CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020986Orig1s002

Trade Name: NovoLog®

Generic or Proper Name: insulin aspart (rDNA origin)

Sponsor: Novo Nordisk Pharmaceuticals Inc.

Approval Date: 06/07/2000

Indication: NovoLog® is indicated for the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia. Because NovoLog® has a more rapid onset and a shorter duration of action than regular insulin, NovoLog® should normally be used in regimens together with an intermediate or long-acting insulin.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-986/S-002

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

Please refer to your supplemental new drug application dated October 30, 2000, received October 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog (insulin aspart [rDNA origin] injection).

We acknowledge receipt of your submissions dated February 14 and 16, and April 19, 2001; February 8, and March 8, 15, and 20, 2002. Your submission of February 8, 2002, constituted a complete response to our February 2, 2001, action letter.

This supplemental new drug application provides for the use of NovoPen 3 Demi insulin delivery device with NovoLog PenFill 3 mL cartridges and NovoFine needles. This supplemental new drug application also provides for a revised physician and patient package insert for NovoLog PenFill 3 mL cartridges to include the use of NovoPen 3 Demi insulin delivery device with the PenFill 3 mL cartridges.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the NovoPen 3 Demi Instruction Manual, package insert, and patient package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-986/S-002." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Julie Rhee, Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
1. NovoPen 3 Demi Instruction Manual
2. NovoLog insert
3. NovoLog patient insert

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff

4/11/02 07:25:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-002

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-986/S-002

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

Please refer to your supplemental new drug application dated October 30, 2000, received October 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog™ (insulin aspart [rDNA origin] injection).

We acknowledge receipt of your submissions dated November 6 and 15, 2000.

This supplement proposes the following change: A new [redacted] (b) (4) to be used in conjection with the 3 mL PenFill cartridges and NovoFine needles.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. The [redacted] (b) (4) is labeled with dosing precision of 0.5 IU and claims [redacted] (b) (4) Testing did not include an evaluation at the half-unit level. Please submit the following:

   a. Testing for the actual minimum dose of 0.5 IU [redacted] (b) (4)

   b. An intermediate dose test that compares the dose accuracy profiles for the next lower and higher doses (17.5 IU and 18.5 IU).

   c. A maximum dose evaluation that includes 34.5 IU.

2. The standard deviations for the 18 IU and the 35 IU doses appear to be very large when compared to the [redacted] (b) (4) setting precision in the endurance test which equals or exceeds the precision of the device.

3. Data to support the accuracy and reliability of the [redacted] (b) (4) function check, which uses fill levels to confirm the proper functioning of the device was not submitted.

4. A package insert that incorporates the use of [redacted] (b) (4) with NovoLog was not submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

David Orloff
2/2/01 05:13:05 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-002

LABELING

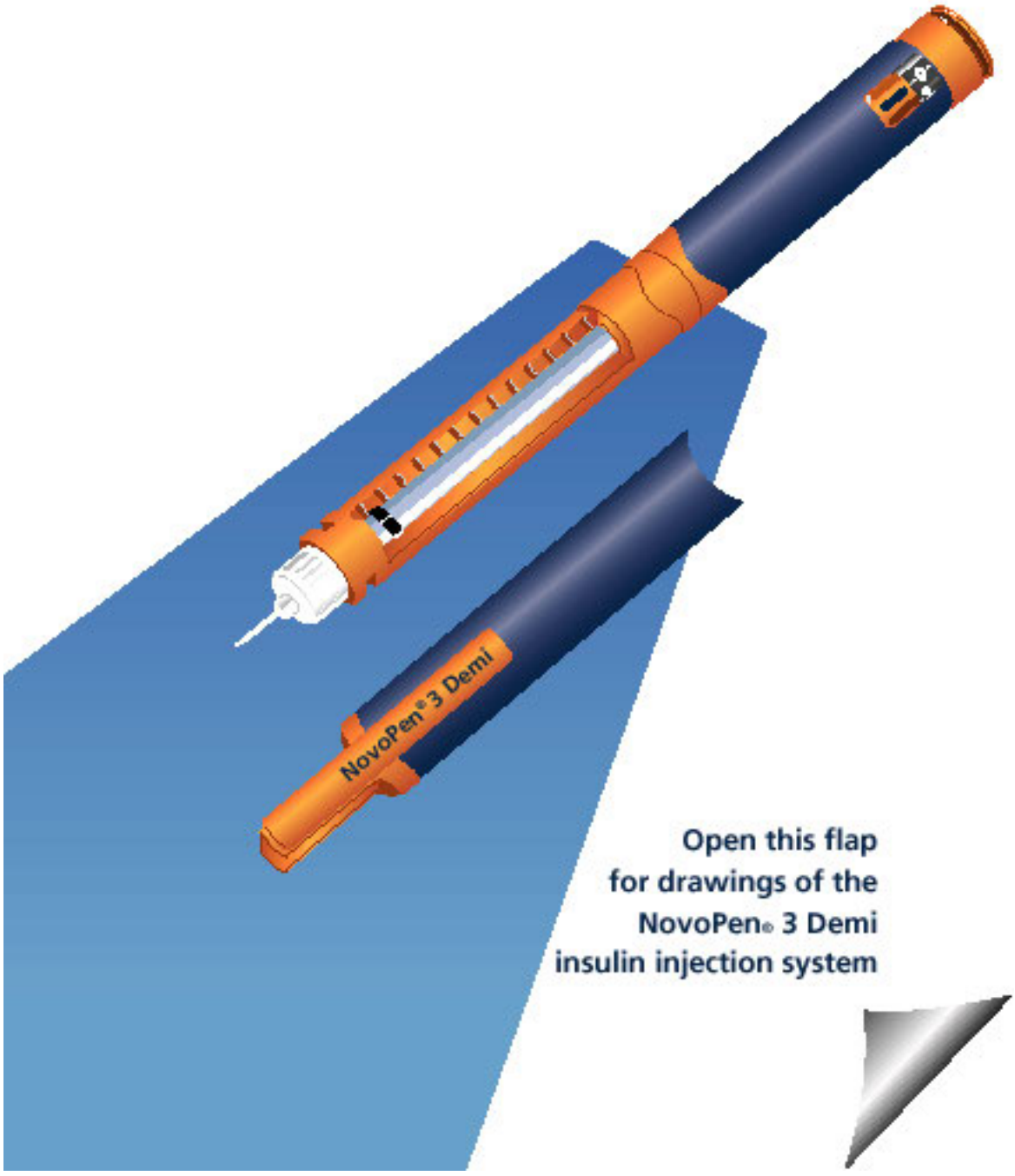
NovoPen® 3 Demi

Dial-A-Dose
Insulin Delivery System

Instructions For Use

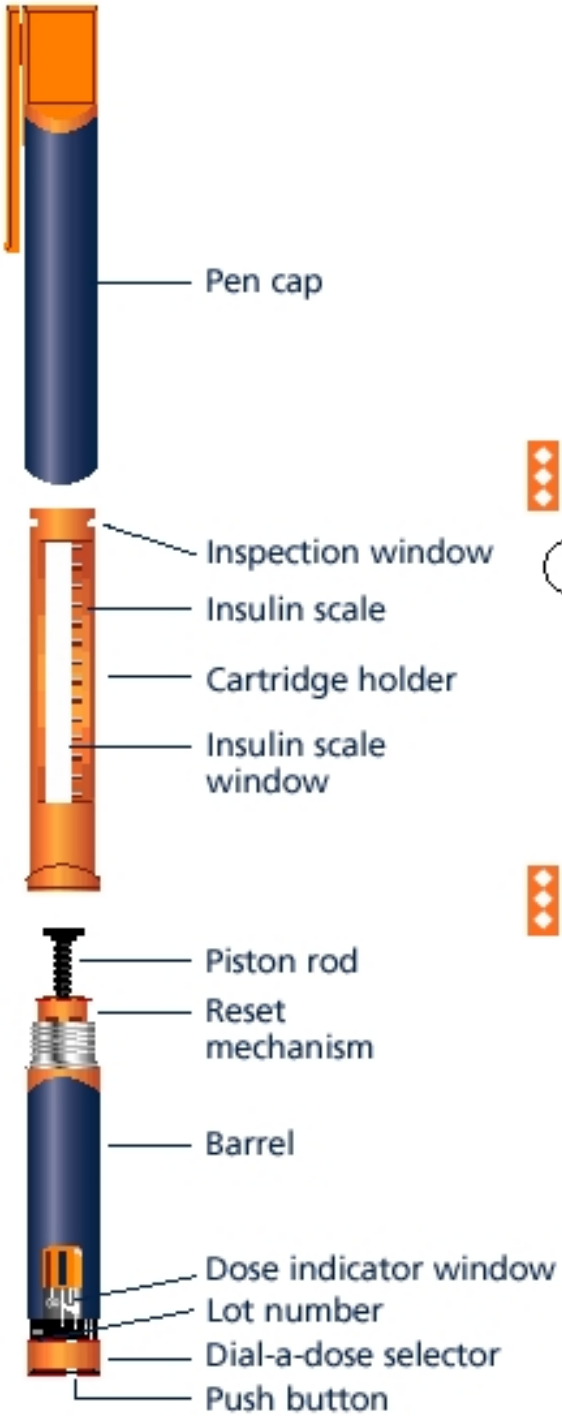
Notex - Tryk & Design as
Order no. 128826
NovoPen 3 Demi, USA
3. proof 00-10-26

Novo Nordisk

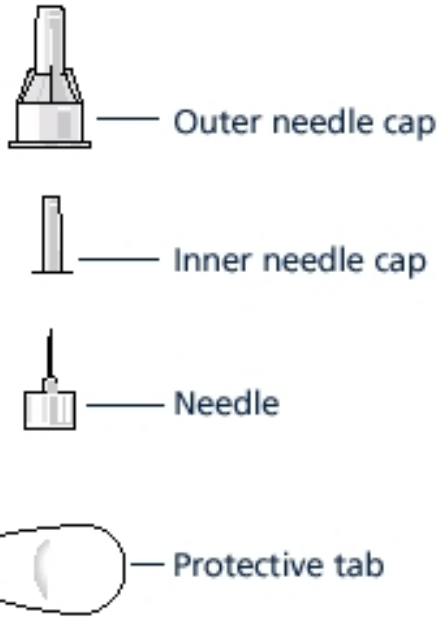

NovoPen® 3 Demi
Open this flap
for drawings of the
NovoPen® 3 Demi
insulin injection system

Corrections on this page = ◆◆◆

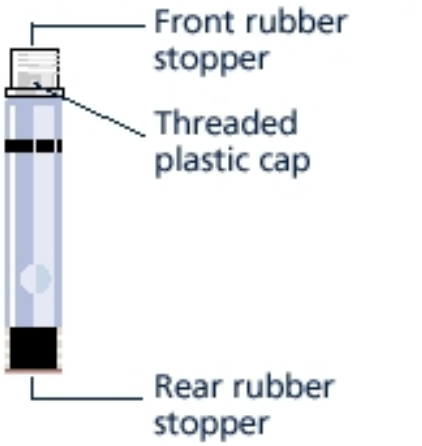
NovoPen® 3 Demi Insulin Delivery Device



NovoFine® Disposable Needle



PenFill® Cartridge (3 mL)



Need Help?
Call 1-800-727-6500

NovoPen®3 Demi Instruction Manual

Dial-A-Dose Insulin Delivery System

INTRODUCTION

NovoPen®3 Demi delivers a minimum dose of 1 unit to a maximum dose of 35 units of insulin in half unit steps. A raised circle on the push button makes it easy for you to know your NovoPen 3 Demi from the ordinary NovoPen 3. This booklet includes everything you need to know about using the NovoPen 3 Demi. Please read it carefully before using your NovoPen 3 Demi for the first time.

The NovoPen 3 Demi is designed for use with:
- PenFill® 3 mL cartridges.
- NovoFine® disposable needles.

NovoFine disposable needles are for single-use only.
You will also need alcohol swabs.

If you have any questions about your NovoPen 3 Demi insulin delivery system, please call Novo Nordisk Pharmaceuticals, Inc. at 1-800-727-6500.

Please complete and return the NovoPen 3 Demi warranty card.

See **Important Things to Know** and **Important Notes** on pages 33-35.

HOW TO USE THIS BOOKLET

This booklet gives you step-by-step instructions for using the NovoPen 3 Demi.

Begin by reviewing the drawing layout of the parts of the NovoPen 3 Demi, PenFill 3 mL cartridge, and NovoFine disposable needle. The inside front cover opens out so you have a handy reference while you read the rest of the booklet.

Most pages contain a drawing on the right with numbered instructions to the left of the drawing.
Important additional information is given below the drawing.

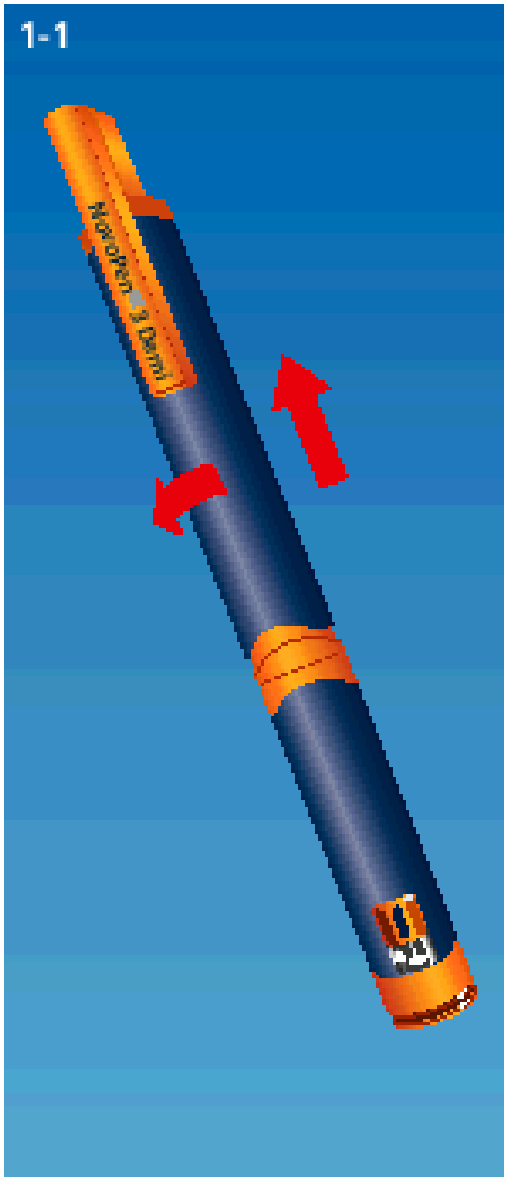
We suggest that you **read the text and look at the drawing** to make sure that you understand each step thoroughly.

