CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number :018623/S027

Trade Name :NPH Purified Pork Isophane Insulin Suspension USP

Generic Name:NPH Purified Pork Isophane Insulin Suspension USP

Sponsor : Novo Nordisk Pharmaceuticals, Inc.

Approval Date: April 16, 1997

NDA 19-938/S-020 plus 7 more

APR 16 1997

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
Suite 200
100 Overlook Center
Princeton, New Jersey 08540

Dear Dr. Reit:

Please refer to your supplemental new drug applications dated November 12, 1996, received November 14, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for the following products:

NDA 19-938/S-020	Novolin® R [human insulin (rDNA origin) injection]
NDA 19-959/S-021	Novolin® N [human insulin (rDNA origin) isophane suspension]
NDA 19-965/S-017	Novolin® N [human insulin (rDNA origin) isophane suspension]
NDA 19-991/S-021	Novolin® 70/30 [70% human insulin isophane suspension and 30% human insulin injection (rDNA origin)]
NDA 19-450/S-017	Velosulin® BR Buffered Regular Human Insulin Injection (semi-synthetic)
NDA 18-381/S-027	Regular Purified Pork Insulin Injection USP
NDA 18-383/S-025	Lente Purified Pork Insulin Zinc Suspension USP
NDA 18-623/S-027	NPH Purified Pork Isophane Insulin Suspension USP

These supplemental applications provide for (1) changes in the GIVING THE INJECTION, Directions for Use, and IMPORTANT NOTES sections of the package insert, and (2) use of NovoPen® 1.5 as one of the insulin delivery devices for the PenFill® cartridges.

We have completed the review of these supplemental applications including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling in the submissions dated November 12, 1996, with the revision listed below:

PenFill package inserts, Item #4, GIVING THE INJECTION section (addition is noted by redline):

This section should read "Release the skin and push the push-button all the way in to inject insulin beneath the skin. To ensure that all the insulin is injected, keep the needle in the skin for several seconds after injection . . . never inject insulin into a vein. Follow the directions for use of your Insulin Delivery Device."

This revision is a term of approval of these supplemental NDAs.

Accordingly, the supplemental applications are approved.

Please submit 20 copies of the FPL as soon as it is available, in no case 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 "FINAL PRINTED LABELING" for approved supplemental NDAs 19-938/S-020 plus 7 more. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for these products. 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 material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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, please contact Julie Rhee, Consumer Safety Officer, at (301) 443-3510.

Sincerely yours,

4/15/97

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

cc:
Original NDA 19-938, 19-959, 19-965, 19-991, 19-450, 18-381, 18-383, and 18-623
HFD-510/Div. files 19-938, 19-959, 19-965, 19-991, 19-450, 18-381, 18-383, and 18-623
HFD-510/CSO/J.Rhee
HFD-510/Misbin/Berlin/HRhee
DISTRICT OFFICE
HF-2/Medwatch (with labeling)*
HFD-92/DDM-DIAB (with labeling)*
HFD-40/DDMAC (with labeling)*
HFD-613/OGD (with labeling)*
HFI-20/Press Office (with labeling)*
* For paper reduction purpose, the draft labeling from the lead NDA (19-938) only is attached

Drafted by: JRhee /April 2, 1997/ c:wpfiles/supplement/19938s20.ap
Initialed by:Galliers 4-7-97/Misbin 4-9-97/Fleming 4-10-97/Berlin 4-14-97/SMoore 4-14-97
final: JRhee 4-14-97 4-14-97

SUPPLEMENT APPROVAL (AP)

Front side - top

R HUMAN

Novo Nordisk™

Information for the patient who uses

Novolin® R

Regular,
Human Insulin Injection
(recombinant DNA origin) USP

100 units/ml

Please read this leaflet carefully

WARNING

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN PURITY, STRENGTH, BRAND (MANUFACTURER), TYPE (REGULAR, NPH, LENTE®, ETC.), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN) AND/OR METHOD OF MANUFACTURE (RECOMBINANT DNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

SPECIAL CARE SHOULD BE TAKEN WHEN THE TRANSFER IS FROM A STANDARD BEEF OR MIXED SPECIES INSULIN TO A PURIFIED PORK OR HUMAN INSULIN. IF A DOSAGE ADJUSTMENT IS NEEDED, IT WILL USUALLY BECOME APPARENT EITHER IN THE FIRST FEW DAYS OR OVER A PERIOD OF SEVERAL WEEKS. ANY CHANGE IN TREATMENT SHOULD BE CAREFULLY MONITORED.

PLEASE READ THE SECTIONS "INSULIN REACTION AND SHOCK" AND "DIABETIC KETOACIDOSIS AND COMA" FOR SYMPTOMS OF HYPOGLYCEMIA (LOW BLOOD GLUCOSE) AND HYPERGLYCEMIA (HIGH BLOOD GLUCOSE).

INSULIN USE IN DIABETES

Your physician has explained that you have diabetes and that your treatment involves injections of insulin. Insulin is normally produced by the pancreas, a gland that lies behind the stomach. Without insulin, glucose (a simple sugar made from digested food) is trapped in the bloodstream and cannot enter the cells of the body. Some patients who don't make enough of their own insulin, or who cannot use the insulin they do make properly, must take insulin by injection in order to control their blood glucose levels.

Each case of diabetes is different and requires direct and continued medical supervision. Your physician has told you the type, strength and amount of insulin you should use and the time(s) at which you should inject it, and has also discussed with you a diet and exercise schedule. You should contact your physician if you experience any difficulties or if you have questions.

