5,840,680; 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.

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

For information about NovoLog® Mix 70/30 contact:
Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540, 1-800-727-6500

www.novonordisk-us.com

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143845 January 2011

NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

Patient Information

NovoLog® Mix 70/30
(NÓ-vó-log-MIX-SEV-en-tee-THIR-tee)

Read the Patient Information leaflet that comes with NovoLog® Mix 70/30 before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment. Make sure you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is NovoLog® Mix 70/30?

NovoLog® Mix 70/30 is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus. It is not known if NovoLog® Mix 70/30 is safe or effective in children.

Who should not use NovoLog® Mix 70/30?

Do not take NovoLog® Mix 70/30 if:
• Your blood sugar is too low (hypoglycemia)
• You are allergic to any of the ingredients in NovoLog® Mix 70/30. See the end of this leaflet for a complete list of ingredients in NovoLog® Mix 70/30. Check with your healthcare provider if you are not sure.

What should I tell my healthcare provider before taking NovoLog® Mix 70/30?

Before you use NovoLog® Mix 70/30, tell your healthcare provider if you:
• have kidney or liver problems
• have any other medical conditions. Medical conditions can affect your insulin needs and your dose of NovoLog® Mix 70/30.
• are pregnant or plan to become pregnant. It is not known if NovoLog® Mix 70/30 will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant. You and your healthcare provider should decide about the best way to manage your diabetes while you are pregnant.
• are breastfeeding or plan to breastfeed. It is not known if NovoLog® Mix 70/30 passes into your breast milk. You and your healthcare provider should decide if you will take NovoLog® Mix 70/30 while you breastfeed.

Tell your healthcare provider about all medicines you take, including prescriptions and non-prescription medicines, vitamins and herbal supplements.

NovoLog® Mix 70/30 may affect the way other medicines work, and other medicines may affect how NovoLog® Mix 70/30 works. Your NovoLog® Mix 70/30 dose may change if you take other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers and pharmacist when you get a new medicine.

How should I take NovoLog® Mix 70/30?

• Take NovoLog® Mix 70/30 exactly as your healthcare provider tells you to take it.
• Your healthcare provider will tell you how much NovoLog® Mix 70/30 to take and when to take it.
• Do not make any changes to your dose or type of insulin unless your healthcare provider tells you to.

NovoLog Mix 70/30 starts acting fast. If you have Type 1 diabetes, inject it up to 15 minutes before you eat a meal. Do not inject NovoLog® Mix 70/30 if you are not planning to eat within 15 minutes.

• If you have Type 2 diabetes, you may inject NovoLog® Mix 70/30 up to 15 minutes before or after starting your meal.

• Do Not mix NovoLog® Mix 70/30 with other insulin products.
• Do Not use NovoLog® Mix 70/30 in an insulin pump.

Inject NovoLog® Mix 70/30 under the skin (subcutaneously) of your stomach area, upper arms, buttocks or upper legs. NovoLog® Mix 70/30 may affect your blood sugar levels faster if you inject it under the skin of your stomach area. Never inject NovoLog® Mix 70/30 into a vein or into a muscle.

• Change (rotate) injection sites within the area you choose with each dose. Do not inject into the exact same spot for each injection.

• Read the instructions for use that come with your NovoLog® Mix 70/30. Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject NovoLog® Mix 70/30 before you start using it.

• NovoLog® Mix 70/30 comes in:
– 10 mL vials for use with a syringe
– 3 mL NovoLog® Mix 70/30 FlexPen®

• If you take too much NovoLog® Mix 70/30, your blood sugar may fall too low (hypoglycemia). You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and you could pass out (loss of consciousness).
NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

If you forget to take your dose of NovoLog® Mix 70/30, your blood sugar may go too high (hyperglycemia). If high blood sugar (hyperglycemia) is not treated it can lead to serious problems, like passing out (loss of consciousness), coma or even death. Follow your healthcare provider's instructions for treating high blood sugar.

Know your symptoms of high blood sugar which may include:
- increased thirst
- loss of appetite
- frequent urination
- drowsiness
- fruity smell on the breath

Do not share needles, insulin pens or syringes with others.