TABLE OF CONTENTS

SECTION 1 Preparing the NovoPen 3 Demi

Remove the device cap:

1. Remove the NovoPen 3 Demi from the case.
2. Gently twist the pen cap until the cap separates from the barrel.
3. Pull the pen cap straight up to remove it.

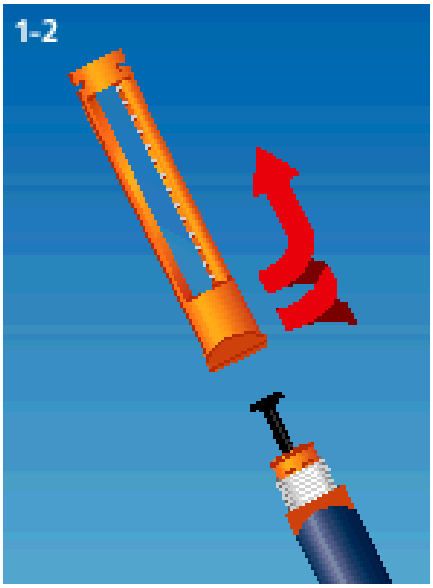


If you use more than one insulin product (such as Novolin® R, Novolin® N, Novolin® 70/30, or NovoLog®), use a separate insulin delivery device for each product.

SECTION 1 (cont.)

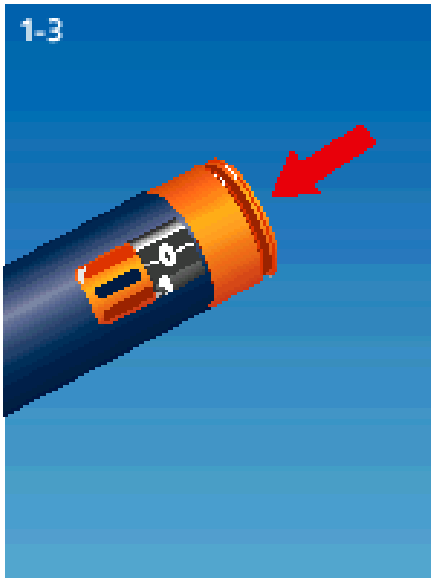
Separate the cartridge holder from the barrel:

4. Unscrew and remove the cartridge holder from the barrel.



Make sure the dose indicator window shows zero:

5. Press the push button all the way in until zero (0) appears in the window. The zero should be lined up with the stripe below the dose indicator window.



144 6

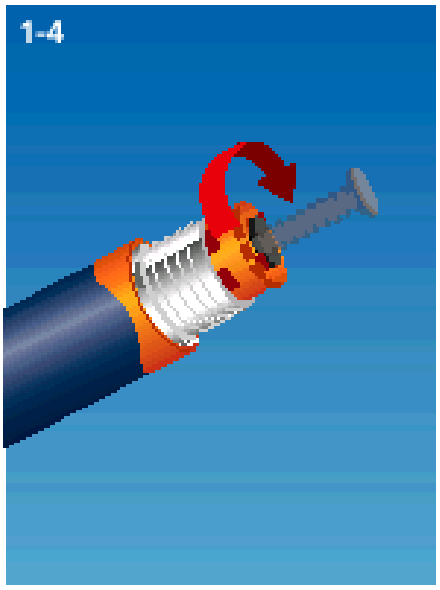
APPEARS THIS WAY ON ORIGINAL

SECTION 1 (cont.)

The end of the piston rod should be flat against the end of the reset mechanism prior to inserting each new PenFill 3 mL cartridge. It should not be sticking out.

If the piston rod is sticking out:

Turn the end of the reset mechanism in a clockwise direction until it is no longer sticking out. Never push the piston rod back in.

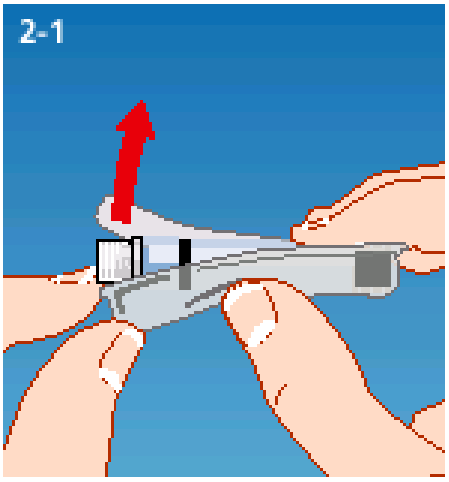


You should never reset the piston rod until it is time to remove the used PenFill 3 mL cartridge and insert a new one.

If the reset mechanism locks, it is usually due to improper technique. Gently turn the mechanism side to side until it unlocks. Then call our toll free number (1-800-727-6500) so that we may go over your technique with you.

SECTION 2 Inserting the PenFill 3 mL Cartridge

1. To remove the PenFill cartridge from its wrapper, push the cartridge through the foil side of the packaging. Always make sure that the PenFill cartridge you use contains the correct type of insulin (such as Novolin R, Novolin N, Novolin 70/30, or NovoLog). If you are treated with more than one type of insulin in PenFill cartridges, you should use a separate insulin delivery device for each type of insulin. Before use, check that the PenFill cartridge is full and intact. If not, do not use it.



2. In the PenFill Information For The Patient leaflet, you will find instructions on how to prepare the insulin if the PenFill contains a suspension insulin (white and cloudy) such as Novolin N or Novolin 70/30.

Each PenFill 3 mL cartridge contains a total of 300 units of insulin. Make sure you are using the correct type of insulin. On the glass part of the cartridge is the name of the insulin.

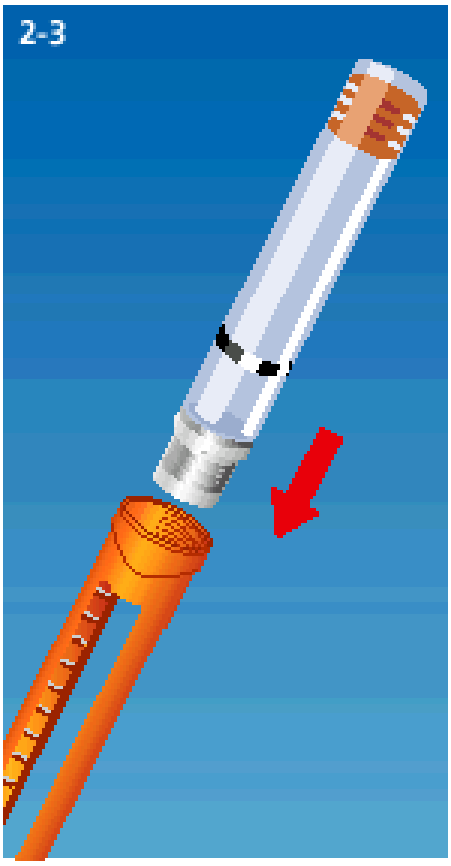
Each PenFill cartridge is for single-person use only. DO NOT share the same cartridge with anyone even if you attach a new disposable needle for each injection. Sharing the cartridge can spread disease.
Use only a new PenFill 3 mL cartridge when loading the NovoPen 3 Demi.
Never load a partially filled cartridge.
Never try to refill a used PenFill 3 mL cartridge.

9

SECTION 2 (cont.)

Insert the PenFill cartridge:

2. Hold the cartridge holder so the wider opening is up.
3. Drop the PenFill cartridge into the cartridge holder, plastic cap first.



A threaded plastic cap surrounds the end of the PenFill® cartridge, like the cap on a bottle. In the center is the front rubber stopper.

The rear rubber stopper is at the other end of the PenFill cartridge.

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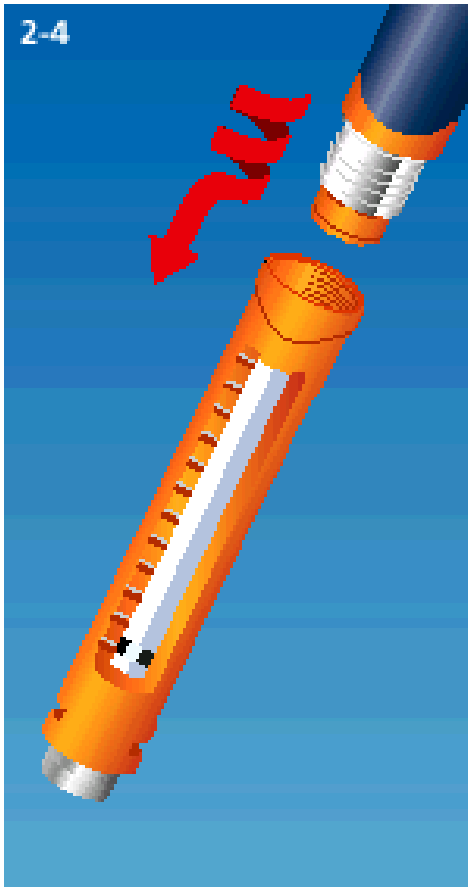
SECTION 2 (cont.)

Re-attach the cartridge holder:

4. Screw the barrel into the cartridge holder completely until it is tight.



You can see the cartridge in the insulin scale window. The cartridge holder has a scale with marks showing about how much insulin is left in the PenFill cartridge.

SECTION 3 Attaching the NovoFine® Disposable Needle

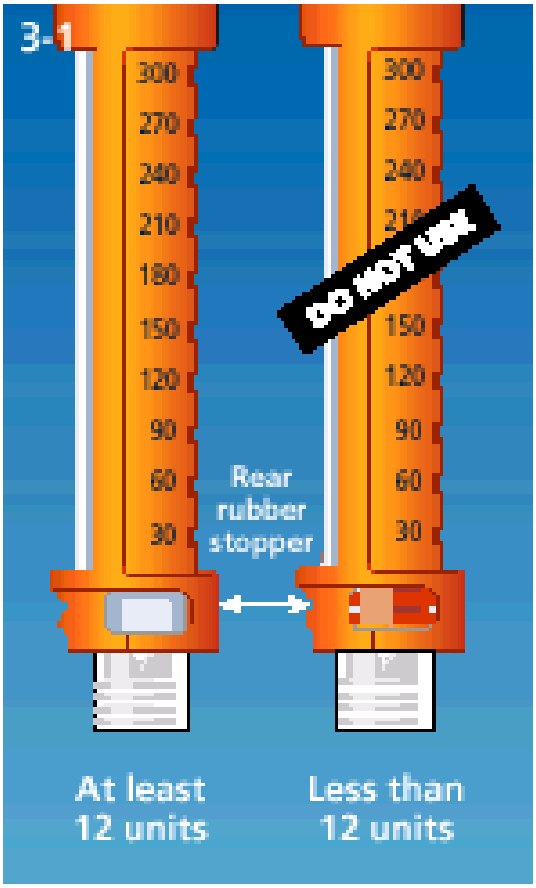
At the end of the cartridge holder are two inspection windows. You can see the cartridge through these windows.

If you use a suspension insulin (white and cloudy) such as Novolin® N or Novolin® 70/30, use the windows to check if there is enough insulin left for proper mixing. (see below)

Check the amount of insulin remaining:

- If the rear rubber stopper cannot be seen in the inspection window, you have enough insulin for mixing left in the cartridge.
- If the rear rubber stopper can be seen in the inspection window, you do not have enough insulin left in the cartridge and must insert a new PenFill 3 mL cartridge.

See Section 7 for instructions on removing a PenFill cartridge and Section 2 for inserting a new one.



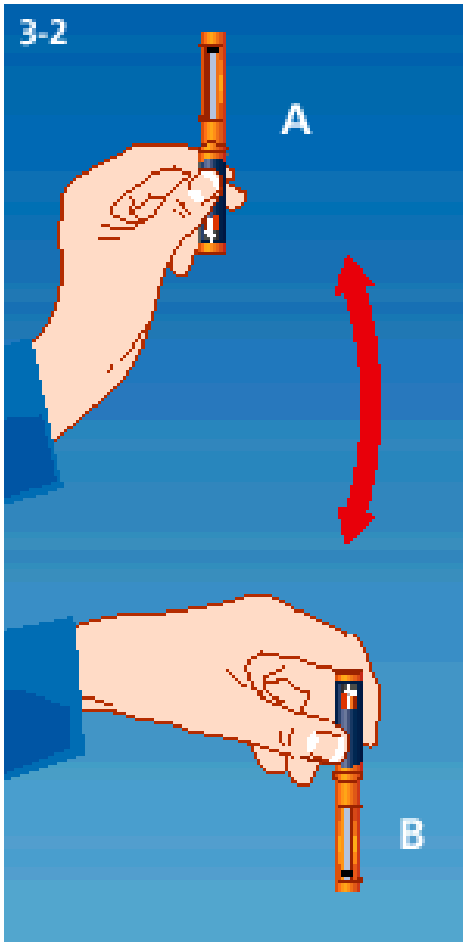
248 12

SECTION 3 (cont.)