TYPES OF INSULINS

Standard and purified animal insulins as well as human insulins are available. Standard and purified insulins differ in their degree of purification and content of noninsulin material. Standard and purified insulins also vary in species source: they may be of beef, pork, or mixed beef and pork origin. Human insulin is identical in structure to the insulin produced by the human pancreas, and thus differs from animal insulins. Insulins vary in time of action and in strength; see PRODUCT DESCRIPTION and SYRINGES for additional information.

Your physician has prescribed the insulin that is right for you; be sure you have purchased the correct insulin and check it carefully before you use it.

PRODUCT DESCRIPTION

This vial contains **Novolin® R**, commonly known as Regular, Human Insulin Injection (recombinant DNA origin) USP. The concentration of this product is 100 units of insulin per milliliter. It is a clear, colorless solution which has a short duration of action. The effect of **Novolin® R** begins approximately ½ hour after injection. The effect is maximal between 2½ and 5 hours and ends approximately 8 hours after injection.

The time course of action of any insulin may vary considerably in different individuals, or at different times in the same individual. Because of this variation, the time periods listed here should be considered as general guidelines only.

This human insulin (recombinant DNA origin) is structurally identical to the insulin produced by the human pancreas. This human insulin is produced by recombinant DNA technology utilizing Saccharomyces cerevisiae (bakers' yeast) as the production organism.

Front side - bottom

STORAGE

Insulin should be stored in a cold place, preferably in a refrigerator, but not in the freezing compartment. **Do not let it freeze.** Keep the insulin vial in its carton so that it will stay clean and protected from light. If refrigeration is not possible, the bottle of insulin which you are currently using can be kept unrefrigerated as long as it is kept as cool as possible and away from heat and sunlight.

Never use **Novolin® R** if it becomes viscous (thickened) or cloudy; use it only if it is clear and colorless.

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

SYRINGES

Use the Correct Syringe

Doses of insulin are measured in units. Some insulins are available in two strengths: U-100 and U-40. One milliliter (ml) of U-100 contains 100 units of insulin. One milliliter (ml) of U-40 contains 40 units of insulin. Be sure to use the proper syringe for the strength of the insulin prescribed for you. Syringes are clearly marked **"For use with U-100 insulin"** or **"For use with U-40 insulin"**. Low dose U-100 syringes are also available. Failure to use the proper syringe can lead to mistakes in dosage.

Novo Nordisk insulin vials are intended for use with standard insulin syringes. Novo Nordisk has not evaluated the use of these vials with other devices for insulin delivery or with devices intended to aid in giving injections. Consult your doctor and the manufacturer of these devices before use with this product.

Disposable Syringes

Disposable syringes and needles require no sterilization provided the package is intact. They should be used only once and discarded.

Reusable Syringes

Reusable syringes and needles must be sterilized before each use.

1. Boil the syringe parts and needles in a pan of water for at least five minutes. Keep a special pan for this purpose. Heavily chlorinated water should not be used; distilled water is preferable.
   If boiling is not possible, the syringe parts and needles may be sterilized by immersion in 70% ethyl alcohol or 91% isopropyl alcohol for at least five minutes. **Do not use bathing, rubbing or medicated alcohol for sterilization.**
2. Assemble the syringe and fit the needle on the tip of the syringe being careful not to touch the surface of the plunger or needle.
3. Push the plunger in and out several times until the water (or alcohol) has been completely expelled. (The syringe should be thoroughly dried before its use.)

IMPORTANT

Failure to comply with the above and the following antiseptic measures may lead to infections at the injection site.

PREPARING THE INJECTION

1. Clean your hands and the injection site with soap and water or with alcohol. Wipe the rubber stopper with an alcohol swab. (Note: remove the tamper-resistant cap at first use. If the cap has already been removed, do not use this product, return it to your pharmacy.)

0203-31-021-4

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DIABETIC KETOACIDOSIS AND COMA

Diabetic ketoacidosis may develop if your body has too little insulin. The most common causes are acute illness or infection or failure to take enough insulin by injection. If you are ill you should check your urine for ketones. The symptoms of diabetic ketoacidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst and loss of appetite. Notify your physician right away if the urine test is positive for ketones (acetone) or if you have any of these symptoms. Fast, heavy breathing and rapid pulse are more severe symptoms and you should have medical attention right away. Severe, sustained hyperglycemia may result in diabetic coma and death.

ADVERSE REACTIONS

A few people with diabetes develop red, swollen and itchy skin where the insulin has been injected. This is called a "local reaction" and it may occur if the injection is not properly made, if the skin is sensitive to the cleansing solution, or if you are allergic to the insulin being used. If you have a local reaction, tell your physician.

Generalized insulin allergy occurs rarely, but when it does it may cause a serious reaction, including skin rash over the body, shortness of breath, fast pulse, sweating, and a drop in blood pressure. If any of these symptoms develop, you should seek emergency medical care.

If severe allergic reactions to insulin have occurred (i.e., generalized rash, swelling or breathing difficulties) you should be skin-tested with **each** new insulin preparation before it is used.

IMPORTANT NOTES

1. Due to risk of precipitation in some pump catheters, Novoline® R is not recommended for use in insulin pumps.
2. A change in the type, strength, species or purity of insulin could require a dosage adjustment. Any change in insulin should be made under medical supervision.
3. You may have learned how to test your urine or your blood for glucose. It is important to do these tests regularly and to record the results for review with your physician or nurse educator.
4. If you have an acute illness, especially with vomiting or fever, continue taking your insulin. If possible, stay on your regular diet. If you have trouble eating, drink fruit juices, regular soft drinks, or clear soups; if you can, eat small amounts of bland foods. Test your urine for glucose and ketones and, if possible, test your blood glucose. Note the results and contact your physician for possible insulin dose adjustment. If you have severe and prolonged vomiting, seek emergency medical care.
5. You should always carry identification which states that you have diabetes.

