CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-781/S027

Trade Name: Humulin N

Generic Name: [human insulin (rDNA origin) isophane suspension]

Sponsor: Lilly Research Laboratories

Approval Date: April 3, 1991

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-781/S027

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-781/S027

APPROVAL LETTER

NDA 18-781/S-027

APR 3 1991

Lilly Research Laboratories
Attention: M. W. Talbott, Ph.D.
Director, Medical Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Talbott:

Reference is made to your supplemental new drug application (S-027) dated February 6, 1990, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humulin N [human insulin (rDNA origin) isophane suspension].

The supplement provides for a revision of the "Information for the Patient" insert.

We also acknowledge receipt of your amendment dated March 8, 1991.

We have completed our review of this supplemental application and it is approved, effective on the date of this letter.

Please submit twelve (12) copies of the final printed labeling (FPL) identical to the draft labeling to FDA as soon as possible. Seven of the copies should be individually mounted on heavy weight paper or similar material. The submission should be designated for administrative purposes as "FPL for Approved NDA 18-781/S-027." Approval of the submission by FDA is not required before the labeling is used. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

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

Sincerely yours,

4/2/91

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

LCB 4/2/91

cc: NDA Arch.
HFD-510
HFD-500/LRipper
HFD-630
HFD-80
HFD-510/SShen/AFleming/YYChiu
HFD-511/LBraithwaite/FT/MMM/4/2/91/N17871AP.S27
Concurrence:EGallliers/3/29/SShen/AFleming/YYChiu/4/1/91

SUPPLEMENT APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-781/S027

APPROVABLE LETTER

NDA 18-781/S-027

OCT 11 1990

Lilly Research Laboratories
Attention: M. W. Talbott, Ph.D.
Director, Medical Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Talbott:

Reference is made to your supplemental new drug application dated February 6, 1990, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humulin N [human insulin (rDNA origin) isophane suspension].

The supplement provides for an extensive revision of the "Information for the Patient" insert. Major changes are as follows: additional information on hypoglycemia, instructions on discarding old insulin, additional detail on mixing procedures, additional information on conditions which might affect dosage, and the addition of lipodystropy to the list of common diabetes problems.

We have completed our review of this supplemental application and find that the information presented is inadequate and the application is not approvable. The application fails to provide information as required under section 505(b)(1) of the Act and 21 CFR 314.125(b)(6) of FDA's implementing regulations as follows:

1. In the WARNINGS section, the last sentence should be revised by replacing "1ST" with the word "FIRST".

2. The subsection entitled "Syringe Use" in the INJECTION PROCEDURES section [redacted] b(4) capitalized: "NEEDLES AND SYRINGES MUST NOT BE SHARED".

3. [redacted] "Storage" subsection of the NPH HUMAN INSULIN section [redacted] b(4) [redacted] the insulin as cool as possible. Also, please delete the word [redacted] b(4) ."

4. In the same "Storage" subsection, [redacted] b(4)

5. In the COMMON PROBLEMS OF DIABETES section, the paragraph starting "A few patients have experienced hypoglycemic reactions . . ." should be in bold-faced print.

As you know, 21 CFR 429.11(c)(3) requires that batches of insulin containing 40 or 100 U.S.P. units of insulin per millimeter include in their labeling "A description of a practicable method for sterilizing the needle and syringe before use." The Humulin N "Information for the Patient" insert includes a section on techniques (boiling and the use of isopropyl alcohol) for sterilizing reusable syringes and needles to comply with the regulation. The problem is that the techniques described will not sterilize; they merely disinfect the syringes and needles. The only way to achieve sterilization would be by autoclaving, x-ray exposure, or ethylene oxide exposure, none of which would be reasonable for patients to perform in their home or while on a trip. This Division intends to resolve this problem by revising the regulation. b(5) b(5)

The Center is currently revising insulin regulations and will include this change in that total revision. b(5) b(5)

that portion of the insert must remain the same. When the regulation is finalized, the Division will accept a "Changes-Being-Effected Supplement" [21 CFR 314.70(c)(2)(iii)] to implement the change.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the FDA may proceed to withdraw the supplemental application. Any amendment should respond to all the deficiencies listed. A partial reply will not be processed as a major amendment unless it addresses all remaining outstanding deficiencies, and, therefore, the review clock will not be activated.

If you have any questions, please contact Ms. Lana L. Braithwaite at (301) 443-3510.