For users of suspension insulin (white and cloudy) such as Novolin N or Novolin 70/30:

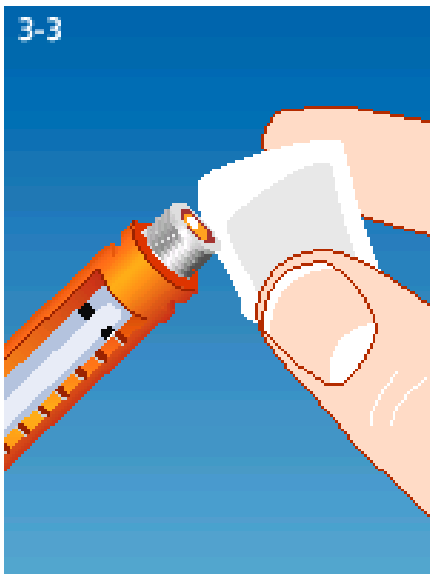
Always remix the insulin before each injection.

To remix the insulin, turn the NovoPen 3 Demi up and down between positions **A** and **B** 10 times or until the insulin looks uniformly white and cloud



SECTION 3 (cont.)

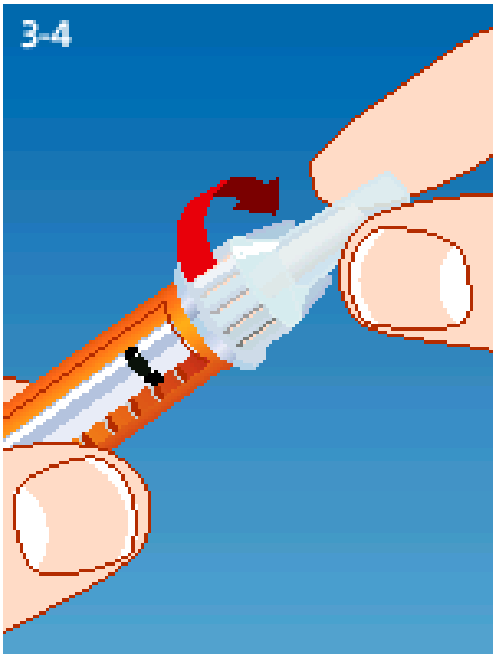
1. Wipe the front rubber stopper with an alcohol swab.



You must wipe the front rubber stopper with an alcohol swab before each injection, even if you are using the same PenFill cartridge.

SECTION 3 (cont.)

2. Remove the protective tab from the NovoFine disposable needle.
3. Screw the NovoFine disposable needle firmly onto the PenFill 3 mL cartridge until it is tight.



Never place a NovoFine disposable needle on your NovoPen 3 Demi until you are ready to do an air shot and give an injection.
If the NovoFine needle is left on, some liquid may leak out of the PenFill cartridge. This may cause a change in the strength of the suspension insulin such as Novolin N or Novolin 70/30.

SECTION 4 Doing an Air Shot

The PenFill cartridge may contain an air bubble, and small amounts of air may collect in the needle and PenFill cartridge when you use them. To avoid injecting air and to ensure proper dosing, you must perform an air shot before each injection.

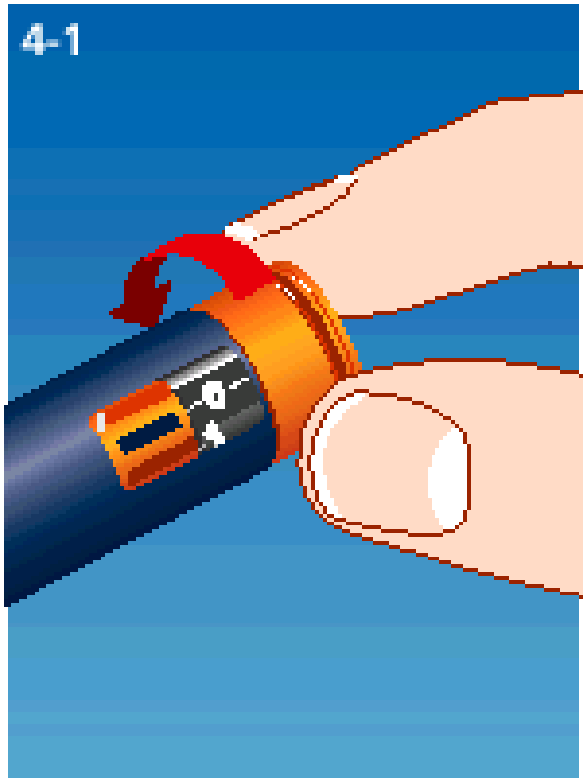
Before doing the air shot, the dose indicator window must show zero (0).

If you use a suspension insulin, such as Novolin N or Novolin 70/30 and have used the PenFill cartridge for previous injections, make sure there is enough insulin left in the PenFill cartridge to properly mix the insulin (see page 12). If there is enough insulin left in the PenFill cartridge, see the next page for instructions.

SECTION 4 (cont.)

Set the NovoPen 3 Demi for the air shot:

1. Turn the dial-a-dose selector to 2 units. Full units are shown as numbers. Half units are shown as long lines between the numbers.



If you dial more than 2 units, DO NOT turn the dial back to zero (0). If you do, the extra insulin will squirt out of the needle. You may complete the air shot with the number of units you have dialed or refer to Section 5 on page 21 for instructions on how to reset the dose to zero.

SECTION 4 (cont.)

Uncap the NovoFine needle:

2. Pull off the outer needle cap and set aside.
3. Pull off the inner needle cap and discard.

Do not use the needle if it is bent or damaged.

4. Hold the NovoPen 3 Demi with the NovoFine needle pointing up.
5. Tap the cartridge holder with your finger a few times to raise any air bubbles that may be present to the top of the cartridge.

SECTION 4 (cont.)

Do the air shot:

6. Press the push button all the way in. A drop of insulin should appear at the needle tip.

If no insulin appears, repeat the following steps, until a drop of insulin appears:

a. Make sure the NovoFine needle is securely attached.
b. Dial 2 units.
c. Tap the cartridge holder with your finger.
d. Press the push button all the way in.

There may still be some small air bubble(s) in the PenFill cartridge after this, but they will not affect your dose and they will not be injected.

When you press the push button, the piston rod presses against the rear rubber stopper. This moves the rear rubber stopper and pushes the correct amount of insulin up through the needle.

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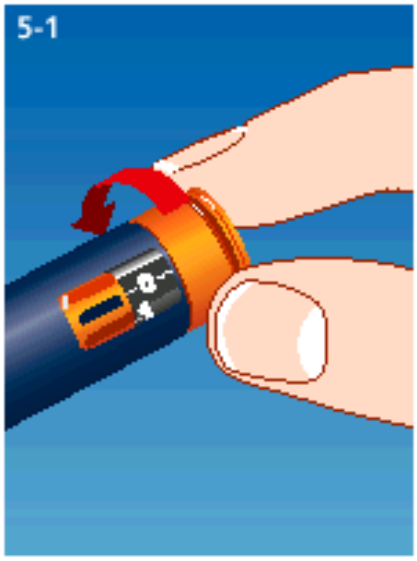
SECTION 5 Giving the Injection

Be sure to do an air shot before giving each injection (see pages 16-19).
Select the dose:

1. Check that the dial-a-dose selector is set to zero. If not, follow the instructions on the next page. Turn the dial-a-dose selector until you see the correct number of units in the dose indicator window. Full units are shown as numbers. Half units are shown as long lines between the numbers.

DO NOT use the clicking sound as a guide for selecting your dose.



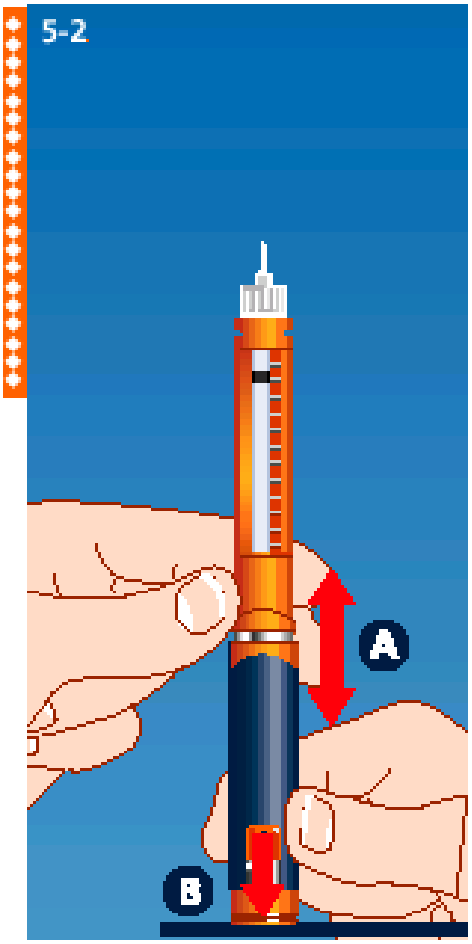
The NovoPen 3 Demi can deliver insulin in half unit steps from a minimum dose of 1 unit to a maximum dose of 35 units.

If you dial more than your dose, DO NOT turn the dial back to zero (0). If you do, the extra insulin will squirt out of the needle. For instructions on how to reset the dose to zero (0) so you can start again, see the next page.

SECTION 5 (cont.)

If you dial a larger dose than you need, pull the barrel and the cartridge holder apart, as shown in the drawing **A**. While holding them apart, gently press the push button against a hard surface and release your grip **B**. Your dose indicator window should be back to zero (0).

You can now dial the correct number of units.



SECTION 5 (cont.)

Giving the injection:

2. After the air shot is done and you have chosen the correct number of units, insert the NovoFine needle in the correct injection site on your body. (Use the injection technique recommended by your health care professional). If you use a suspension insulin such as Novolin N or Novolin 70/30, mix the insulin (see page 13, Section 3) and make sure the insulin looks uniformly white and cloudy before you inject.

3. Press the push button **as far as it will go** to deliver the insulin. Do not force it.

To ensure that all the insulin is injected, keep the NovoFine needle in the skin for several seconds after the injection with your thumb on the push button. Keep the push button fully depressed until after the NovoFine needle has been withdrawn.

Important: Never turn the dial-a-dose selector to inject the insulin.

When you get near the end of a PenFill cartridge, you may need to give yourself two injections to receive your full dose. Check the dose indicator window after

giving an injection. If zero does not appear in the dose indicator window, you did not receive your full dose. See the next page for instructions on how to get the remaining part of your dose.

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SECTION 5 (cont.)

4. **Check the dose indicator window to make sure it shows zero (0). If zero does not appear, you did not receive the full dose.**

If the dose indicator window does not show zero, there were not enough units of insulin in the PenFill cartridge for you to receive the full dose. The dose indicator window shows the number of units that you did not receive.

For example, if you dial **25** units and there are only **20** units left in the PenFill cartridge, after the injection the number in the dose indicator window will be **5** (25-20 = 5). If this happens, proceed with the following steps to get the remaining part of your dose:

a. Note the number of units in the dose indicator window.
b. Remove the NovoFine needle (see Section 6).
c. Remove the empty PenFill 3 mL cartridge (see Section 7).
d. Insert a new PenFill 3 mL cartridge (see Section 2).
e. Attach a NovoFine needle (see Section 3).
f. Do an air shot (see Section 4).
g. Dial the number of units noted in step a.
h. Give the injection.

SECTION 6 Removing the NovoFine Disposable Needle

Remove the NovoFine disposable needle:

1. After the injection, remove the needle without replacing the cap.

2. Hold the cartridge holder firmly while you unscrew the NovoFine disposable needle.

3. Place the NovoFine disposable needle in a puncture-resistant disposable container.

Health care professionals, relatives, and other caregivers should also follow the above instructions to eliminate the risk of unintended needle penetration.

The NovoFine disposable needle must be removed immediately after each injection without replacing the cap. If the NovoFine disposable needle is not removed, some liquid may leak out of the PenFill cartridge. This may cause a change in the strength of suspension insulins (white and cloudy) such as Novolin N or Novolin 70/30.

For information on how to throw away needle containers properly, contact your local trash company.

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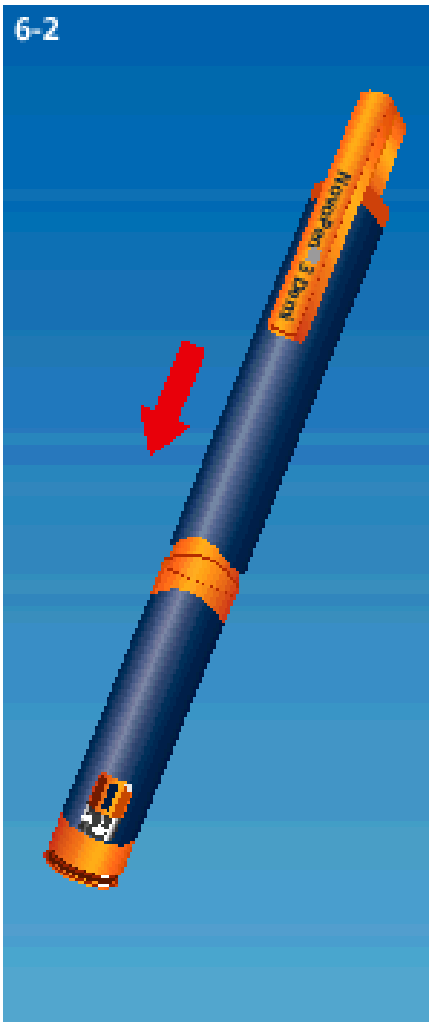
SECTION 6 (cont.)

Replace the pen cap:

4. After you remove the disposable needle, hold the pen cap so that the clip is lined up with the dose indicator window.

5. **Gently slide** the pen cap onto the barrel.



SECTION 7 Removing the PenFill 3 mL Cartridge

You will need to remove the PenFill cartridge for the following reasons:

- ~~When t~~The PenFill cartridge is empty.

- **If you use a suspension insulin such as Novolin N or Novolin 70/30:**

  When you see the rear rubber stopper in the inspection window, then you do not have enough insulin left in the PenFill cartridge for proper mixing.

Remove the barrel:

1. Remove the pen cap.

2. Hold the NovoPen 3 Demi with the dose indicator window at the top.

3. Unscrew the barrel from the cartridge holder.

SECTION 7 (cont.)