Always consult your physician if you have any questions about your condition or the use of insulin.

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

For information contact: Novo Nordisk Pharmaceuticals Inc., Princeton, NJ 08540

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

Printed in Denmark

Date of issue: December 1993

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2. For insulin suspensions, roll the vial of insulin gently in your hands to mix it. Vigorous shaking immediately before the dose is drawn into the syringe may result in the formation of bubbles or froth which could cause dosage errors.
3. Pull back the plunger until the black tip reaches the marking for the number of units you will inject.
4. Push the needle through the rubber stopper into the vial.
5. Push the plunger all the way in. This inserts air into the bottle.
6. Turn the vial and syringe upside down and slowly pull the plunger back to a few units beyond the correct dose.
7. If there are air bubbles, flick the syringe firmly with your finger to raise the air bubbles to the needle, then slowly push the plunger to the correct unit marking.
8. Lift the vial off the syringe.

GIVING THE INJECTION

1. The following areas are suitable for subcutaneous insulin injection: thighs, upper arms, buttocks, abdomen. Do not change areas without consulting your physician. The actual point of injection should be changed each time; injection sites should be about an inch apart.
2. The injection site should be clean and dry. Pinch up skin area to be injected and hold it firmly.
3. Hold the syringe like a pencil and push the needle quickly and firmly into the pinched-up area. ~~If you go straight in it will probably sting less. Pull back the plunger slightly. If blood comes into the syringe, the needle has entered a blood vessel. Remove the needle and make the injection in another spot.~~ R the
4. ~~If blood does not appear in the syringe,~~ release skin and push plunger all the way in to inject insulin beneath the skin. Do not inject into a muscle unless your physician has advised it. You should never inject insulin into a vein.
5. Remove needle. If slight bleeding occurs, press lightly with a dry cotton swab for a few seconds – **do not rub.**

To ensure that all the insulin is injected keep the needle in the skin for several seconds after injection with your finger on the plunger.

Note:
The dose should be injected over 2-4 seconds. Preparations of insulin suspensions which are injected slowly may clog the tip of the needle, resulting in an inability to complete the injection. Syringe plugging does not occur when the drug is injected more rapidly.

Use the injection technique recommended by your physician.

MIXING TWO TYPES OF INSULIN

Different insulins should be mixed only under instruction from a physician. Hypodermic syringes may vary in the amount of space between the bottom line and the needle ("dead space"), so if you are mixing two types of insulin be sure to discuss any change in the model and brand of syringe you are using with your physician or pharmacist. When you are mixing two types of insulin, always draw the Regular (clear) insulin into the syringe first.

USAGE IN PREGNANCY

It is particularly important to maintain good control of your diabetes during pregnancy and special attention must be paid to your diet, exercise and insulin regimens. If you are pregnant or nursing a baby, consult your physician or nurse educator.

INSULIN REACTION AND SHOCK

Insulin reaction ("hypoglycemia") occurs when the blood glucose falls very low. This can happen if you take too much insulin, miss or delay a meal, exercise more than usual or work too hard without eating, or become ill (especially with vomiting or fever). The first symptoms of an insulin reaction usually come on suddenly. They may include a cold sweat, fatigue, nervousness or shakiness, rapid heartbeat, or nausea. Personality change or confusion may also occur. If you drink or eat something right away (a glass of milk or orange juice, or several sugar candies), you can often stop the progression of symptoms. If symptoms persist, call your physician – an insulin reaction can lead to unconsciousness. If a reaction results in loss of consciousness, emergency medical care should be obtained immediately. If you have had repeated reactions or if an insulin reaction has led to a loss of consciousness, contact your physician. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death.

In certain cases, the nature and intensity of the warning symptoms of hypoglycemia may change. A few patients have reported that after being transferred to human insulin, the early warning symptoms of hypoglycemia were less pronounced than they had been with animal-source insulin.

Front side - top

Novo Nordisk™

R HUMAN

Information for the patient who uses

Novolin® R PenFill®

Regular,
Human Insulin Injection
(recombinant DNA origin)

100 units/ml

Please read this leaflet carefully before using this product.

Novolin® R PenFill® is for use with NovoPen® and NovolinPen® Insulin Delivery Devices and NovoFine® disposable needles or other products specifically recommended by Novo Nordisk. PenFill® cartridge is for single person use only.
See Important Notes section.

WARNING

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN PURITY, STRENGTH, BRAND (MANUFACTURER), TYPE (REGULAR, NPH, LENTE®, ETC.), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN), AND/OR METHOD OF MANUFACTURE (RECOMBINANT DNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

SPECIAL CARE SHOULD BE TAKEN WHEN THE TRANSFER IS FROM A STANDARD BEEF OR MIXED SPECIES INSULIN TO A PURIFIED PORK OR HUMAN INSULIN. IF A DOSAGE ADJUSTMENT IS NEEDED, IT WILL USUALLY BECOME APPARENT EITHER IN THE FIRST FEW DAYS OR OVER A PERIOD OF SEVERAL WEEKS. ANY CHANGE IN TREATMENT SHOULD BE CAREFULLY MONITORED.

PLEASE READ THE SECTIONS "INSULIN REACTION AND SHOCK" AND "DIABETIC KETOACIDOSIS AND COMA" FOR SYMPTOMS OF HYPOGLYCEMIA (LOW BLOOD GLUCOSE) AND HYPERGLYCEMIA (HIGH BLOOD GLUCOSE).

the correct insulin and check it carefully before you use it.