Sincerely yours,

10/10/90

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: NDA Arch
HFD-510
HFD-80
HFD-33/SSpungen
HFZ-420/TUlatowski
HFD-510/YYChiu, SShen, AFleming, LBraithwaite
HFD-511/JShort 9/29/90/ft/dj/10.3.90/N18781NA.003
Concurrence: Chiu/Shen/Fleming10.3.90
Revised as per Dr. Shen's comment--10/4/90
NA

JShort 10/10/90

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-781/S027

LABELING

INFORMATION FOR THE PATIENT
HUMULIN® N

NPH
HUMAN INSULIN (RECOMBINANT DNA ORIGIN)
ISOPHANE SUSPENSION

WARNINGS

THIS LILLY HUMAN INSULIN PRODUCT DIFFERS FROM ANIMAL-SOURCE INSULINS BECAUSE IT IS STRUCTURALLY IDENTICAL TO THE INSULIN PRODUCED BY YOUR BODY'S PANCREAS AND BECAUSE OF ITS UNIQUE MANUFACTURING PROCESS.

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.

SOME PATIENTS TAKING HUMULIN® (HUMAN INSULIN, RECOMBINANT DNA ORIGIN, LILLY) MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH ANIMAL-SOURCE INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.

DIABETES

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood glucose at a nearly normal level. Proper control of your diabetes requires close and constant cooperation with your doctor. In spite of diabetes, you can lead an active, healthy, and useful life if you eat a balanced diet daily, exercise regularly, and take your insulin injections as prescribed.

You have been instructed to test your blood and/or your urine regularly for glucose. If your blood tests consistently show above- or below-normal glucose levels or your urine tests consistently show the presence of glucose, your diabetes is not properly controlled and you must let your doctor know.

Always keep an extra supply of insulin as well as a spare syringe and needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

NPH HUMAN INSULIN

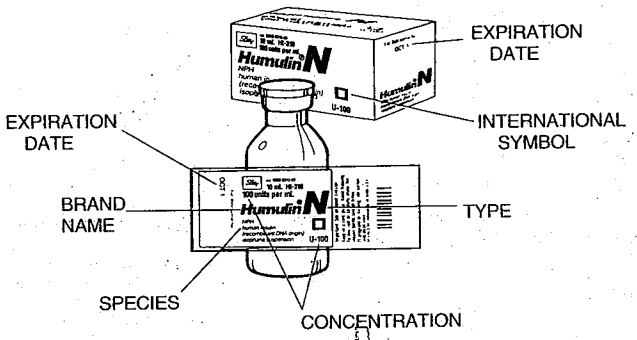
Description

Humulin is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for human insulin production. Humulin N is a crystalline suspension of human insulin with protamine and zinc providing an intermediate-acting insulin with a slower onset of action and a longer duration of activity (up to 24 hours) than that of regular insulin. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of Humulin N is dependent on dose, site of injection, blood supply, temperature, and physical activity. Humulin N is a sterile suspension and is for subcutaneous injection only. It should not be used intravenously or intramuscularly. The concentration of Humulin N is 100 units/mL (U-100).

Identification

Human insulin manufactured by Eli Lilly and Company has the trademark Humulin and is available in 6 formulations—Regular (**R**), Buffered Regular (**BR**), NPH (**N**), Lente (**L**), Ultralente® (**U**), and 70% Human Insulin Isophane Suspension [NPH]/30% Human Insulin Injection [buffered regular] (**70/30**). Your doctor has prescribed the type of insulin that he/she believes is best for you. **DO NOT USE ANY OTHER INSULIN EXCEPT ON HIS/HER ADVICE AND DIRECTION.**

Always check the carton and the bottle label for the name and letter designation of the insulin you receive from your pharmacy to make sure it is the same as that your doctor has prescribed. Humulin N can be identified as follows:



Always examine the appearance of your bottle of insulin before withdrawing each dose. A bottle of Humulin N must be carefully shaken or rotated before each injection so that the contents are uniformly mixed. Humulin N should look uniformly cloudy or

milky after mixing. Do not use it if the insulin substance (the white material) remains at the bottom of the bottle after mixing. Do not use a bottle of Humulin N if there are clumps in the insulin after mixing (Figure 1). Do not use a bottle of Humulin N if solid white particles stick to the bottom or wall of the bottle, giving it a frosted appearance (Figure 2). Always check the appearance of your bottle of insulin before using, and if you note anything unusual in the appearance of your insulin or notice your insulin requirements changing markedly, consult your doctor.