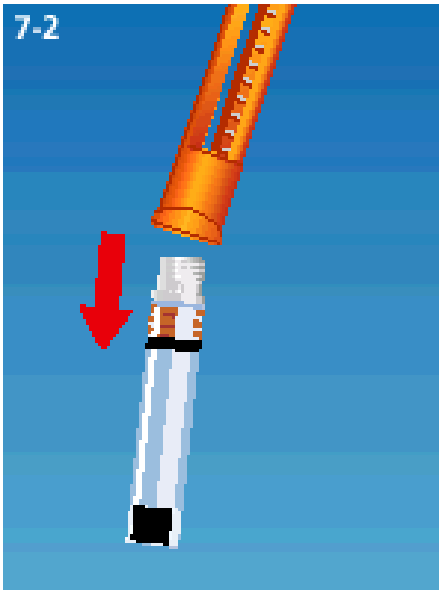
Remove the PenFill 3 mL cartridge:

4. Tip the cartridge holder. The PenFill cartridge will drop out.

5. Press the push button all the way in until zero (0) appears in the window.

6. Turn the end of the reset mechanism in a clockwise direction until the piston rod is no longer sticking out (refer to figure 1-4 on page 7).

7. To insert a new PenFill cartridge, please refer to Section 2.



If the reset mechanism locks, it is usually due to improper technique. Gently turn the mechanism side to side until it unlocks and then call our toll free number (1-800-727-6500) so that we may go over your technique with you.

FUNCTION CHECK

You should regularly check the functioning of your NovoPen 3 Demi, (for example, once a month or before starting a new box of PenFill cartridges). The function check is done by delivering 20 units of insulin into the outer needle cap. You will not be injecting insulin into your body.

Always check the functioning of the NovoPen 3 Demi if you suspect it has been damaged or if you are uncertain that it is delivering the correct dose.

Do not use NovoPen 3 Demi unless you are sure that it is working properly.

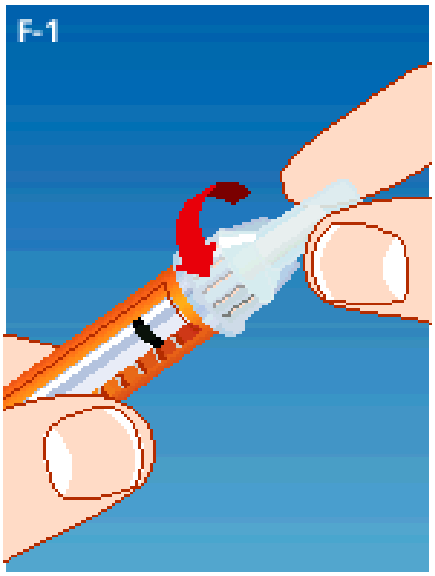
To perform the function check:

1. Attach a NovoFine disposable needle(see pages 12-15).

2. Do an air shot (see pages 16-19).

FUNCTION CHECK (cont.)

3. **Do not replace the inner needle cap.** Place the outer needle cap securely over the exposed NovoFine needle.



Expel 20 units of insulin into the outer needle cap:

4. Turn the dial-a-dose selector so the dose indicator window shows 20.

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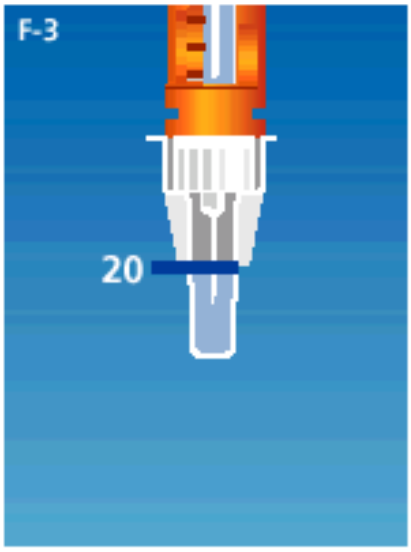
FUNCTION CHECK (cont.)

5. Hold the NovoPen 3 Demi so the NovoFine disposable needle is pointing down.

6. Slowly press the push button **as far as it will go.**

7. Check the dose indicator window to see if it shows zero (0). If it does not show zero (0), there is not enough insulin in the cartridge to do a function check. Insert a new PenFill cartridge (see pages 8-11) and repeat the function check. If there is enough insulin in the cartridge but the dose indicator window does not show zero, repeat the FUNCTION CHECK. If you do not see zero after repeating the above steps, do not use your NovoPen 3 Demi. Contact Novo Nordisk Pharmaceuticals, Inc. at our tool free number (1-800-727-6500).



The insulin should fill the bottom part of the outer needle cap. This indicates the device is functioning properly.

If the insulin **does not fill or overfills** this part of the cap, review the function check procedure. Then repeat the function check with a new NovoFine disposable needle and outer needle cap.

If the second function check also shows under- or over-filling, do not use your NovoPen 3 Demi.

DO NOT try to repair a NovoPen 3 Demi that you think is not working properly.

See Warranty section for further information.

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STORAGE

Guidelines for storing the NovoPen 3 Demi and PenFill 3 mL cartridges:

- PenFill cartridges should be stored in a cool place, such as in a refrigerator, but not in ~~the~~a freezer.

- After the first use of PenFill cartridge in the NovoPen 3 Demi, the NovoPen 3 Demi (with the PenFill cartridge inside) can be kept at room temperature below 86°F (30°C) for the amount of ~~time~~ days ~~specified~~ listed in the PenFill Information for the Patient leaflet for the type of insulin you are using.

- **Do not store** the NovoPen 3 Demi (with the PenFill cartridge inside) in a refrigerator or areas where there may be extreme temperatures or moisture, such as in your car.

- **The expiration date printed on the cartridge is for unused cartridges under refrigeration. Never use the cartridge after the expiration date on the cartridge or its box.**

- Store the NovoPen 3 Demi **without** the NovoFine needle attached and **with** the pen cap in position.

- For information on storing PenFill cartridges, see the package leaflet that comes in the PenFill cartridge box.

MAINTENANCE

Guidelines for maintaining the NovoPen 3 Demi.

Be sure to:

1. Clean it by wiping with a soft cloth moistened with alcohol.

2. Protect it from dust, dirt, and moisture when not in its case.

Make certain you:

1. **Do not** soak it in alcohol, do not wash it in soap and water, or do not lubricate it, since this may cause damage.

2. **Do not** expose it to excessive pressure or blows.

3. **Do not** drop it.

IMPORTANT THINGS TO KNOW

- The NovoPen 3 Demi is not recommended for the blind or visually impaired, without the assistance of a sighted individual trained to use it.

- If you use more than one type of insulin (such as Novolin R, Novolin N, or Novolin 70/30, or NovoLog), use a separate insulin delivery device for each type of insulin.

- Use only a new PenFill 3 mL cartridge when loading the NovoPen 3 Demi Never load the NovoPen 3 Demi with a partially filled PenFill cartridge.

- Always keep a spare insulin delivery system available, in case your NovoPen 3 Demi is lost or damaged.

- Keep the NovoPen 3 Demi, PenFill cartridges, and NovoFine needles out of the reach of children. The American Diabetes Association recommends that insulin should be self-administered. The proper age for initiating this should be assessed by the adult caregiver.

- Keep the NovoPen 3 Demi away from areas where temperatures may get too hot or too cold such as a car or refrigerator.

- The NovoPen 3 Demi is designed for use with PenFill 3 mL insulin cartridges and NovoFine single-use disposable needles.

Novo Nordisk is not responsible for any consequences arising from the use of the NovoPen 3 Demi with products other than PenFill 3 mL insulin cartridges and NovoFine single-use disposable needles.

IMPORTANT NOTES

The following is a review of some important information about the use and care of your NovoPen 3 Demi.

Before each injection, be certain:

1. The NovoPen 3 Demi contains the correct insulin cartridge (such as Novolin R, Novolin N, Novolin 70/30, or NovoLog), if you use more than one type of insulin.

2. The PenFill cartridge contains enough insulin for mixing, if you use a suspension insulin (white and cloudy) such as Novolin N or Novolin 70/30.

3. To do an air shot with the NovoFine needle pointing up before each injection.

Be sure to:

1. Check the dose indicator window after each injection to make sure you have received your full dose (see page 23, Section 5).

2. Remove the NovoFine needle immediately after each injection without replacing the cap.

3. Select your dose only by using the number in the dose indicator window.

4. Perform the function check regularly or if you think your NovoPen 3 Demi is not working properly.

IMPORTANT NOTES (cont.)

Make certain you:

1. **DO NOT** place a NovoFine needle on the NovoPen 3 Demi until you are ready to do an air shot and give an injection or do a function check. Remove the needle immediately after each injection without recapping the needle. If the NovoFine needle is not removed, some liquid may leak out of the PenFill cartridge. This may cause a change in the strength of suspension insulin (white and cloudy) such as Novolin N or Novolin 70/30.

2. **DO NOT** use the clicking sound to set your insulin dose.

3. **DO NOT** try to refill a PenFill cartridge.

4. **DO NOT** share the same PenFill cartridge with anyone else even if you attach a new NovoFine needle for each injection. Sharing cartridge can spread disease. Each PenFill cartridge is for single-person use only.

Blood glucose levels should be tested frequently to monitor your insulin regimen.

Any change in insulin should be made cautiously and only under medical supervision.

WHAT TO DO IF…

The dose indicator window does not show zero after the injection:

1. **You did not receive your full dose.**
   Follow the steps on page 23 to get the remaining part of your dose.

2 Your NovoPen 3 Demi is malfunctioning.
Do not use your NovoPen 3 Demi. Contact Novo Nordisk Pharmaceuticals, Inc. at our tool free number (1-800-727-6500).

No insulin appears when you do the air shot:

1. **The piston rod is not far enough down the cartridge holder to reach the rear rubber stopper.**
   Repeat the air shot (see pages 16-19).

2. **The NovoFine needle may not be securely attached.**
   a. Put the plastic outer cap back on the NovoFine needle.
   b. Turn the plastic outer cap in a clockwise direction to tighten the NovoFine needle.

3. **The NovoFine needle may be blocked.**
   Change the NovoFine needle (see pages 14-15) and do an air shot (see pages 16-19).

The piston rod is sticking out too far to attach the cartridge holder to the barrel:

You must screw the piston rod back into the barrel (see page 7). Never try to push it in or you can damage the mechanism.

The push button will not return to zero or the piston rod will not turn back into the reset mechanism:

The return mechanism may be locked. This is usually due to improper technique. Gently turn the mechanism side to side until it unlocks and then call our toll free number (1-800-727-6500) so that we may review go over your technique with you.

WARRANTY

Should your NovoPen® 3 Demi device be defective in materials or workmanship within two (2) years of purchase, Novo Nordisk Pharmaceuticals, Inc. will replace it at no charge if you mail the defective unit along with a description of the problem and the sales receipt or other proof of purchase to:

Novo Nordisk Pharmaceuticals, Inc.
Product Safety
100 College Road West
Princeton, NJ 08540

Protected by U.S. Patent Nos. 5,693,027; 5,626,566; 6,126,646 and Des. 347,894 (cartridge) restricted to use with Novo Nordisk insulin cartridges and Novo Nordisk pen needles.

No other warranty is made with respect to NovoPen® 3 Demi. This warranty will be invalid and Novo Nordisk A/S, Novo Nordisk Pharmaceuticals, Inc., Bristol-Myers Squibb Co., Nipro Medical Industries Ltd., and Bang & Olufsen A/S cannot be held responsible in the case of defects or damages arising from:

- The use of the NovoPen® 3 Demi with products other than PenFill 3 mL cartridges and NovoFine single-use disposable needles.

- The use of the NovoPen® 3 Demi not in accordance with the instructions in this booklet.

- Physical damage to the NovoPen® 3 Demi caused by neglect, misuse, unauthorized repair, accident, or other breakage.

For assistance or further information, write to:

Novo Nordisk Pharmaceuticals, Inc.
Customer Relations
100 College Road West
Princeton, NJ 08540

Or call: 1-800-727-6500

Novo Nordisk Pharmaceuticals, Inc.
Princeton, NJ 08540

http://www.novonordisk-us.com

8-4241-31-002-1

NovoLog®
Insulin aspart (rDNA origin) Injection

DESCRIPTION

NovoLog® (insulin aspart [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. 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) as the production organism. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}0_{79}S_6$ and a molecular weight of 5825.8.

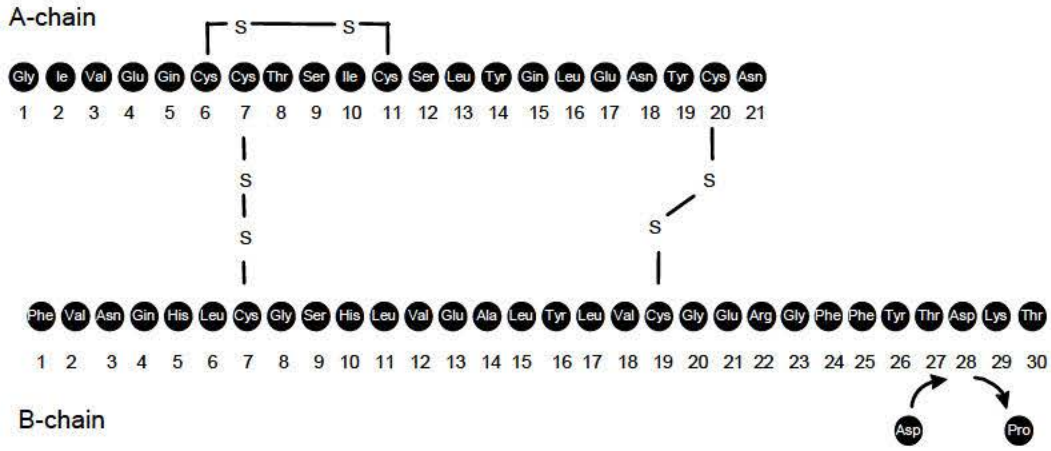

Figure 1. Structural formula of insulin aspart.

NovoLog is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart (B28 asp regular human insulin analog) 100 Units/mL, glycerin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 µg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, and sodium chloride 0.58 mg/mL. NovoLog has a pH of 7.2-7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

CLINICAL PHARMACOLOGY

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.