PRODUCT DESCRIPTION

This package contains five (5) **Novolin® R PenFill®** cartridges. **Novolin® R** is commonly known as Regular, Human Insulin Injection (recombinant DNA origin). The concentration of this product is 100 units of insulin per milliliter. It is a clear, colorless solution which has a short duration of action. The effect of **Novolin® R** begins approximately ½ hour after injection. The effect is maximal between 2½ and 5 hours and ends approximately 8 hours after injection.

The time course of action of any insulin may vary considerably in different individuals, or at different times in the same individual. Because of this variation, the time periods listed here should be considered as general guidelines only.

This human insulin (recombinant DNA origin) is structurally identical to the insulin produced by the human pancreas. This human insulin is produced by recombinant DNA technology utilizing Saccharomyces cerevisiae (bakers' yeast) as the production organism.

INSULIN DELIVERY SYSTEMS

These **Novolin® PenFill®** cartridges are for use with **NovoPen®** and **NovolinPen®** Insulin Delivery Devices and **NovoFine®** disposable needles or other products specifically recommended by Novo Nordisk. NovoPen® 1.5

STORAGE

Insulin should be stored in a cold place, preferably in a refrigerator, but not in the freezing compartment. **Do not let it freeze.** Keep **Novolin® R PenFill®** cartridges in the carton so they will stay clean and protected from light. **Novolin® R PenFill®** cartridges can be kept unrefrigerated for one (1) month. Unrefrigerated cartridges must be used within this time period or discarded. Be sure to protect cartridges from sunlight and extreme heat or cold.

Never use any **Novolin® R PenFill®** if it becomes viscous (thickened) or cloudy; use it only if it is clear and colorless.

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

IMPORTANT

Failure to comply with the following antiseptic measures may lead to infections at the injection site.

- Disposable needles are for single use; they should be used only once and destroyed.
- Clean your hands and the injection site with soap and water or with alcohol.
- Wipe the rubber stopper on the cartridge with an alcohol swab.

Front side - bottom

INSULIN USE IN DIABETES

Your physician has explained that you have diabetes and that your treatment involves injections of insulin. Insulin is normally produced by the pancreas, a gland that lies behind the stomach. Without insulin, glucose (a simple sugar made from digested food) is trapped in the bloodstream and cannot enter the cells of the body. Some patients who don't make enough of their own insulin, or who cannot use properly the insulin they do make, must take insulin by injection in order to control their blood glucose levels.

Each case of diabetes is different and requires direct and continued medical supervision. Your physician has told you the type, strength and amount of insulin you should use and the time(s) at which you should inject it, and has also discussed with you a diet and exercise schedule. You should contact your physician if you experience any difficulties or if you have questions.

TYPES OF INSULINS

Standard and purified animal insulins as well as human insulins are available. Standard and purified insulins differ in their degree of purification and content of noninsulin material. Standard and purified insulins also vary in species source: they may be of beef, pork, or mixed beef and pork origin. Human insulin is identical in structure to the insulin produced by the human pancreas, and thus differs from animal insulins. Insulins vary in time of action; see PRODUCT DESCRIPTION for additional information.

Your physician has prescribed the insulin that is right for you; be sure you have purchased

0205-31-081-4

PREPARING THE INJECTION

Place a single-use needle on the device. ~~Be sure there is sufficient insulin in the cartridge to complete the injection~~. Refer to the instruction manual for your insulin delivery device for assistance in estimating the amount of insulin remaining in the cartridge.

GIVING THE INJECTION

1. The following areas are suitable for subcutaneous insulin injection: thighs, upper arms, buttocks, abdomen. Do not change areas without consulting your physician. The actual point of injection should be changed each time; injection sites should be about an inch apart.
2. The injection site should be clean and dry. Pinch up skin area to be injected and hold it firmly.
3. Hold the device like a pencil and push the needle quickly and firmly into the pinched-up area. ~~If you go straight in it will probably sting less.~~
4. Follow the directions for use of your Insulin Delivery Device.
5. ~~Do not inject into a muscle unless your physician has advised it. You should never inject insulin into a vein.~~
6. ~~Remove needle. If slight bleeding occurs, press lightly with a dry cotton swab for a few seconds - do not rub.~~

USAGE IN PREGNANCY

It is particularly important to maintain good control of your diabetes during pregnancy and special attention must be paid to your diet, exercise and insulin regimens. If you are pregnant or nursing

Note: Use the injection technique recommended by your physician.

To ensure that all the insulin is injected keep the needle in the skin for several seconds **after** injection with your thumb on the push button. Do not inject into a muscle unless your physician has advised it. You should never inject insulin into a vein.

5. Remove the needle. If slight bleeding occurs, press lightly with a dry cotton swab for a few seconds - **do not rub.**

a baby, consult your physician or nurse educator.

INSULIN REACTION AND SHOCK

Insulin reaction ("hypoglycemia") occurs when the blood glucose falls very low. This can happen if you take too much insulin, miss or delay a meal, exercise more than usual or work too hard without eating, or become ill (especially with vomiting or fever). The first symptoms of an insulin reaction usually come on suddenly. They may include a cold sweat, fatigue, nervousness or shakiness, rapid heartbeat, or nausea. Personality change or confusion may also occur. If you drink or eat something right away (a glass of milk or orange juice, or several sugar candies), you can often stop the progression of symptoms. If symptoms persist, call your physician - an insulin reaction can lead to unconsciousness. If a reaction results in loss of consciousness, emergency medical care should be obtained immediately. If you have had repeated reactions or if an insulin reaction has led to a loss of consciousness, contact your physician. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death.