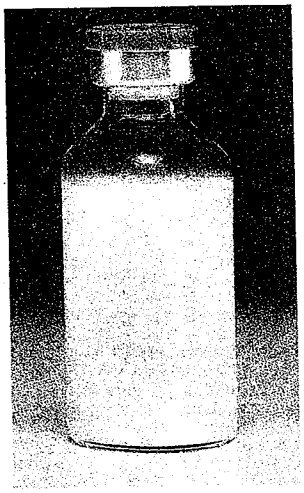


Fig 1.—Do not use if there are clumps in the insulin after mixing.

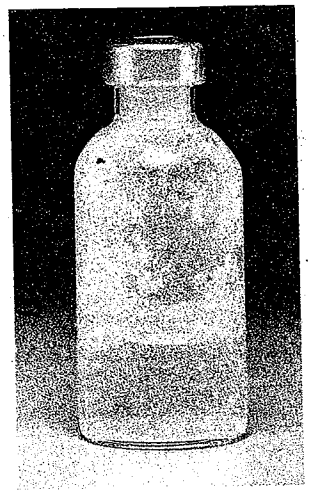


Fig 2.—Do not use if particles on the bottom or wall give the bottle a frosted appearance.

Storage

Insulin should be stored in a refrigerator but not in the freezer. If refrigeration is not possible, the bottle of insulin that you are currently using can be kept unrefrigerated as long as it is kept as cool as possible (below 86°F [30°C]) and away from heat and light. Do not use insulin if it has been frozen. Do not use a bottle of insulin after the expiration date stamped on the label.

INJECTION PROCEDURES

Correct Syringe

Doses of insulin are measured in **units**. U-100 insulin contains 100 units/mL (1 mL = 1 cc). With Humulin N, it is important to use a syringe that is marked for U-100 insulin preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems for you, such as a blood glucose level that is too low or too high.

Syringe Use

To help avoid contamination and possible infection, follow these instructions exactly.

Disposable syringes and needles should be used only once and then discarded. **NEEDLES AND SYRINGES MUST NOT BE SHARED.**

Reusable syringes and needles must be sterilized before each injection. **Follow the package directions supplied with your syringe.** Described below are 2 methods of sterilizing.

Boiling

1. Put syringe, plunger, and needle in strainer, place in saucepan, and cover with water. Boil for 5 minutes.
2. Remove articles from water. When they have cooled, insert plunger into barrel, and fasten needle to syringe with a slight twist.
3. Push plunger in and out several times until water is completely removed.

Isopropyl Alcohol

If the syringe, plunger, and needle cannot be boiled, as when you are traveling, they may be sterilized by immersion for at least 5 minutes in Isopropyl Alcohol, 91%. Do not use bathing, rubbing, or medicated alcohol for this sterilization. If the syringe is sterilized with alcohol, it must be absolutely dry before use.

Preparing the Dose

1. Wash your hands.
2. Carefully shake or rotate the insulin bottle several times to completely mix the insulin.
3. Inspect the insulin. Humulin N should look uniformly cloudy or milky. Do not use it if you notice anything unusual in the appearance.
4. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper. When using a new bottle, wipe the top of the bottle with an alcohol swab.
5. If you are mixing insulins, refer to the instructions for mixing that follow.
6. Draw air into the syringe equal to your insulin dose. Put the needle through rubber top of the insulin bottle and inject the air into the bottle.
7. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in 1 hand and shake gently.
8. Making sure the tip of the needle is in the insulin, withdraw the correct dose of insulin into the syringe.

9. Before removing the needle from the bottle, check your syringe for air bubbles which reduce the amount of insulin in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
10. Remove the needle from the bottle and lay the syringe down so that the needle does not touch anything.