Check your blood sugar levels. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Your insulin dosage may need to change because of:
- illness
- stress
- other medicines you take
- change in physical activity or exercise
- change in diet

See the end of this patient information for instructions about preparing and giving your injection.

What should I consider while using NovoLog® Mix 70/30?
- Alcohol. Drinking alcohol may affect your blood sugar when you take NovoLog® Mix 70/30.
- Driving and operating machinery. You may have trouble paying attention or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright for you to drive if you often have:
  - low blood sugar
  - decreased or no warning signs of low blood sugar

NovoLog® Mix 70/30 may cause serious side effects, including:
- low blood sugar (hypoglycemia). Symptoms of low blood sugar may include:
  - sweating
  - fast heart beat
  - dizziness or lightheadedness
  - tingling of lips and tongue
  - headache
  - nausea, vomiting (throwing up) or stomach pain
  - increased thirst
  - frequent urination
  - drowsiness
  - fruity smell on the breath

You may have trouble paying attention or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright for you to drive if you often have:
  - low blood sugar
  - decreased or no warning signs of low blood sugar

Very low blood sugar can cause you to pass out (loss of consciousness), seizures, and death. Talk to your healthcare provider about how to tell if you have low blood sugar and what to do if this happens while taking NovoLog® Mix 70/30.

Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating low blood sugar.

Talk to your healthcare provider if low blood sugar is a problem for you. Your dose of NovoLog® Mix 70/30 may need to be changed.

Low potassium in your blood (hypokalemia)

Reactions at the injection site (local allergic reaction). You may get redness, swelling, and itching at the injection site. If you keep having skin reactions or they are serious talk to your healthcare provider.

Serious allergic reaction (whole body reaction). Get medical help right away, if you have any of these symptoms of an allergic reaction:
- a rash over your whole body
- have trouble breathing
- a fast heartbeat
- feel faint

The most common side effects of NovoLog® Mix 70/30 include:

- Skin thickening or pits at the injection site (lipodystrophy). Change (rotate) where you inject your insulin to help prevent these skin changes from happening. Do not inject insulin into this type of skin.
- Weight gain
- Swelling of your hands and feet
- Vision changes

These are not all of the possible side effects from NovoLog® Mix 70/30. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NovoLog® Mix 70/30?

All Unopened NovoLog® Mix 70/30:
- Keep all unopened NovoLog® Mix 70/30 in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze or store next to the refrigerator cooling element. Do not use NovoLog® Mix 70/30 if it has been frozen.
- Keep unopened NovoLog® Mix 70/30 in the carton to protect from light.
- Unopened vials can be used until the expiration date on the NovoLog® Mix 70/30 label, if the medicine has been stored in a refrigerator.
- Unused NovoLog® Mix 70/30 FlexPen® can be used until the expiration date on the NovoLog® Mix 70/30 FlexPen® label, if the medicine has been stored in a refrigerator.

After NovoLog® Mix 70/30 has been opened:

- Vials
  - Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28 days.
  - Keep vials away from direct heat or light.
  - Throw away an opened vial after 28 days of use, even if there is insulin left in the vial.

- NovoLog® Mix 70/30 FlexPen®
  - Keep at room temperature below 86°F (30°C) for up to 14 days.
  - Do not store a NovoLog® Mix 70/30 FlexPen® that you are using in the refrigerator.
  - Keep NovoLog® Mix 70/30 FlexPen® away from direct heat or light.
  - Throw away a used NovoLog® Mix 70/30 FlexPen® after 14 days, even if there is insulin left in the syringe.

Never use insulin after the expiration date that is printed on the label and carton.

Keep NovoLog® Mix 70/30 and all medicines out of the reach of children.

General advice about NovoLog® Mix 70/30

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use NovoLog® Mix 70/30 for a condition for which it was not prescribed. Do not give NovoLog® Mix 70/30 to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about NovoLog® Mix 70/30. If you would like more information about NovoLog® Mix 70/30 or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NovoLog® Mix 70/30 that is written for healthcare professionals. For more information call 1-800-727-6500 or go to www.novonordisk-us.com.