In certain cases, the nature and intensity of the warning symptoms of hypoglycemia may change. A few patients have reported that after being transferred to human insulin, the early warning symptoms of hypoglycemia were less pronounced than they had been with animal-source insulin.

DIABETIC KETOACIDOSIS AND COMA

Diabetic ketoacidosis may develop if your body has too little insulin. The most common causes are acute illness or infection or failure to take enough insulin by injection. If you are ill you should check your urine for ketones. The symptoms of diabetic ketoacidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst and loss of appetite. Notify your physician right away if the urine test is positive for ketones (acetone) or if you have any of these symptoms. Fast, heavy breathing and rapid pulse are more severe symptoms and you should have medical attention right away. Severe, sustained hyperglycemia may result in diabetic coma and death.

possible, test your blood glucose. Note the results and contact your physician for possible insulin dose adjustment. If you have severe and prolonged vomiting, seek emergency medical care.

6. You should always carry identification which states that you have diabetes.

Always consult your physician if you have any questions about your condition or the use of insulin.

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

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ADVERSE REACTIONS

A few people with diabetes develop red, swollen and itchy skin where the insulin has been injected. This is called a "local reaction" and it may occur if the injection is not properly made, if the skin is sensitive to the cleansing solution, or if you are allergic to the insulin being used. If you have a local reaction, tell your physician.

Generalized insulin allergy occurs rarely, but when it does it may cause a serious reaction, including skin rash over the body, shortness of breath, fast pulse, sweating, and a drop in blood pressure. If any of these symptoms develop, you should seek emergency medical care.

If severe allergic reactions to insulin have occurred (i.e., generalized rash, swelling or breathing difficulties) you should be skin-tested with **each** new insulin preparation before it is used.

IMPORTANT NOTES

1. A change in the type, strength, species or purity of insulin could require a dosage adjustment. Any change in insulin should be made under medical supervision.
2. To avoid possible transmission of disease, PenFill® cartridge is for single person use only.
4. You may have learned how to test your urine or your blood for glucose. It is important to do these tests regularly and to record the results for review with your physician or nurse educator.
5. If you have an acute illness, especially with vomiting or fever, continue taking your insulin. If possible, stay on your regular diet. If you have trouble eating, drink fruit juices, regular soft drinks, or clear soups; if you can, eat small amounts of bland foods. Test your urine for glucose and ketones and, if

3. Before use check that the PenFill® cartridge is intact (e.g. no cracks). Do not use if any damage is seen, or if the rear rubber stopper is visible above the white bar code band when the PenFill® is pointing up.

For information contact:
Novo Nordisk Pharmaceuticals Inc.,
Princeton, NJ 08540
Manufactured by
Novo Nordisk A/S,
DK-2880 Bagsvaerd, Denmark

Printed in Denmark Date of issue: August 1994

Front side - top

Novo Nordisk™

Insulin Information For The Patient Using

Novolin R Prefilled™

Regular, Human Insulin Injection
(recombinant DNA origin)
in a 1.5 ml Prefilled Syringe
100 units/ml

Please read both sides of this leaflet carefully before using this product.

Novolin R Prefilled™ syringe is for single person use only.
See Important Notes section.

WARNING

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN PURITY, STRENGTH, BRAND (MANUFACTURER), TYPE (REGULAR, NPH, LENTE®, ETC.), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN), AND/OR METHOD OF MANUFACTURE (RECOMBINANT DNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

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PLEASE READ THE SECTIONS "INSULIN REACTION AND SHOCK" AND "DIABETIC KETOACIDOSIS AND COMA" FOR SYMPTOMS OF HYPOGLYCEMIA (LOW BLOOD GLUCOSE) AND HYPERGLYCEMIA (HIGH BLOOD GLUCOSE).

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Each case of diabetes is different and requires direct and continued medical supervision. Your physician has told you the type, strength and amount of insulin you should use and the time(s) at which you should inject it, and has also discussed with you a diet and exercise schedule. You should contact your physician if you experience any difficulties or if you have questions.

tion, the time periods listed here should be considered as general guidelines only.

This human insulin (recombinant DNA origin) is structurally identical to the insulin produced by the human pancreas. This human insulin is produced by recombinant DNA technology utilizing Saccharomyces cerevisiae (bakers' yeast) as the production organism.

STORAGE

Novolin R Prefilled™ insulin syringes should be stored in a cold place, preferably in a refrigerator, but not in the freezing compartment. **Do not let it freeze.** Keep **Novolin R Prefilled™** in the carton so that they will stay clean and protected from light. **Novolin R Prefilled™** can be kept unrefrigerated for one (1) month. Unrefrigerated syringes must be used within this time period or discarded. Be sure to protect syringes from sunlight and extreme heat or cold.

Never use any **Novolin R Prefilled™** if the insulin becomes viscous (thickened) or cloudy; use it only if it is clear and colorless.

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

IMPORTANT

Failure to comply with the following antiseptic measures may lead to infections at the injection site.

- Disposable needles are for single use; they should be used only once and discarded properly.
- Clean your hands and the injection site with soap and water or with alcohol.
- Wipe the rubber stopper with an alcohol swab.

PREPARING THE INJECTION

Never place a single-use disposable needle on your insulin delivery device until you are ready to give an injection, and remove it immediately after each injection. Follow the directions for use of this syringe on the reverse side of this insert.