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 Figure 2 and Figure 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.

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 3). The relative bioavailability of NovoLog compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

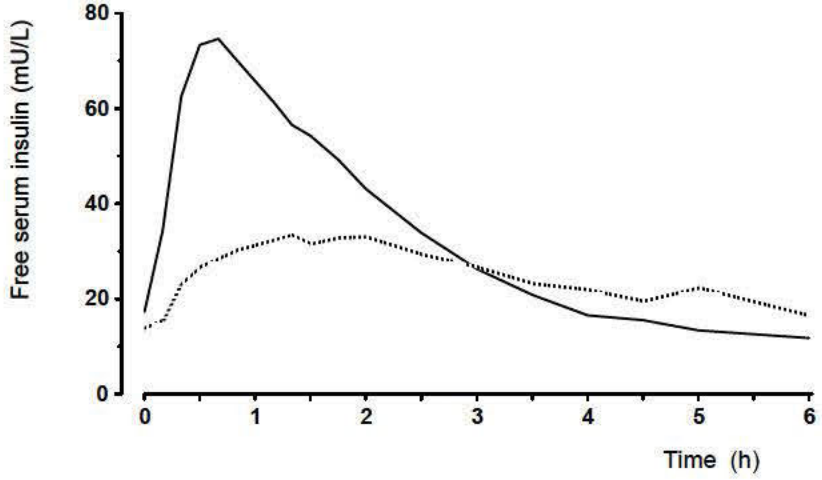

Figure 2. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

In studies in healthy volunteers (total n=l07) 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 82.1 and 35.9 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 injection site (abdomen, thigh, or upper arm).

Distribution and Elimination - NovoLog has a low binding to plasma proteins, 0-9%, 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.

Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that NovoLog has a more rapid onset of action than regular human insulin.

In a 6-hour 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 3). The duration of action for NovoLog is 3 to 5 hours compared to 5 to 8 hours for regular human insulin. 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 3 should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General).

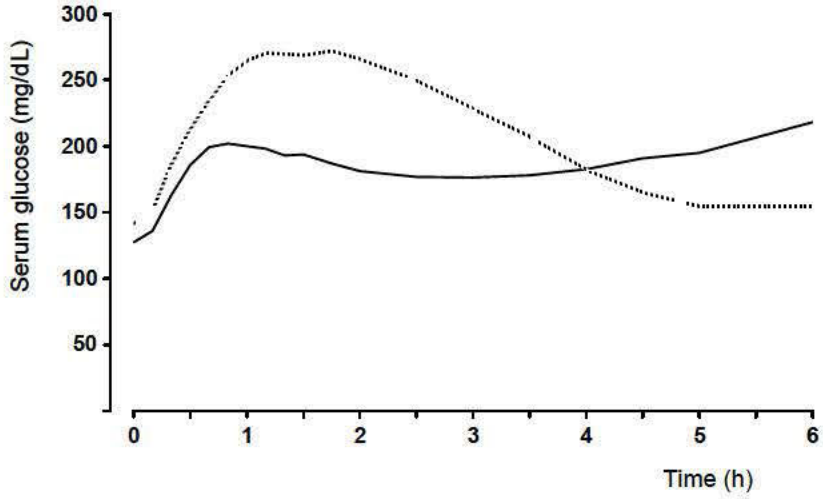

Figure 3. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

Special Populations

Children and Adolescents - The pharmacokinetic and pharmacodynamic properties of NovoLog and regular human insulin were evaluated in a single dose study in 18 children (6-12 years, n=9) and adolescents (13-17 years [Tanner grade $\geq$ 2], n=9) with Type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics in children and adolescents with Type 1 diabetes between NovoLog and regular human insulin were similar to those in healthy adult subjects and adults with Type 1 diabetes.

Geriatrics - The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied.

Gender - In healthy volunteers, no difference in insulin aspart levels was seen between men and women when body weight differences were taken into account. There was no significant difference in efficacy noted (as assessed by HbAlc) between genders in a trial in patients with Type 1 diabetes.

Obesity - The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of NovoLog has not been studied.

Ethnic Origin - The effect of ethnic origin on the pharmacokinetics of NovoLog has not been studied.

Renal Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. The effect of renal impairment on the phamacokinetics of NovoLog has not been studied. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. The effect of hepatic impairment on the pharmacokinetics of NovoLog has not been studied. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

Pregnancy - The effect of pregnancy on the pharmacokinetics and glucodynamics of Novolog has not been studied (see PRECAUTIONS, Pregnancy).

Smoking - The effect of smoking on the pharmacokinetics/pharmacodynamics of NovoLog has not been studied.

CLINICAL STUDIES

To evaluate the safety and efficacy of NovoLog in patients with Type 1 diabetes, two six-month, open-label, active-control (NovoLog® vs. Novolin® R) studies were conducted (see Table 1). 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. Glycemic control (as measured by HbA1c), the rates of hypoglycemia (as determined from the number of events requiring intervention from a third party), and the incidence of ketosis were clinically comparable for the two treatment regimens. The mean total daily doses of insulin were greater (1-3 U/day) in the NovoLog-treated patients compared to patients who received regular human insulin. This difference was primarily due to basal insulin requirements. To achieve the stated levels of glycemic control, some patients required more

than three doses of meal-related insulin and/or more than one dose of basal insulin (see Table 1). No serum glucose measurements were obtained in these studies.

To evaluate the safety and efficacy of NovoLog in patients with Type 2 diabetes, one six-month, open-label, active-control (NovoLog® vs. Novolin® R) study was conducted (see Table 1). 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. Glycemic control (as measured by HbAlc) and the rates of hypoglycemia (as determined from the number of events requiring intervention from a third party) were clinically comparable for the two treatment regimens. The mean total daily dose of insulin was greater (2 U/day) in the NovoLog-treated patients compared to patients who received regular human insulin. This difference was primarily due to basal insulin requirements. To achieve the stated levels of glycemic control, some patients required more than three doses of meal-related insulin and/or more than one dose of basal insulin (see Table 1).

Table 1. Results of two six-month, active-control, open-label trials in patients with Type 1 diabetes (Studies A and B) and one six-month, active-control, open-label trial in patients with Type 2 diabetes (Study C).

Study	Treatment (n)	Mean HbA1c (%)		Hypoglycemia[1] (events / month / patient)	% of Patients Using Various Numbers of Insulin Injections / Day[2]				
		Baseline	Month 6		Rapid-acting			Basal	
					1 - 2	3	4 - 5	1	2
A	NovoLog (n=694)	8.0	7.9	0.06	3	75	22	54	46
	Novolin R (n=346)	8.0	8.0	0.06	6	75	19	63	37
B	NovoLog (n=573)	7.9	7.8	0.08	4	90	6	94	6
	Novolin R (n=272)	8.0	7.9	0.06	4	91	4	93	7
C	NovoLog (n=90)	8.1	7.7	0.02	4	93	4	97	4
	Novolin R (n=86)	7.8	7.8	0.01	2	93	5	93	7

[1] Events requiring intervention from a third party during the last three months of treatment
[2] Percentages are rounded to the nearest whole number

To evaluate the use of NovoLog by subcutaneous infusion with an external pump, two open-label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog versus Velosulin (buffered regular human insulin) in patients with Type 1 diabetes. Glycemic control (as measured by HbA1c) and rates of hypoglycemia were comparable. Patients with Type 2 diabetes were also studied in an open-label, parallel design trial (16 weeks [n=127]) using NovoLog by subcutaneous infusion compared to pre-prandial injection (in conjunction with basal NPH injections). Reductions in HbA1c and rates of hypoglycemia were comparable. (See INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, Mixing of Insulins, Information for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

INDICATIONS AND USAGE

NovoLog is indicated for the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, NovoLog given by injection should normally be used in regimens with an intermediate or long-acting insulin. NovoLog may also be infused subcutaneously by external insulin pumps. (See WARNINGS, PRECAUTIONS [especially Usage in Pumps], Information for Patients [especially For Patients Using Pumps], Mixing of Insulins, DOSAGE AND ADMINISTRATION, RECOMMENDED STORAGE.)

CONTRAINDICATIONS

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

WARNINGS

NovoLog differs from regular human insulin by a more rapid onset and a shorter duration of activity. Because of the fast onset of action, the injection of NovoLog should immediately be followed by a meal. Because of the short duration of action of NovoLog, patients with diabetes also require a longer-acting insulin to maintain adequate glucose control. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

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

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

Insulin Pumps: When used in an external insulin pump for subcutaneous infusion, NovoLog should not be diluted or mixed with any other insulin. Physicians and patients should carefully evaluate information on pump use in the NovoLog physician and patient package inserts and in the pump manufacturer's manual (e.g. NovoLog-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to NovoLog usage, because NovoLog-specific information may differ from general pump manual instructions). Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time 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 shorter duration of action. These differences may be particularly relevant when patients are switched from multiple injection therapy or infusion with buffered regular insulin. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required. (See PRECAUTIONS,

Mixing of Insulins, Information for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

PRECAUTIONS

General

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

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 site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Hypoglycemia - As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog. 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 PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Renal Impairment - Although there are no specific data in patients with diabetes and renal impairment treated with NovoLog, NovoLog dose requirements may be reduced in the presence of renal impairment, similar to observations with other insulins (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment - Although there are no specific data in patients with diabetes and hepatic disease treated with NovoLog, NovoLog dose requirements may be reduced in the presence of impaired hepatic function, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Allergy - Local Allergy - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor 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.

Systemic Allergy - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing,

reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.
Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.
In controlled clinical trials using injection therapy, allergic reactions were reported in 3 of 735 patients (0.4%) who received regular human insulin and 10 of 1394 patients (0.7%) who received NovoLog. During these and other trials, 3 of 2341 patients treated with NovoLog were discontinued due to allergic reactions.

Antibody Production - Insulin antibodies may develop during treatment with insulin. In large clinical trials, levels of antibodies that cross react with human insulin and insulin aspart were higher in patients treated with NovoLog compared to regular human insulin. The clinical significance of these antibodies is uncertain.

Pregnancy and Lactation
Female patients should be advised to tell their physician if they intend to become, or if they become pregnant. Information is not available on the use of NovoLog during pregnancy or lactation.

Usage in Pumps
NovoLog is recommended for use in Disetronic H-TRON® plus V100 with Disetronic 3.15 plastic cartridges and Classic or Tender infusion sets; MiniMed Models 505, 506, or 507 with MiniMed 3 mL syringes and Polyfin® or Sof-set® infusion sets.

In-vitro studies have shown that pump malfunction, loss of cresol, and insulin degradation, may occur with the use of NovoLog for more than two days at 37°C (98.6°F) in infusion sets and reservoirs. NovoLog in clinical use should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog should not be mixed with other insulins or with a diluent when it is used in the pump.** (See WARNINGS, PRECAUTIONS, Mixing of Insulins, Information for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

Information for Patients

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

Female patients should be advised to tell their physician if they intend to become, or if they become pregnant. Information is not available on the use of NovoLog during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

For 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. NovoLog is recommended for use with Disetronic H-TRON plus V100 with Disetronic 3.15 plastic cartridges and Classic or Tender infusion sets; MiniMed Models 505, 506, and 507 with MiniMed 3 mL syringes and Polyfin or Sof-set infusion sets. The use of NovoLog in quick-release infusion sets and cartridge adapters has not been assessed.

To avoid insulin degradation, infusion set occlusion, and loss of the preservative (cresol), the infusion sets (reservoir syringe, tubing, and catheter) and the NovoLog in the reservoir should be replaced, and a new infusion site selected every 48 hours or less. 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 alter the absorption of NovoLog.

Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time 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 shorter duration of action. These differences are particularly relevant when patients are switched from infused buffered regular insulin or 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 WARNINGS, PRECAUTIONS, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

Laboratory Tests

As with all insulin therapy, the therapeutic response to NovoLog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin 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 increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

- The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent (see CLINICAL PHARMACOLOGY).

Mixing of Insulins

- A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog with NPH human insulin immediately before injection produced some attenuation in the peak concentration of NovoLog, but that the time to peak and the total bioavailability of NovoLog were not significantly affected. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first. The injection should be made immediately after mixing. Because there are no data on the compatibility of NovoLog and crystalline zinc insulin preparations, NovoLog should not be mixed with these preparations.
- The effects of mixing NovoLog with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (see WARNINGS).
- Mixtures should not be administered intravenously.
- When used in external subcutaneous infusion pumps for insulin, NovoLog should not be mixed with any other insulins or diluent.

Carcinogenicity, Mutagenicity, 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 and female fertility, or general reproductive performance of animals was observed.

Pregnancy - Teratogenic Effects - Pregnancy Category C

There are no adequate well-controlled clinical studies of the use of NovoLog in pregnant women. NovoLog should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

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 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.

Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when NovoLog is administered to a nursing mother.

Pediatric Use

Safety and effectiveness of NovoLog in children have not been studied.

Geriatric Use

In the large controlled clinical trials, 36 patients $\geq$ 65 years of age were treated with NovoLog. No conclusions regarding the safety and efficacy of NovoLog in the elderly patients compared to younger adults can be reached from this limited data set.

ADVERSE REACTIONS

Clinical trials comparing NovoLog with regular human insulin did not demonstrate a difference in frequency of adverse events between the two treatments.

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

Body as Whole - *Allergic reactions* (see PRECAUTIONS, Allergy).

Skin and Appendages - *Injection site reaction, lipodystrophy, pruritus, rash* (see PRECAUTIONS, Allergy; Information for Patients, Usage in Pumps).

Other – *Hypoglycemia, Hyperglycemia and ketosis* (see WARNINGS and PRECAUTIONS).