What are the ingredients in NovoLog® Mix 70/30?

- Active Ingredients NovoLog® Mix 70/30 FlexPen® and Vial: 70% insulin aspart protamine suspension and 30% insulin aspart injection (rDNA origin).
- Inactive Ingredients NovoLog® Mix 70/30 FlexPen®:
  - glycerol, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride, protamine sulfate, water for injection, hydrochloric acid or sodium hydroxide.
- Inactive Ingredients NovoLog® Mix 70/30 Vial:
  - mannitol, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride, protamine sulfate, water for injection, hydrochloric acid or sodium hydroxide.

All NovoLog® Mix 70/30 vials and NovoLog® Mix 70/30 FlexPen® are latex free.

Helpful information for people with diabetes is published by the American Diabetes Association, 1701 N Beauregard Street, Alexandria, VA 22311 and is available at www.diabetes.org.

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Novo Nordisk®, NovoLog®, and FlexPen® are registered trademarks of Novo Nordisk A/S.
NovoLog® Mix 70/30 is covered by US Patent Nos. 5,547,930; 5,618,913; 5,834,422; 5,840,680; 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.
Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
For information about NovoLog® Mix 70/30 contact:
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www.novonordisk-us.com
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143845 January 2011
NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

Patient Instructions for Use

NovoLog® Mix 70/30 FlexPen®

Read the following instructions carefully before you start using your NovoLog® Mix 70/30 FlexPen® and each time you get a refill. There may be new information. You should read the instructions even if you have used NovoLog® Mix 70/30 FlexPen® before.

NovoLog® Mix 70/30 FlexPen® is a disposable dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. NovoLog® Mix 70/30 FlexPen® is designed to be used with NovoFine® needles.

NovoLog® Mix 70/30 FlexPen® should not be used by people who are blind or have severe visual problems without the help of a person who has good eyesight and who is trained to use the NovoLog® Mix 70/30 FlexPen® the right way.

Getting ready

Make sure you have the following items:

- New NovoFine® needle
- Wash your hands with soap and water.
- Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin. NovoLog® Mix 70/30 should look cloudy after mixing.

Before your first injection with a new NovoLog® Mix 70/30 FlexPen® you must mix the insulin:

A. Let the insulin reach room temperature before you use it. This makes it easier to mix.

B. Roll the pen between your palms 10 times – it is important that the pen is kept horizontal (see diagram A).

C. Then gently move the pen up and down ten times between position 1 and 2 as shown, so the glass ball moves from one end of the cartridge to the other (see diagram C).

Repeat rolling and moving the pen until the liquid appears white and cloudy.

For every following injection move the pen up and down between positions 1 and 2 at least ten times until the liquid appears white and cloudy.

After mixing, complete all the following steps of the injection right away. If there is a delay, the insulin will need to be mixed again.

Wipe the rubber stopper with an alcohol swab.

Before you inject, there must be at least 12 units of insulin left in the cartridge to make sure the remaining insulin is evenly mixed. If there are less than 12 units left, use a new NovoLog® Mix 70/30 FlexPen®.

Attaching the needle

D. Remove the protective tab from a disposable needle.

Screw the needle tightly onto your NovoLog® Mix 70/30 FlexPen®. It is important that the needle is put on straight (see diagram D).

Never place a disposable needle on your NovoLog® Mix 70/30 FlexPen® until you are ready to take your injection.

E. Pull off the big outer needle cap (see diagram E).

F. Pull off the inner needle cap and dispose of it (see diagram F).

Always use a new needle for each injection to help ensure sterility and prevent blocked needles.

Be careful not to bend or damage the needle before use.

To reduce the risk of a needle stick, never put the inner needle cap back on the needle.

Giving the airshot before each injection

Before each injection small amounts of air may collect in the cartridge during normal use. To avoid injecting air and to make sure you take the right dose of insulin:

G. Turn the dose selector to select 2 units (see diagram G).

H. Hold your NovoLog® Mix 70/30 FlexPen® with the needle pointing up. Tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge (see diagram H).