GIVING THE INJECTION

1. The following areas are suitable for subcutaneous insulin injection: thighs, upper arms, buttocks, abdomen. Do not change areas without consulting your physician. The actual point of injection should be changed each time; injection sites should be about an inch apart.
2. The injection site should be clean and dry. Pinch up skin area to be injected and hold it firmly.
3. Hold the device like a pencil and push the needle quickly and firmly into the pinched-up area. ~~If you go straight in it will probably sting less.~~
4. Do not inject into a muscle unless your physician has advised it. You should never inject insulin into a vein.
5. Remove needle. If slight bleeding occurs, press lightly with a dry cotton swab for a few seconds - **do not rub.**

USAGE IN PREGNANCY

It is particularly important to maintain good control of your diabetes during pregnancy and special attention must be paid to your diet, exercise and insulin regimens. If you are pregnant or nursing a baby, consult your physician or nurse educator.

Release the skin and push the push-button all the way in to inject insulin beneath the skin. To ensure that all the insulin is injected keep the needle in the skin for several seconds after injection with your thumb on the push-button.

insulin by injection. If you are ill you should check your urine for ketones. The symptoms of diabetic ketoacidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst and loss of appetite. Notify your physician right away if the urine test is positive for ketones (acetone) or if you have any of these symptoms. Fast, heavy breathing and rapid pulse are more severe symptoms and you should have medical attention right away. Severe, sustained hyperglycemia may result in diabetic coma and death.

ADVERSE REACTIONS

A few people with diabetes develop red, swollen and itchy skin where the insulin has been injected. This is called a "local reaction" and it may occur if the injection is not properly made, if the skin is sensitive to the cleansing solution, or if you are allergic to the insulin being used. If you have a local reaction, tell your physician.

Generalized insulin allergy occurs rarely, but when it does it may cause a serious reaction, including skin rash over the body, shortness of breath, fast pulse, sweating, and a drop in blood pressure. If any of these symptoms develop, you should seek emergency medical care.

If severe allergic reactions to insulin have occurred (i.e., generalized rash, swelling or breathing difficulties) you should be skin-tested with **each** new insulin preparation before it is used.

IMPORTANT NOTES

1. A change in the type, strength, species or purity of insulin could require a dosage adjustment. Any change in insulin should be made under medical supervision.
2. To avoid possible transmission of disease, **Novolin R Prefilled™** syringe is for single person use only.
3. You may have learned how to test your urine or your blood for glucose. It is important to do these tests regularly and to record the results for review with your physician or nurse educator.
4. If you have an acute illness, especially with vomiting or fever, continue taking your insulin. If possible, stay on your regular diet. If you have trouble eating, drink fruit juices, regular soft drinks, or clear soups; if you can, eat small amounts of bland foods. Test your urine for glucose and ketones and, if possible, test your blood glucose. Note the results and contact your physician for possible insulin dose adjustment. If you have severe and prolonged vomiting, seek emergency medical care.
5. You should always carry identification which states that you have diabetes.

Always consult your physician if you have any questions about your condition or the use of insulin.

For additional information see **GIVING THE INJECTION** on the reverse side of this insert.

Front side - bottom

TYPES OF INSULINS
Standard and purified animal insulins as well as human insulins are available. Standard and purified insulins differ in their degree of purification and content of noninsulin material. Standard and purified insulins also vary in species source: they may be of beef, pork, or mixed beef and pork origin. Human insulin is identical in structure to the insulin produced by the human pancreas, and thus differs from animal insulins. Insulins vary in time of action; see PRODUCT DESCRIPTION for additional information.
Your physician has prescribed the insulin that is right for you; be sure you have purchased the correct insulin and check it carefully before you use it.

PRODUCT DESCRIPTION
This package contains five (5) **Novolin R Prefilled-** insulin syringes. **Novoline R** is commonly known as Regular, Human Insulin Injection (recombinant DNA origin). The concentration of this product is 100 units of insulin per milliliter. It is a clear, colorless solution which has a short duration of action. The effect of **Novoline R** begins approximately ½ hour after injection. The effect is maximal between 2½ and 5 hours and ends approximately 8 hours after injection.
The time course of action of any insulin may vary considerably in different individuals, or at different times in the same individual. Because of this variation, **in certain cases, the nature and intensity of the warning symptoms of hypoglycemia may change. A few patients have reported that after being transferred to human insulin, the early warning symptoms of hypoglycemia were less pronounced than they had been with animal-source insulin.**

INSULIN REACTION AND SHOCK
Insulin reaction ("hypoglycemia") occurs when the blood glucose falls very low. This can happen if you take too much insulin, miss or delay a meal, exercise more than usual or work too hard without eating, or become ill (especially with vomiting or fever). The first symptoms of an insulin reaction usually come on suddenly. They may include a cold sweat, fatigue, nervousness or shakiness, rapid heartbeat, or nausea. Personality change or confusion may also occur. If you drink or eat something right away (a glass of milk or orange juice, or several sugar candies), you can often stop the progression of symptoms. If symptoms persist, call your physician - an insulin reaction can lead to unconsciousness. If a reaction results in loss of consciousness, emergency medical care should be obtained immediately. If you have had repeated reactions or if an insulin reaction has led to a loss of consciousness, contact your physician. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death.