In controlled clinical trials, small, but persistent elevations in alkaline phosphatase result were observed in some patients treated with NovoLog. The clinical significance of this finding is unknown.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

NovoLog should generally be given immediately before a meal (start of meal within 5-10 minutes after injection) because of its fast onset of action. The dosage of NovoLog should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. The total daily individual insulin requirement is usually between 0.5-1.0 units/kg/day. When used in a meal-related subcutaneous injection treatment regimen, 50-70% of total insulin requirements may be provided by NovoLog and the remainder provided by an intermediate-acting or long-acting insulin. When used in external insulin infusion pumps, the initial programming of the pump is based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is given as meal-related boluses of NovoLog and the remainder as basal infusion. 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 hyperglycemia when using NovoLog than when using human regular insulin. Additional basal insulin injections, or higher basal rates in external subcutaneous infusion pumps may be necessary. **Infusion sets and the insulin in the infusion sets must be changed every 48 hours or sooner to assure the activity of NovoLog and proper pump function.** (See WARNINGS, PRECAUTIONS, Information for Patients)

NovoLog should be administered by subcutaneous injection in the abdominal wall, the thigh, or the upper arm, or by continuous subcutaneous infusion in the abdominal wall. Injection sites and infusion 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.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use any NovoLog if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. NovoLog should not be used after the printed expiration date.

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

* NovoLog® PenFill® cartridges are for use with NovoPen®3, NovoPen®3 Demi, and NovoPen Junior Insulin Delivery Devices
and NovoFine® disposable needles.

RECOMMENDED STORAGE

NovoLog in unopened vials and cartridges should be stored between 2° and 8°C (36° to 46°F). *Do not freeze.* **Do not use NovoLog if it has been frozen or exposed to temperatures that exceed 37°C (98.6°F).** After a vial or cartridge has been punctured, it 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. Cartridges should not be refrigerated after insertion into the NovoPen 3. Infusion sets (reservoirs, tubing, and catheters) and the NovoLog in the reservoir should be discarded after no more than 48 hours of use or after exposure to temperatures that exceed 37°C (98.6°F).

Rx only

Date of Issue: December 21, 2001
8-XXXX-XX-XXX-X

Manufactured For Novo Nordisk Pharmaceuticals Inc., Princeton, New Jersey 08540
www.novonordisk-us.com
Manufactured By Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

Information For The Patient
NovoLog® (Insulin aspart [rDNA origin] Injection)
3 mL PenFill® Disposable Cartridge (300 units per cartridge)
10 mL Vial (1000 units per vial)
100 units/mL (U-100)

Read this information carefully before you begin treatment. Read the information you get whenever you get more medicine. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about NovoLog® (NO-voe-log), ask your doctor. Only your doctor can determine if NovoLog® is right for you.

What is the most important information I should know about NovoLog?

For All NovoLog Users

- NovoLog (NO-voe-log) is different from regular human insulin and buffered regular human insulin (Velosulin). It works faster (rapid onset of action) and will not work as long (shorter duration of action) as regular human insulin or buffered regular human insulin (Velosulin).

- Because the onset of action is fast, you should eat a meal 5-10 minutes after a NovoLog injection or NovoLog bolus infusion dose given by an external pump. (A bolus is a large dose.) Eating right after the dose will reduce the risk of low blood sugar (hypoglycemia).

- The shorter duration of NovoLog's action means that you may need to use an intermediate or longer-acting insulin (basal insulin) or higher basal rates of NovoLog insulin infusion in the pump. This will give the best glucose control and will help you avoid hyperglycemia (high blood sugar) and ketoacidosis (too much acid [low pH] in your body).

- Glucose monitoring is recommended for all patients who use insulin.

If you use NovoLog by injection, you may need to increase some or all of the following:

- your total dose of insulin
- your dose of intermediate or long-acting insulin (for example, NPH)
- the number of injections of basal insulin

If you infuse NovoLog into the skin (subcutaneous tissue) by pump, you may need to increase some or all of the following:

- your total insulin dose
- the basal infusion dose
- the proportion of total insulin given as a basal infusion

Age and exposure to heat affect the stability of NovoLog and its preservative. Also, NovoLog does not work well after it has been frozen. Therefore, do not use old insulin or insulin that has been exposed to temperature extremes. Hyperglycemia may be a sign that the insulin is no longer working and needs to be replaced.

Do not mix NovoLog:

- with any other insulins when used in a pump
- with Lantus® (insulin glargine [rDNA origin] injection) when used with injections by syringe

(You may, however, mix NovoLog with NPH when used with injections by syringe. See: How should I mix insulins?)

For Pump Users

- Glucose monitoring is very important for patients using external pump subcutaneous infusion therapy. You should be aware that pump or infusion set malfunctions that result in inadequate insulin infusion can quickly lead to hyperglycemia and ketosis. Accordingly, problems with the infusion pump, the flow of insulin, or the quality of the insulin should be identified and corrected as quickly as possible. There is only a small amount of insulin infused into the skin with a pump. The faster absorption through the skin of rapid-acting insulin analogs and shorter duration of action may give you less time to identify and correct the problem than with buffered regular insulin.

- Therefore, you should dose with insulin from a new vial of NovoLog if unexplained hyperglycemia or pump alarms do not respond to all of the following:
  - a repeat dose (injection or bolus) of NovoLog

- a change in the infusion set, including the NovoLog in the reservoir
- a change in the infusion site

If these measures do not work, you may need to resume skin (subcutaneous) injections with syringes or insulin pens. Continue to monitor your glucose and ketones. If problems continue, you must contact your doctor.

- When NovoLog is used in an external subcutaneous insulin infusion pump, you should use only recommended pumps and infusion sets (insulin reservoirs, tubing, catheters). The infusion set, reservoir insulin, and infusion site should be changed:
  - at intervals of 48 hours or less
  - with unexpected hyperglycemia or ketosis
  - when alarms sound, as specified by your MiniMed or Disetronic pump manual
  - if the insulin or pump has been exposed to temperatures over 98.6^{o}F (37^{o}C), as it might be in a sauna, with long showers, or on a hot day
  - if the insulin or pump could have absorbed radiant heat, for example from sunlight, that would heat the insulin to over 98.6^{o}F (37^{o}C). Dark colored pump cases or sport covers can increase this type of heat. The location where the pump is worn may also affect the temperature

Patients who develop "pump bumps" (skin reactions at the infusion site) may need to change infusion sites more often.

For your safety, read the section "What are the possible side effects of NovoLog?" to review the symptoms of low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia).

What is NovoLog?

NovoLog is a clear, colorless, sterile solution for injection or infusion under the skin (subcutaneously). NovoLog is a human-made form of insulin to lower your blood sugar faster than human regular insulin. Because the insulin is human-made by recombinant DNA technology (rDNA) and is chemically different from the insulin made by the human body, it is called an insulin analog. The active ingredient in NovoLog is insulin aspart. The concentration of insulin aspart is 100 units per milliliter, or U100. NovoLog also contains: glycerin, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, and sodium chloride. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. These ingredients help to preserve or stabilize NovoLog insulin. The pH (balance between acid and alkaline conditions) is important to the stability of NovoLog. Increases in temperature can affect the stability of NovoLog, so it may not work well.

Who should not use NovoLog?

Do not use NovoLog if:

- your blood sugar (glucose) is too low (hypoglycemia)
- you do not plan to eat right after your injection or infusion

- you are allergic to insulin aspart or any of the ingredients contained in NovoLog (check with your doctor if you are not sure)

The effects of NovoLog on an unborn child or on a nursing baby are unknown. Therefore, tell your doctor if you plan to become pregnant or breast feed, or if you become pregnant. You may need to use another medicine.

Tell your doctor about all medicines and supplements that you are using. Some medicines, including non-prescription medicines and dietary supplements, may affect your diabetes.

What should I know about using insulin?

- Make any change of insulin cautiously and only under medical supervision. Changes in the strength, manufacturer, type (for example: Regular, NPH, Lente®), species (beef, pork, beef-pork, human) or method of manufacture (recombinant [rDNA] or animal source insulin) may cause a need for a change in the timing or dose of the new insulin.
- Glucose monitoring will help you and your health care provider adjust dosages.
- Always carry a quick source of sugar, such as candy or glucose tablets, to treat low blood sugars (hypoglycemia).
- Always carry identification that states that you have diabetes.

What should I know about using NovoLog?

See the end of this Patient Information for instructions for using NovoLog in injections and pumps.

- NovoLog starts working 10-20 minutes after injection or infusion. The greatest blood sugar lowering effect is between 1 and 3 hours after injection or infusion. This blood sugar lowering lasts for 3 to 5 hours. (The time periods are only general guidelines.)

- Because the onset of action is rapid, you should eat a meal within 5-10 minutes after a NovoLog injection or a NovoLog bolus dose from an external pump to avoid low blood sugar (hypoglycemia).

- The shorter duration of NovoLog's action means that you may need to use an intermediate or longer-acting insulin (basal insulin) or higher basal rates of NovoLog insulin infusion in the pump. This will help you avoid hyperglycemia and ketoacidosis.

- Do not inject or infuse in skin that has become reddened or bumpy or thickened after infusion or injection. Insulin absorption in these areas may not be the same as that in normal skin, and may change the onset and duration of insulin action.

- Use NovoLog only if it appears clear and colorless. Do not use NovoLog if it appears cloudy, thickened, or colored, or if it contains solid particles.

What should I avoid while using NovoLog?

- Drinking alcohol may lead to hypoglycemia.
- Do not miss meals after injections of NovoLog or bolus infusions of NovoLog.

What are the possible side effects of NovoLog?

Insulins can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (insulin reaction). This is the most common side effect. It occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, **hypoglycemia can occur with**:

- **The wrong insulin dose.** This can happen with any of the following:
  - too much insulin is injected
  - the bolus dose of insulin infusion is set too high
  - the basal infusion dose is set too high
  - the pump does not work right, delivering too much insulin
- **Medicines that directly lower glucose or increase sensitivity to insulin.** This can happen with oral (taken by mouth) antidiabetes drugs, sulfa antibiotics (for infections), ACE inhibitors (for blood pressure and heart failure), salicylates, including aspirin and NSAIDS (for pain), some antidepressants, and with other medicines.
- **Medical conditions that limit the body's glucose reserve, lengthen the time insulin stays in the body, or that increase sensitivity to insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Not enough carbohydrate (sugar or starch) intake**. This can happen if:
  - a meal or snack is missed or delayed
  - you have vomiting or diarrhea that decreases the amount of glucose absorbed by your body
  - alcohol interferes with carbohydrate metabolism
- **Too much glucose use by the body.** This can happen from:
  - too much exercise
  - higher than normal metabolism rates due to fever or an overactive thyroid

Hypoglycemia can be mild or severe. Its onset may be rapid. Patients with very good (tight) glucose control, patients with diabetic neuropathy (nerve problems), or patients using some Beta-blockers (used for high blood pressure and heart conditions) may have few warning symptoms before severe hypoglycemia develops. Hypoglycemia may reduce your ability to drive a car or use mechanical equipment without risk of injury to yourself or others. Severe hypoglycemia can cause temporary or permanent harm to your heart or brain. **It may cause unconsciousness, seizures, or death.** Symptoms of hypoglycemia include:

- anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, or other abnormal behavior
- tingling in your hands, feet, lips, or tongue
- dizziness, light-headedness, or drowsiness
- nightmares or trouble sleeping
- headache
- blurred vision or slurred speech
- palpitations (rapid heart beat)
- sweating
- tremor (shaking) or unsteady gait (walking)

Mild to moderate hypoglycemia can be treated by eating or drinking carbohydrates (milk, orange juice, sugar candies, or glucose tablets). More severe or continuing hypoglycemia may require the help of another person or emergency medical personnel. Patients who are unable to take sugar by mouth or who are unconscious may need treatment with a glucagon injection or glucose given intravenously (in the vein).

Talk with your doctor about severe, continuing, or frequent hypoglycemia, and hypoglycemia for which you had few warning symptoms.

Hyperglycemia (high blood sugar) is another common side effect. It also occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, **hyperglycemia can occur with:**

- **The wrong insulin dose.** This can happen from any of the following:
  - too little or no insulin is injected
  - the bolus dose of insulin infusion is set too low
  - the basal infusion dose is set too low
  - the pump or catheter system does not work right, delivering too little insulin
  - the insulin's ability to lower glucose is changed by incorrect storage (freezing, excessive heat), or usage after the expiration date
- **Medicines that directly increase glucose or decrease sensitivity to insulin.** This can happen, for example, with thiazide water pills (used for blood pressure), corticosteroids, birth control pills, and protease inhibitors (used for AIDS).
- **Medical conditions that increase the body's production of glucose or decrease sensitivity to insulin**. These medical conditions include fevers, infections, heart attacks, and stress.
- **Too much carbohydrate intake**. This can happen if you
  - eat larger meals
  - eat more often
  - increase the proportion of carbohydrate in your meals

Hyperglycemia can be mild or severe. It can **progress to diabetic acidosis (DKA) (ketoacidosis) or very high glucose levels (hyperosmolar coma) and result in**

unconsciousness and death. Although diabetic acidosis occurs most often in patients with Type 1 diabetes, it can occur in patients with Type 2 diabetes who become severely ill. Urine or blood tests will show acetone, ketones, and high levels of glucose. Hyperosmolar coma occurs most often in patients with Type 2 diabetes. Urine and blood tests will show very high levels of glucose.

Glucose monitoring is very important for patients using external pump infusion therapy. You should be aware that pump or infusion set malfunctions that result in inadequate insulin infusion can quickly lead to hyperglycemia and ketosis. Accordingly, problems with the infusion pump, the flow of insulin, or the quality of the insulin should be identified and corrected as quickly as possible. The faster absorption of rapid-acting insulin analogs through the skin and shorter duration of action may give you less time to identify and correct the problem.