I. Keep the needle pointing upwards, press the push-button all the way in (see diagram I). The dose selector returns to 0.

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

If you do not see a drop of insulin after 6 times, do not use the NovoLog® Mix 70/30 FlexPen® and contact Novo Nordisk at 1-800-727-6500.

A small air bubble may remain at the needle tip, but it will not be injected.

SELECTING YOUR DOSE

Check and make sure that the dose selector is set at 0.

J. Turn the dose selector to the number of units you need to inject. The pointer should line up with your dose.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer (see diagram J). When turning the dose selector, be careful not to press the push-button as insulin will come out.

You cannot select a dose larger than the number of units left in the cartridge.

You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

Do not use the cartridge scale printed on the cartridge to measure your dose of insulin.

GIVING THE INJECTION

Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting. Wipe the skin with an alcohol swab and let the area dry.

K. Insert the needle into your skin.

Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see diagram K). Be careful only to push the button when injecting.

Turning the dose selector will not inject insulin.

L. Keep the needle in the skin for at least 6 seconds, and keep the push-button pressed all the way in until the needle has been pulled out from the skin (see diagram L). This will make sure that the full dose has been given.

You may see a drop of NovoLog® Mix 70/30 at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with an alcohol swab. Do not rub the area.

After the injection

Do not recap the needle. Recapping can lead to a needle stick injury. Remove the needle from the NovoLog® Mix 70/30 FlexPen® after each injection. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

M. Put the needle and any empty NovoLog® Mix 70/30 FlexPen® or any used NovoLog® Mix 70/30 FlexPen® still containing insulin in a sharps container or some type of hard plastic or metal container with a screw top such as a detergent bottle or empty coffee can. These containers should be sealed and thrown away the right way. Check with your healthcare provider about the right way to throw away used syringes and needles. There may be local or state laws about how to throw away used needles and syringes. Do not throw away used needles and syringes in household trash or recycling bins.

The NovoLog® Mix 70/30 FlexPen® prevents the cartridge from being completely emptied. It is designed to deliver 300 units.

N. Put the pen cap on the NovoLog® Mix 70/30 FlexPen® and store the NovoLog® Mix 70/30 FlexPen® without the needle attached (see diagram M).
FUNCTION CHECK

N. If your NovoLog® Mix 70/30 FlexPen® is not working the right way, follow the steps below:

- Screw on a new NovoFine® needle.
- Remove the big outer needle cap and the inner needle cap.
- Do an airshot as described in “Giving the airshot before each injection”.
- Put the big outer needle cap onto the needle. Do not put on the inner needle cap.
- Turn the dose selector so the dose indicator window shows 20 units.
- Hold the NovoLog® Mix 70/30 FlexPen® so the needle is pointing down.
- Press the push-button all the way in.

The insulin should fill the lower part of the big outer needle cap (see diagram N). If NovoLog® Mix 70/30 FlexPen® has released too much or too little insulin, do the function check again. If the same problem happens again, do not use your NovoLog® Mix 70/30 FlexPen® and contact Novo Nordisk at 1-800-727-6500.

Maintenance

Your NovoLog® Mix 70/30 FlexPen® is designed to work accurately and safely. It must be handled with care. Avoid dropping your NovoLog® Mix 70/30 FlexPen® as it may damage it. If you are concerned that your NovoLog® Mix 70/30 FlexPen® is damaged, use a new one. You can clean the outside of your NovoLog® Mix 70/30 FlexPen® by wiping it with a damp cloth. Do not soak or wash your NovoLog® Mix 70/30 FlexPen® as it may damage it. Do not refill your NovoLog® Mix 70/30 FlexPen®.