DIABETIC KETOACIDOSIS AND COMA
Diabetic ketoacidosis may develop if your body has too little insulin. The most common causes are acute illness or infection or failure to take enough

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

Novo Nordisk Pharmaceuticals Inc.,
Princeton, NJ 08540

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

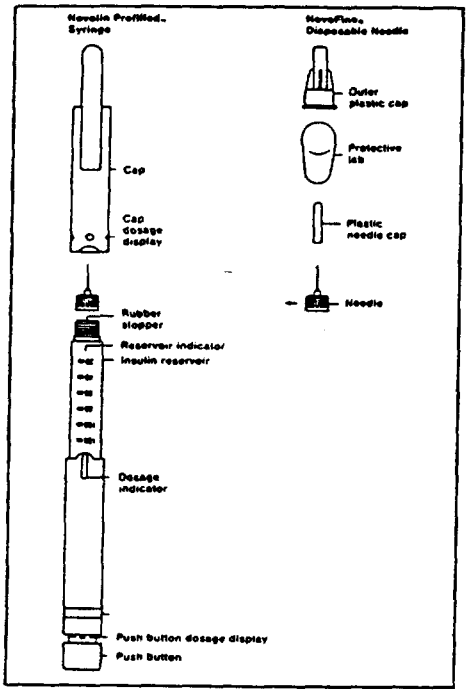
Printed in Denmark Date of issue: August 1994

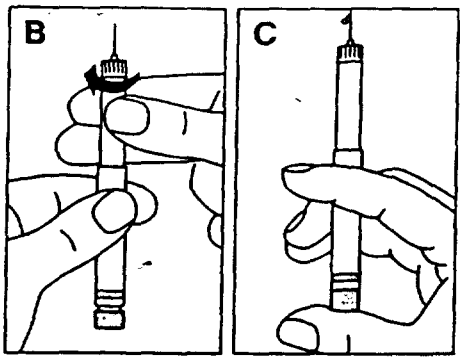
Back side - top

Prefilled syringe directions for use

This is a disposable dial-a-dose insulin delivery system able to deliver 2-58 units in increments of 2 units. **Novolin R Prefilled** syringe must only be used with **NovoFine** single-use needle or other products specifically recommended by Novo Nordisk. **Novolin R Prefilled** syringe is not recommended for the blind or visually impaired without the assistance of a sighted individual trained in the proper use of this product.

Please read these instructions completely before using this device.

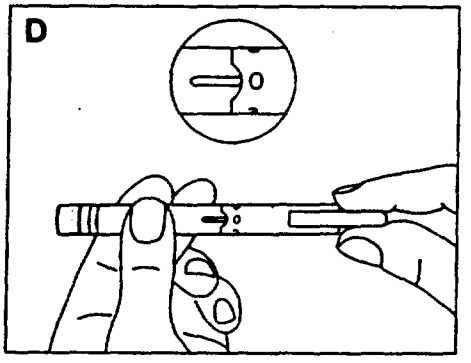




B. Holding the syringe with the needle pointing upwards, **slowly** turn the insulin reservoir clockwise (in the direction of the arrow, fig. B) to the first notch where resistance is felt (1/5 of a full rotation).

C. Still with the needle pointing upwards, press the push button as far it will go and see if a drop of insulin appears at the needle tip (Fig. C).
If not, repeat the procedure until insulin appears.
A small air bubble may remain but it will not be injected because the operating mechanism prevents the reservoir from being completely emptied.

2. Setting the dose



D. Replace the cap, so **0** is opposite the dosage indicator.

Before the first use of Novolin R Prefilled you may need to perform up to 6 air shots to get a droplet of insulin at the needle tip. If you need to make more than 6 air shots, do not use and return the product to Novo Nordisk.

To check the dose set, add the figure on the cap opposite the dosage indicator to the highest number showing on the push button display.

Dosage examples

- **8 units:**
  Turn the cap until **8** is opposite the dosage indicator.
- **16 units:**
  Turn the cap 1 full turn so **0** is opposite the dosage indicator. The 10-line will show on the push button scale. Continue turning until **6** is opposite the dosage indicator (see **F**).

If you have set a wrong dose, simply turn the cap forwards or backwards until the right number of units has been set.

58 units is the maximum dose. If you attempt to set a higher dose, insulin will be expelled from the needle and the dose will be wrong. If you set more than 58 units, turn the cap back as far as you can until resistance is felt and the push button is fully depressed. If the dosage indicator is not lined up with **0** when resistance is felt, remove the cap and replace it with **0** opposite the dosage indicator. Now start again, remembering that **58** units is the maximum dose. After the dose is set, remove the cap.

3. Giving the injection

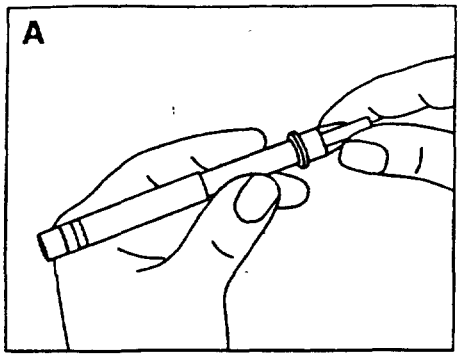
Use the injection technique recommended by your doctor. Check that you have set the proper dose and depress the push button as far as it will go. When depressing the push button you may hear a clicking sound. Do not rely on this clicking sound as a means of determining or confirming your dose.
After making the injection, replace the plastic outer cap. Unscrew the needle and discard appropriately. Replace the cap with **0** opposite the dosage indicator.
For additional information see **GIVING THE INJECTION** on the reverse side of this insert.

4. Subsequent injections

Always check that the push button is fully depressed before using the syringe again. If not, turn the cap until the push button is completely down. Then proceed as stated under steps 1-3.
The numbers on the insulin reservoir can be used to estimate the amount of insulin left in the syringe. These numbers **are not** used for measuring the insulin dose.
You cannot set a dose greater than the number of units remaining in the reservoir.