Because some patients experience few symptoms of hyperglycemia and ketosis, it is important to monitor your glucose several times a day. Symptoms of hyperglycemia include:

- confusion or drowsiness
- fruity smelling breath
- rapid, deep breathing
- increased thirst
- decreased appetite, nausea, or vomiting
- abdominal (stomach area) pain
- rapid heart rate
- increased urination and dehydration (too little fluid in your body)

Mild hyperglycemia can be treated by extra doses of insulin and drinking fluids (rehydration). Patients using pumps should check pump function and replace the insulin in the reservoir-syringe, as well as change the tubing and catheter and the infusion site. **Patients using pumps may need to resume insulin injections with syringes or injection pens.** Glucose and acetone-ketone levels should be monitored more often until they return to normal. **More severe or continuing hyperglycemia requires prompt evaluation and treatment by your health care provider.**

Allergy can be serious. Generalized allergy is an uncommon, but possibly life-threatening, reaction to insulin products. Symptoms include:

- itchy rash over the entire body
- shortness of breath or wheezing
- confusion
- low blood pressure
- rapid heart beat
- sweating

If you think you are having a generalized allergic reaction, get emergency medical help right away.

Allergic reactions at the injection site (itching, redness, hardness, or swelling) are more common than generalized allergy. They may need several days or weeks to clear up.

Pump patients with site reactions may need to change their infusion sites more often than every 48 hours. Patients should avoid injection or infusion of insulin into skin areas that have reactions. Tell your doctor about such reactions, because they can become more severe, or they may change the absorption of insulin.

Lipodystrophy is a common change in the fat below the injection site. These changes include loss of fat (depressions in the skin called lipoatrophy) or thickening of the tissue under the skin (lipohypertrophy). Pump patients with lipodystrophy may need to change their infusion sites more often than every 48 hours. Patients should avoid injection or infusion of insulin into skin areas that have these reactions. Tell your doctor about such reactions because they can become more severe, or they may change the absorption of insulin.

How should I store NovoLog?

- **NovoLog can be damaged by high temperatures.** Therefore, be sure to protect it from high air temperatures, heat from the sun, saunas, long showers, and other heat sources. This is especially important if you use a pump or an insulin pen, because you carry these devices with you and they may be exposed to different temperatures as you go about your daily activities. **Throw NovoLog away if it has been in temperatures greater than 98.6°F (37°C).**

- **Unopened NovoLog** should be stored in a refrigerator but not in the freezer and protected from light. Even if it has been refrigerated and protected from sunlight and unopened, it should not be used after the expiration date on the label and the carton. Unopened vials and cartridges can be stored unrefrigerated at temperatures below 86°F (30°C) and protected from light for up to 28 days.

- **Punctured vials and cartridges** can be stored unrefrigerated at temperatures below 86°F (30°C) and protected from light for up to 28 days. Punctured vials may be stored in the refrigerator. Cartridges inserted into their NovoPen® 3 device should not be stored in the refrigerator.

- **The NovoLog in the pump reservoir and the complete infusion set** (reservoir, tubing, catheter-needle) should be replaced **at least every 48 hours.** Replacement should be more often than every 48 hours if you have hyperglycemia, the pump alarm sounds, or the insulin flow is blocked (occlusion).

- Never use NovoLog if it has been stored improperly.

General advice

This leaflet summarizes the most important information about NovoLog. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about NovoLog that is written for health professionals.

Injection and pump infusion instructions

- NovoLog comes in 10 mL (milliliter) vials or in 3 mL cartridges. NovoLog can be withdrawn from vials with syringes for injection or for insertion into the reservoirs of external subcutaneous infusion pumps (Disetronic H-TRON® plus V100 or MiniMed Models 505, 506, or 507).
- Doses of insulin are measured in units. NovoLog is available as a U-100 insulin. One milliliter (mL) of U-100 contains 100 units of insulin aspart (1 mL=1 cc). Only U-100 type syringes should be used for injection to ensure proper dosing.
- Disposable syringes and needles are sterile if the package is sealed. They should be used only once and thrown away properly, to protect others from harm.
- NovoLog PenFill® 3 mL cartridges are for use with the NovoPen 3, NovoPen 3 Demi, and NovoPen Junior Insulin Delivery Devices and NovoFine® disposable needles. Never share needles.

How should I inject NovoLog?

Using Vials

1. The vial and the insulin should be inspected. The insulin should be clear and colorless. The tamper-resistant cap should be in place to be removed by you. If the cap had been removed before your first use of the vial, or if the insulin is cloudy or colored, you should return the vial to the pharmacy. Do not use it.
2. Both the injection site and your hands should be cleaned with soap and water or with alcohol. The injection site should be dry before you inject.
3. The rubber stopper should be wiped with an alcohol wipe.
4. The plunger of the syringe should be pulled back until the black tip is at the level for the number of units to be injected.
5. Insert the needle of the syringe through the rubber stopper of the vial. Push in the syringe plunger completely to put air into the vial.
6. Turn the vial upside-down with the needle-syringe still attached, and pull the plunger back a few units past the correct dose.
7. Remove any air bubbles by flicking the syringe and squirting air bubbles out the needle. Continue pushing the plunger until you have the correct dose.
8. Lift the vial off the syringe.
9. Inject NovoLog into the subcutaneous (under the skin) tissue (not into muscle or blood vessels) in the abdomen, thighs, upper arms, or buttocks. Pinch the skin fold between your fingers and push the needle straight into the pinched skin. Because insulin absorption and activity can be affected by the site you choose, you should discuss the injection site with your doctor.
10. Release the pinched skin and push the plunger in completely. Keep the needle in the skin for a few seconds before withdrawing the syringe.
11. Press the injection site for a few seconds to reduce bleeding. Do not rub.
12. To avoid needle sticks, throw away the syringe and needle without recapping. Discuss sterile technique and proper disposal of your used insulin supplies with your doctor.

Using Cartridges

1. The cartridge and the insulin should be inspected. The insulin should be clear and colorless. The tamper-resistant foil should be in place to be removed by you. If the foil had been punctured or removed before your first use of the cartridge or if the insulin is cloudy or colored, you should return the cartridge to the pharmacy. Do not use it.
2. Both the injection site and your hands should be cleaned with soap and water or with alcohol. The injection site should be dry before you inject. Do not use skin that is reddened, itchy, or thickened as an infusion site.
3. Insert a 3 mL cartridge in the pen-device barrel. Attach a new needle to the end of the cartridge and turn the pen device upside-down so that any air bubbles can be eliminated by flicking the pen device and squirting air bubbles out the needle. (This should eliminate extra air for all future doses from that cartridge. However, the needle will need to be changed for each dose.)
4. Set the dose to be delivered by twisting the top of the pen-device until the correct number appears in the window.
5. Inject NovoLog into the subcutaneous (under the skin) tissue (not into muscle or blood vessels) in the abdomen, thighs, upper arms, or buttocks. Pinch the skin fold between your fingers and push the needle straight into the pinched skin. Because insulin absorption and activity can be affected by the site you choose, you should discuss the injection site with your doctor.
6. Release the pinched skin. Inject the dose by pressing the flat plunger button on the top of the pen-device. Keep the needle in the skin for a few seconds before withdrawing the pen-device.
7. Press the injection site for a few seconds to reduce bleeding. Do not rub.
8. Throw away the disposable needle without recapping to avoid needle sticks. Discuss sterile technique and proper disposal of your used insulin supplies with your doctor.

How should I infuse NovoLog with an external subcutaneous insulin infusion pump?

NovoLog is recommended for use with the Disetronic H-TRON® plus V100 and MiniMed 505, 506, and 507 pumps. The Disetronic 3.15 plastic cartridge and Tenders or Classic tubing can be used with the Disetronic pump. The MiniMed 3 mL syringe and Polyfin® or Sof-set® tubing can be used in the MiniMed pumps. The use of NovoLog in quick-release infusion sets and cartridge adapters has not been assessed.

1. Inspect your insulin as you would for an injection. The insulin should be clear and colorless and without particles. The tamper-resistant cap should be in place to be removed by you. If the cap had been removed before your first use of the vial or if the insulin is cloudy or colored, you should return the vial to the pharmacy. Do not use it.
2. Both the infusion site and your hands should be cleaned with soap and water or with alcohol. The infusion site should be dry before you insert the catheter-needle and tubing. Do not use skin that is reddened, itchy, bumpy or thickened as an infusion site because the onset and duration of NovoLog action may not be the same as that in normal skin.

3. Fill the reservoir-syringe with 2 days worth of NovoLog plus about 25 extra units to prime the pump and fill up the dead space of the infusion tubing.
4. Remove air bubbles from the reservoir according to the pump manufacturers' instructions.
5. Attach the infusion set to the reservoir. Make sure the connection is tight. Prime the infusion set until you see a drop of insulin coming out of the infusion needle-catheter. Flick the tubing to remove air bubbles. Follow the pump manufacturers' instructions for additional priming.
6. Prime the needle-catheter and insert the infusion set into the skin according to the pump manufacturer.
7. Program the pump for mealtime NovoLog boluses and NovoLog basal insulin infusion according to instructions from your doctor and the manufacturer of your pump equipment.
8. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the insulin every 48 hours or less, even if you have not used all of the insulin. This will help ensure that NovoLog and the pump works well. (See "What is the most important information I should know about NovoLog?")
9. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the insulin if you experience a pump alarm, catheter blockage, hyperglycemia, or if your pump insulin has been exposed to heat greater than 98.6^{o}F (37^{o}C). (See "What is the most important information I should know about NovoLog?") Hyperglycemia identified with glucose monitoring may be the first indication of a problem with the pump, infusion set, or NovoLog. Hyperglycemia in the absence of an alarm still requires you to investigate because pump alarms are designed to detect back-pressure and occlusion. The alarms may not detect all the changes to NovoLog that could result in hyperglycemia. You may need to resume subcutaneous insulin injections if the cause of the problem cannot be promptly identified or fixed. (See "Hyperglycemia" under "What are the possible side effects of NovoLog?") Remember that long stretches of tubing increase the risk for kinking and expose the insulin in the tubing to more variations in temperature.

These instructions give you specific information for use of NovoLog in external subcutaneous infusion pumps, but are not a substitute for pump education.

How should I mix insulins?

NovoLog should be mixed only when syringe injections are used. NovoLog can be mixed with NPH human insulin immediately before use. The NovoLog should be drawn into the syringe before the NPH. Mixing with other insulins has not been studied. **NovoLog should not be mixed with Lantus® (insulin glargine [rDNA origin] injection). Mixed insulins should NEVER be used in a pump or for intravenous infusion.**

1. Add together the doses of NPH and NovoLog. The total dose will determine the final volume in the syringe after drawing up both insulins into the syringe.
2. Roll the NPH vial between your hands until the liquid is equally cloudy throughout.

3. Draw into the syringe the same amount of air as the NPH dose. Inject this air into the NPH vial and then remove the needle without withdrawing or touching any of the NPH insulin. (Transferring NPH to the NovoLog vial will contaminate the NovoLog vial and may change how quickly it works.)
4. Draw into the syringe the same amount of air as the NovoLog dose. Inject this air into the NovoLog vial. With the needle in place, turn the vial upside-down and withdraw the correct dose of NovoLog. The tip of the needle must be in the NovoLog to get the full dose and not an air dose.
5. Insert the needle into the NPH vial. Turn the NPH vial upside down with the syringe-needle still in it. Withdraw the correct dose of NPH.
6. Inject immediately to reduce changes in how quickly the insulin works.

Helpful information for people with diabetes is published by the American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314

For information contact:
Novo Nordisk Pharmaceuticals Inc.,
100 College Road West
Princeton, New Jersey 08540
1-800-727-6500
www.novonordisk-us.com

Manufactured by
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

Date of Issue: December 21, 2001

8-XXXX-XX-XXX-X

Printed in Denmark

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/s/

David Orloff

4/11/02 07:25:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. Organization CDER/HFD-510
Division of Metabolism and Endocrine Drug Products

2. NDA # 20-986

3. Name and Address of Applicant:
Novo Nordisk Pharmaceutical Inc.
100 College Road West
Princeton, NJ 08540

Phone: (609) 987-5822
Fax: (609) 987-3916

4. Supplement(s)
SCP 002 Doc.30-OCT-2000 Rec.31-OCT-2000
SCP 004 Doc. 09-FEB-2001 Rec. 12-FEB-2001

5. Name Of The Drug
NovoLog® (rDNA origin)

6. Nonproprietary Name
Insulin aspart [rDNA origin] injection

7. Supplement provides for a new NovoPen Junior and (b) (4) delivery devices to be used in conjunction with the 3 mL PenFill cartridge and NovoFine needles.

8. Amendments
SCP 002 14-FEB & 19-APR-2001,
08-FEB & 08,15, & 20-MAR-2002
SCP 004 27-MAR & 19-APR-2001,
08-FEB & 08, 15, & 20-MAR-2002

9. Pharmacological Category Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM.

10. How Dispensed Rx
Subcutaneous injection

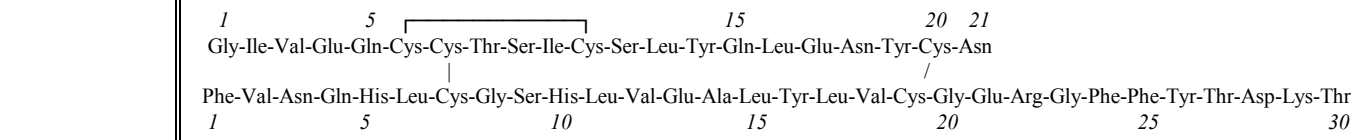
11. Related
NDA (b) (4)
NDA 19-959 SCP-034 & -035
NDA 19-991 SCP-035 & -036

12. Dosage Form Sterile parenteral suspension

13. Strength(s) 100 U/mL

14. Chemical Name and Structure

Insulin Aspart (B28-Asp-*human* Insulin) $C_{256}H_{381}N_{65}O_{79}S_5$ MW = 5825.8



15. Comments: The use of the NovoPen Junior and (b) (4) delivery devices to be used in conjunction with the 3 mL PenFill cartridges and NovoFine needles was reviewed under NDAs (b) (4) (Novolin R), 19-959 (Novolin N) and 19-991 (Novolin (b) (4) 70/30) by Janice Brown, MSc. As per Janice Brown's review "The applicant responded to the Not Approvable (NA) letter addressing the deficiencies from the CDRH review. The CDRH indicates that the sponsor has satisfactorily addressed the outstanding issues in the NA letter. The review states that CDRH determined that NovoPen Junior and (b) (4) are substantially equivalent to marketed pen injectors. The existing labeling provides for the use of NovoPen 3. The revised labeling provides for the addition of the NovoPen Junior and the (b) (4). There are no other outstanding issues preventing the approval of these supplements."