- Remove the needle from the NovoLog® Mix 70/30 FlexPen® after each injection. This helps to ensure sterility, prevent leakage of insulin, and will help to make sure you inject the right dose of insulin for future injections.
- Be careful when handling used needles to avoid needle sticks and transfer of infectious diseases.
- Keep your NovoLog® Mix 70/30 FlexPen® and needles out of the reach of children.
- Use NovoLog® Mix 70/30 FlexPen® as directed to treat your diabetes. Needles and NovoLog® Mix 70/30 FlexPen® must not be shared.
- Always use a new needle for each injection.
- Novo Nordisk is not responsible for harm due to using this insulin pen with products not recommended by Novo Nordisk.
- As a precautionary measure, always carry a spare insulin delivery device in case your NovoLog® Mix 70/30 FlexPen® is lost or damaged.
- Remember to keep the disposable NovoLog® Mix 70/30 FlexPen® with you. Do not leave it in a car or other location where it can get too hot or too cold.
novo nordisk is dedicated to diabetes

Diabetes is our passion and our business

As a leader in diabetes, Novo Nordisk is dedicated to improving diabetes care worldwide. Novo Nordisk first marketed insulin for commercial use in 1923. Today we offer a broad line of medicines for diabetes. Novo Nordisk created the world’s first prefilled pen device for injections.

If you are having trouble affording your Novo Nordisk brand medicine, you may qualify for help. Call the Customer Care Center at 1-800-727-6500 to see if you qualify for assistance.

For more information about Novo Nordisk products for diabetes care, call 1-800-727-6500.

Go to Cornerstones4Care.com to register today. Or fill in the information below. Then tear off this card, fold and seal it, and mail it back to us.

First name_________________________ MI_____ Last name_____________________________
Address 1_______________________________________________________________________
Address 2_______________________________________________________________________
City______________________________________ State_______ZIP________________________
E-mail address_____________________________  Phone number_________________________
Birth date (mm/dd/yyyy)_____________________  Gender:  Male  Female

1. What type of diabetes do you have?  Type 1 diabetes  Type 2 diabetes

2. What year were you diagnosed with diabetes?____________________________________

3. What type of diabetes medicine do you take now? (Check all that apply)
   Insulin
   Diabetes pills (also called oral antidiabetic drugs, or OADs)
   GLP-1 medicine (Please list product name)_____________________________________
   None
   Other

4. Please write down the product names of the diabetes medicines you are currently taking:
   ___________________________________       _____________________________________
   ___________________________________       _____________________________________
   ___________________________________       _____________________________________

5. If you checked “diabetes pills” in question 3, how many types are you taking each day?
   1 type of diabetes pill  2 types of diabetes pills
   More than 2 types of diabetes pills

6. How do you take your insulin? (Check all that apply)
   Syringe  Pen  Insulin pump  Other delivery system

7. How long have you been on your current therapy?
   6 months or less  7 months to 1 year  1 to 3 years  3 years or more

8. How well do you feel you currently manage your diabetes?
   Not at all managed  Somewhat managed  Extremely well managed

9. How strongly do you agree with the following statement? “I am willing to give myself injections as often as needed to get control of my diabetes.”
   Not at all  Somewhat  Extremely
   Totally disagree  Neither agree nor disagree  Totally agree

10. I agree that the information I am providing may be used by Novo Nordisk, its affiliates or vendors to keep me informed about new products, services, special offers, or other opportunities that may be of interest to me, as they become available. THESE COMMUNICATIONS MAY CONTAIN MATERIAL MARKETING OR ADVERTISING NOVO NORDISK PRODUCTS, GOODS, OR SERVICES. If you no longer wish to receive communications by calling 1-877-744-2579, sending a brief note with my name and address to Novo Nordisk at PO Box 2003, Shawnee Mission, KS 66201, or by clicking on the “unsubscribe” link which will be available in future email communications. By providing my information to Novo Nordisk and acknowledging below, I certify that I am at least eighteen (18) years of age.

Signature _______________________________ Date______________________
It’s easy to get started with Cornerstones4Care™

Just go to Cornerstones4care.com to register, or fill in this reply card.

The Cornerstones4Care™ educational series is designed to help people with diabetes work with their diabetes care team to learn about and manage diabetes.

- diabetes and you
- your guide to better office visits
- diabetes medicines
- carb counting and meal planning
- your blood sugar diary

The photographs used in this booklet are for illustration only. The models in the photographs do not necessarily have diabetes or other ailments.

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