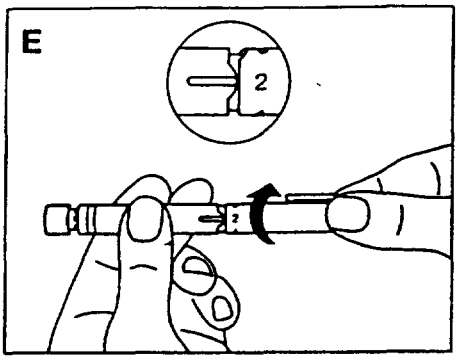
Back side - bottom

1. Preparing the Syringe
Pull off the cap.
Wipe rubber stopper with an alcohol swab.

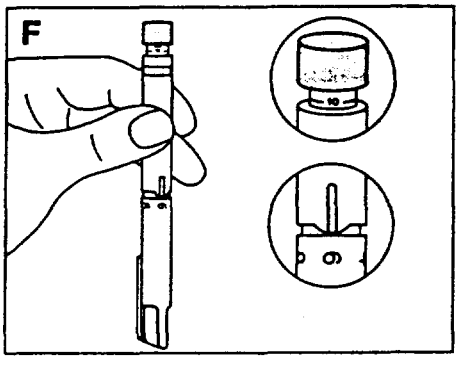


A. Remove the protective tab from the disposable needle and screw the needle onto the syringe. Never place a disposable needle on your syringe until you are ready to give an injection. Remove the needle immediately after use. If the needle is not removed, some liquid may be expelled from the syringe causing a change in insulin concentration (strength).

Giving the air shot prior to each injection:
Small amounts of air may collect in the needle and insulin reservoir during normal use.
To avoid the injection of air and ensure proper dosing, hold the syringe with the needle upwards and tap the syringe gently with your finger so any air bubbles collect in the top of the reservoir. Remove both the plastic outer cap and the needle cap.



E. Hold the syringe horizontally and turn the cap in the direction of the arrow to set the required dose. Do not put your hand over the push button when dialing the dose. If the button is not allowed to rise freely, insulin will be pushed out of the needle.
The dosage display on the cap shows **0, 2, 4, 6** and **8** units.



F. As the cap is turned, the push button rises. The dosage display below the push button shows **10, 20, 30, 40** and **50** units. Every time you fully turn the cap, 10 units will be set.

6 air shots before the first use of Novolin R Prefilled™ to get a droplet of insulin at the needle tip, do not use.

5. Important Notes

- Remember to perform an air shot before each injection. See Figures B and C.
- Care should be taken not to drop the syringe or subject it to impact.
- The compact size of this prefilled syringe makes it easy to use and convenient to carry. Remember to keep it with you; don't leave it in a car or other location where extremes of temperature can occur.
- **Novolin R Prefilled™** is for use with **NovoFine®** disposable needles or other products specifically recommended by Novo Nordisk.
- Never place a disposable needle on this syringe until you are ready to use it. Remove the needle immediately after use.
- Discard the used syringe carefully, without the needle attached.
- Always carry a spare **Novolin R Prefilled™** syringe with you in case your prefilled syringe is damaged or lost.
- Novo Nordisk cannot be held responsible for adverse reactions occuring as a consequence of using this insulin delivery system with products that are not recommended by Novo Nordisk.
- Keep this syringe out of the reach of children.

Call 800-727-6500 for additional information.

Novo Nordisk Pharmaceuticals Inc.,
Princeton, NJ 08540
Manufactured by
Novo Nordisk A/S,
DK-2880 Bagsvaerd, Denmark

Printed in Denmark Date of issue: August 1994

ORIGINAL

NDA SUPPLEMENT

Changes Being Effected Supplement
Labeling Change

Novo Nordisk

November 12, 1996

Solomon Sobel, M.D.
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
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CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 14 1996
HFD-510

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RE:	**NDA 19-938**	**Novolin® R**	**Regular, Human Insulin Injection (recombinant DNA origin) USP**
	NDA 19-959	**Novolin® N**	**NPH, Human Insulin Isophane Suspension (recombinant DNA origin)**
	NDA 19-965	**Novolin® L**	**Lente®, Human Insulin Zinc Suspension (recombinant DNA origin)**
	NDA 19-991	**Novolin® 70/30**	**70% NPH, Human Insulin Isophane Suspension and 30% Regular Human Insulin Injection (rDNA origin)**
	NDA 19-450	**Velosulin® BR**	**Buffered Regular Human Insulin Injection (semi-synthetic)**
	NDA 18-381		**Regular Purified Pork Insulin Injection USP**
	NDA 18-383		**Lente® Purified Pork Insulin Zinc Suspension USP**
	NDA 18-623		**NPH Purified Pork Isophane Insulin Suspension USP**

Accept this revision

Dear Dr. Sobel:

Reference is made to the above-listed NDAs for Novo Nordisk Pharmaceuticals, Inc.'s marketed insulin products. Pursuant to 21CFR § 314.70(c)(iii) we are submitting supplements for revisions to the patient package insert for the above-referenced products to strengthen the instructions concerning administration to increase the safe use of the products.

The request for labeling revisions for the eight referenced NDAs is submitted as a single supplement. A separate 356h form and product specific draft labeling is attached to the common cover letter for each highlighted NDA.

If you have any questions concerning this submission, please contact Lynn Joesten, Manager, Regulatory Affairs at the above telephone number.

Sincerely,
NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

BR/pk
Enclosure

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER (AP) ☐ N.A.I. ☐ MEMO

CSO INITIALS 4-16-97 DATE

f:\...Labeling/nov.supp.ltr