16. Conclusions and Recommendations: NovoPen Junior and (b) (4) are acceptable devices for the delivery of Insulin Aspart in conjunction with the 3 mL NovoLog® PenFill cartridges and NovoFine needles. **Issue an Approval Letter**.

17. Reviewer Name (and signature)

Xavier Ysern, PhD

18. Date Completed: 10-APR-2002

R/D Init.
Stephen Moore, PhD
Chemist Team Leader

filename: /nda//20986s02&04.doc

AP

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/s/

Xavier Ysern
4/11/02 12:01:27 PM
CHEMIST

Stephen Moore
4/11/02 01:19:29 PM
CHEMIST

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP II, HFD-510	See below
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Novo Nordisk Pharmaceuticals, Inc. 100 Overlook Center Suite 200 Princeton, NJ 08540-7810		19938/SCP-032 and SCP-033, 27-Oct-00 19959/SCP-034 and SCP –035, 27-Oct-00 20-986/SCP-002, 27-Oct-00 19991/SCP-035 and SCP-036, 27-Oct-00
5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	7. AMENDMENTS, REPORT, DATE
Novolin® R Novolin® N, NPH Novolog® Novolin® 70/30	Human Insulin (rDNA) origin Human Insulin Isophane Suspension Insulin Aspart (rDNA origin) Injection 70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection, (rDNA origin)	19938/SCP-032 BC, 15-Nov-00 19959/SCP-034 BC, 15-Nov-00 20-986/SCP-002, 15-Nov-00 19991/SCP-035 BC, 15-Nov-00
8. SUPPLEMENT PROVIDES FOR:		
A new NovoPen Junior and (b) (4) to be used in conjunction with the 3 mL PenFill cartridge and NovoFine needles.		
9.PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Hyperglycemia treatment	(b) (4)	
12. DOSAGE FORM	13. POTENCY	
Injection	100 U/ml	
14. CHEMICAL NAME AND STRUCTURE		
See Chemistry Review #1		
15. COMMENTS		
The NovoPen Junior (b) (4) NovoPen 3 Demi device (b) (4). The (b) (4) NovoPen Junior comes in different colors (green and yellow) and the NovoPen 3 Demi is only available in blue and has a different brand name. (b) (4) deliver a minimum dose of 1 IU and a maximum dose of 35 IU. The attached CDRH consult states that the (b) (4) is not substantially equivalent to the NovoPen 3 for dosing accuracy's to 0.5 IU. Since the (b) (4) Testing did not include an evaluation of dose precision at the 0.5 IU; however, the pen can deliver does of 1 IU of insulin. The (b) (4) pen is labeled with dosing precision of 0.5 IU and therefore claims (b) (4).		
16. CONCLUSION AND RECOMMENDATION		
Issue a Not Approval letter with the attached comments (see draft deficiency letter).		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
JANICE T. BROWN		16-Jan-01
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE		

- NA

Draft Deficiency Letter

1. The [redacted] pen is labeled with dosing precision of 0.5 IU and claims [redacted] Testing did not include an evaluation at the half-unit level. Please submit the following:

   a. Testing for the actual minimum dose of 0.5 IU [redacted]
   b. An intermediate dose test that compares the dose accuracy profiles for the next lower and higher doses (17.5 IU and 18.5 IU).
   c. A maximum dose evaluation that includes 34.5 IU.

2. The standard deviations for the 18 IU and the 35 IU doses appear to be very large when compared to the [redacted] dose setting precision in the endurance test which equals or exceeds the precision of the device.

3. Please submit data to support the accuracy and reliability of the [redacted] function check, which uses fill levels to confirm the proper functioning of the device.

/s/

Janice Brown
1/16/01 04:40:14 PM
CHEMIST

Stephen Moore
1/17/01 12:21:48 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-002

OTHER REVIEW(S)

Division of Metabolic and Endocrine Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-986/S-002 (NovoPen 3 Demi) and S-004 (NovoPen Junior

Name of Drug: NovoLog (insulin aspart [rDNA origin] injection)

Sponsor: Novo Nordisk

Material Reviewed: Physician and patient package insert

Submission Date: March 20, 2002

Receipt Date: March 22, 2002

Background and Summary

These supplements provide for an additional insulin delivery devices for use with NovoLog 3 mL PenFill cartridges. The supplement 002 provides for the use of NovoPen 3 Demi with NovoLog 3 mL PenFill cartridges and supplement 004 provides for the use of NovoPen Junior with NovoLog 3 mL PenFill cartridges. The instruction manual for the devices (dated 3/15/02) has incorporated all the recommendations that were suggested by the division.

The last approved physician and patient insert was for supplement 003 that was approved on December 21, 2001.

Review

The March 20, 2002, was compared to the last approved physician and patient insert dated 12/21/01 and found to be identical with the following exceptions:

I Physician insert (date of Issue: December 21, 2001, 8-XXXX-XX-XXX-X):

i. Line 490 and 491: (b) (4) is added.

This change is acceptable.

ii. Line 513: Added "Novolin®"as a trademark of Novo Nordisk A/S.

This change is acceptable since it is made to correct trademark information.

iii. Line 515: "MiniMed®, Polyfin™, and Softset™ are trademarks of MiniMed Inc." is changed to "Polyfin® and Softset® are trademarks of Medtronic MiniMed, Inc."

This change is acceptable. Novo plans to report the change in the annual report.

iv. Line 516: "H-TRON® Classic™, and Tenders™ are trademarks of Disertronic.' is changed to "H-TRON® is a trademark of Disertronic Medical Systems, Inc."

This change is acceptable. Novo plans to report the change in the annual report.

II Patient package insert (Date of Issue: December 21, 2001, 8-XXXX-XX-XXX-X):

Lines 367 – 368: The sponsor added "NovoPen 3 Demi, and NovoPen Junior" to be used with NovoLog PenFill 3 mL cartridges.

This change is acceptable.

Conclusions

The proposed labeling revisions are acceptable. The chemistry review dated 4/11/02 states the all device and chemistry issues have been resolved. An AP letter should be drafted.

CSO LABELING REVIEW

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/s/

Julie Rhee
4/11/02 03:38:15 PM
CSO

Kati Johnson
4/12/02 06:21:07 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2002

To: Mary Ann McElligott, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-5831	**Fax number:** (301) 443-9282
Phone number: (609) 987-3916	**Phone number:** (301) 827-6424

Subject: NDAs 19-938/S-033, 19-959/S-035, 19-991/S-036, and 20-986/S-002
NovoPen 3 Demi

Total no. of pages including cover: 46

Comments:

FDA revision #2.

Document to be mailed: ❑ YES ☑ NO

45 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Julie Rhee

3/15/02 02:23:34 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Barbara Chong, DDMAC, HFD-42

FROM: Julie Rhee, DMEDP, HFD-042

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 12, 2002		20-986/S-002 19-938/S-033 19-959/S-035 19-991/S-036		February 8, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
NovoLog (NDA 20-986) Novolin R (NDA 19-938) Novolin N (NDA 19-959) Novolin 70/30 (NDA 19-991)			February 22, 2002

NAME OF FIRM: Novo Nordisk

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Barbara,

Could you please review the attached manual and let me know of your comments by February 22, if it is possible at all. Thanks.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Julie Rhee

2/12/02 01:43:43 PM

Electronic Mail Message

Date: 6/11/01 10:17:26 AM
From: Nakayama, Von (VON@CDRH.FDA.GOV)
To: Rhee, H Julie (RHEEJ@A1)
Subject: NDA 19-938 NovoPen supplements

Julie,

Here is our review of the supplements for the [redacted] (b) (4) and NovoPen Junior

<<con_19.938 .5IU novopen sponsor response1>>

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
MEMORAMDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Blvd
Rockville, Maryland 20850

CONSULTATION REVIEW

Date: June 1, 2001

To: CDER/Division of Metabolic and Endocrine Drug Products (HFD-510)

Thru: Branch Chief,
Patricia Cricenti

From: Scientific Reviewer/HFZ-480

Document No: NDA 19-938, supplement 032;19-959/S-034; 19-991/S-035; 20-986/S-004
NDA 19-938, supplement 033;19-959/S-035; 19-991/S-036; 20-986/S-002

Company Name: Novo Nordisk Pharmaceuticals, Inc.
Device: (b) (4)
NovoPen® Junior

Indications for Use:
The subcutaneous administration of insulin for treatment of individuals with diabetes.

I. Purpose

The NovoPen® 3 Demi and (b) (4) are pen injectors intended for the subcutaneous administration of insulin. The pen injectors uses the sponsor's 3.0 mL glass cartridges prefilled with Novolin R (NDA 19-938), Novolin N (NDA 19-959), Novolin 70/30 (NDA 19-991), and NovoLog (NDA 20-986) insulin products.

This is a review of the sponsor's responses to requests for addition information about the performance of the pen injectors that arose from previous evaluations of the devices. The pen injectors are drug delivery device that administers selectable, measured, quantities of drugs to a patient in 0.5IU increments. They are Class II devices, classified under 21 CFR 880.5860, product code 80 FMF (piston syringes).

II. Review:

The sponsor provided the following responses to a CDRH request for additional information about the performance of the pen injectors:

1. Additional testing to demonstrate dosing precision at 0.5IU increments was performed using 1.5IU, 17.5IU, 18.5IU, and 34.5IU doses. The pen injectors passed the requirements of ISO 11608-1.2 "Pen

injectors for medical use – Part 1: Requirements and test methods" for these dose levels. Our original request for testing to be performed at a 0.5IU dose (the actual minimum dose that can be set on the device, but not the minimum indicated or labeled dose of 1IU) was withdrawn during a March 20, 2001 teleconference; the sponsor revised the labeling to emphasize1IU as the minimum dose.

2. The sponsor attributed the unusual values of the standard deviations at the middle and high doses to the specifications of the ISO test method. The ISO method recommends that the data from all devices be pooled for reporting, rather than presented for the individual devices.

3. The pen function test is a demonstration that the pen injector is functional, and is not a dose accuracy test as suggested by the fill check into the cap of the pen needle. The sponsor provided labeling to show that the procedures for the pen function test are no different from those previously cleared by CDRH for other legally marketed pen injectors.

III. Conclusion:

The sponsor provided data to demonstrate that the pen injectors can administer insulin doses accurate to 0.5 IU. The pen injectors can be considered to be substantially equivalent to legally marketed pen injectors in terms of intended use, technological characteristics, and safety and effectiveness.

If you have any questions, please call me at (301) 594-1287.

Von Nakayama

RFC-822-headers:
Received: from cdsx02.cder.fda.gov
 ("port 2624"@cdsx02.cder.fda.gov [150.148.145.221])
 by mail.cder.fda.gov (PMDF V6.0-24 #37497)
 with ESMTP id <01K4MY1GPXDI934Q6Z@mail.cder.fda.gov> for RHEEJ@cder.fda.gov
 (ORCPT RHEEJ@a1.cder.fda.gov); Mon, 11 Jun 2001 10:17:21 -0400 (EDT)
Received: by cdsx02.cder.fda.gov with Internet Mail Service (5.5.2653.19)
 id <MTY6XAJY>; Mon, 11 Jun 2001 10:17:13 -0400
Received: from cdswss1.cder.fda.gov ([150.148.150.21])
 by cdsx01.cder.fda.gov with SMTP
 (Microsoft Exchange Internet Mail Service Version 5.5.2653.13)
 id MTYZ6D4W; Mon, 11 Jun 2001 10:17:16 -0400
Received: from 150.148.4.55 by cdswss1.cder.fda.gov with ESMTP
 (Tumbleweed MMS SMTP Relay (MMS v4.7)); Mon, 11 Jun 2001 10:09:59 -0400
Received: by FDARESS13 with Internet Mail Service (5.5.2653.19)
 id <KVSWL3HQ>; Mon, 11 Jun 2001 10:12:15 -0400
X-Mailer: Internet Mail Service (5.5.2653.19)

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/s/

Julie Rhee
8/9/01 11:03:39 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Pat Cricenti, HFZ-480

FROM: Julie Rhee, DMEDP, HFD-510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 25, 2001		19-938/S-033 19-959/S-035 19-991/S-036 20-986/S-002	Response to NA letter for (b) (4)	April 19, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Novolin R (NDA 19-938) Novolin N (NDA 19-959) Novolin 70/30 (NDA 19-991) NovoLog (NDA 20-986)			June 22, 2001

NAME OF FIRM: Novo Nordisk

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Pat,

This submission is the sponsor's response to your recommendations for (b) (4) Please let me know if the sponsor has addressed your concerns satisfactorily. Under the separate cover, I've requested a consult for NovoPen Junior. According to the sponsor, (b) (4) NovoPen Junior (b) (4) (b) (4) difference in color of the device. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff

4/26/01 11:57:18 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Pat Cricenti, HFZ-480			Julie Rhee, HFD-510	
DATE November 3, 2000	IND NO.	NDA NO. NDA 19-938/S-033 NDA 19-959/S-035 NDA 19-991/S-036 NDA 20-986/S-002	TYPE OF DOCUMENT New supplement	DATE OF DOCUMENT October 27, 2000
NAME OF DRUG Novolin R (NDA 19-938) Novolin N (NDA 19-959) Novolin 70/30 (NDA 19-991) NovoLog (NDA 20-986)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE January 12, 2001
NAME OF FIRM: Novo Nordisk Pharmaceuticals				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

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V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This new supplement provides for the [redacted] (b) (4) a [redacted] (b) (4) (i.e., pen injector) to be used in conjunction with Novo Nordisk's 3 mlPenFill® cartridges and NovoFine® needles as part of a dedicated insulin delivery system.

Please review (1) function of the device, (2) dose accuracy, and (3) labeling. When the review is completed, please forward the review with this consult request form to my attention. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

/s/

Julie Rhee
11/3/00 02:30:08 PM