Mixing Humulin N and Regular Human Insulin

1. NPH human insulin should be mixed only with regular human insulin.
2. Draw air into your syringe equal to the amount of Humulin N you are taking. Insert the needle into the Humulin N bottle and inject the air. Withdraw the needle.
3. Now inject air into your regular human insulin bottle in the same manner, but **do not** withdraw the needle.
4. Turn the bottle and syringe upside down.
5. Making sure the tip of the needle is in the insulin, withdraw the correct dose of regular insulin into the syringe.
6. Before removing the needle from the bottle, check your syringe for air bubbles which reduce the amount of insulin in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
7. Remove the needle from the bottle of regular insulin and insert it into the bottle of Humulin N. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in 1 hand and shake gently. Making sure the tip of the needle is in the insulin, withdraw your dose of Humulin N.
8. Remove the needle and lay the syringe down so that the needle does not touch anything.

Follow your doctor's instructions on whether to mix your insulins ahead of time or just before giving your injection. It is important to be consistent in your method.

Syringes from different manufacturers may vary in the amount of space between the bottom line and the needle. Because of this, do not change:

- the sequence of mixing, or
- the model and brand of syringe or needle that the doctor has prescribed.

Injection

Cleanse the skin with alcohol where the injection is to be made. Stabilize the skin by spreading it or pinching up a large area. Insert the needle as instructed by your doctor. Push the plunger in as far as it will go. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.** To avoid tissue damage, give the next injection at a site at least 1/2" from the previous site.

DOSAGE

Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you.

Your usual insulin dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your insulin dose are:

Illness

Illness, especially with nausea and vomiting, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood/urine frequently and call your doctor as instructed.

Pregnancy

Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or are nursing a baby, consult your doctor.

Medication

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin requirements may be reduced in the presence of drugs with hypoglycemic activity, such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants. Always discuss any medications you are taking with your doctor.

Exercise

Exercise may lower your body's need for insulin during and for some time after the activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise involves the area of injection site (for example, the leg should not be used for injection just prior to running). Discuss with your doctor how you should adjust your regimen to accomodate exercise.

Travel

Persons traveling across more than 2 time zones should consult their doctor concerning adjustments in their insulin schedule.

COMMON PROBLEMS OF DIABETES

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. Taking too much insulin
2. Missing or delaying meals
3. Exercising or working more than usual
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease
7. Interactions with other drugs that lower blood glucose, such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants

8. Consumption of alcoholic beverages

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressive mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

Therefore, it is important that assistance be obtained immediately.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, medications such as beta-blockers, change in insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes.

A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility.

You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia and Diabetic Acidosis

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin. Hyperglycemia can be brought about by:

1. Omitting your insulin or taking less than the doctor has prescribed
2. Eating significantly more than your meal plan suggests
3. Developing a fever or infection

In patients with insulin-dependent diabetes, prolonged hyperglycemia can result in diabetic acidosis. The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath. With acidosis, urine tests show large amounts of glucose and acetone. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or diabetic acidosis can result in loss of consciousness or death. Therefore, it is important that you obtain medical assistance immediately.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

Allergy to Insulin

Local Allergy—Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. If you have local reactions, contact your doctor.

Systemic Allergy—Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately.

ADDITIONAL INFORMATION

Additional information about diabetes may be obtained from your diabetes educator.

DIABETES FORECAST is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, National Service Center, 1660 Duke Street, Alexandria, Virginia 22314.

Another publication, **DIABETES COUNTDOWN**, is available from the Juvenile Diabetes Foundation, 432 Park Avenue South, New York, New York 10016-8013.

Literature revised April 12, 1991

ELI LILLY AND COMPANY • Indianapolis, IN 46285, USA

PA 6341 AMP

PRINTED IN USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 18-781/S027

CHEMISTRY REVIEW(S)

AUG 22 1990

CHEMIST'S REVIEW	1. ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER 18-781

3. NAME AND ADDRESS OF APPLICANT	4. SUPPLEMENT NUMBER, DATE
Lilly Research Lab. Indianapolis, IN 46285 0	S027/2-6-90

6. NAME OF THE DRUG	7. NONPROPERIETARY NAME	9. AMENDMENTS/ REPORTS, DATE
Humulin N	human insulin isophane suspension, rDNA origin	

8. REPORT PROVIDES FOR:
a revised packaged insert.

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF,
antihyperglycemia	OTC	

13. DOSAGE FORM	14. POTENCY
Injection	40, 100U/ml

15. CHEMICAL NAME AND STRUCTURE
two-chain polypeptide hormone

16. COMMENTS
Revisions include medical information, storage recommendation, procedures of mixing insulins and other editorial changes. The new wording in the section "Storage" is not acceptable. The package insert had been sent to HFD-520 for a consultation on the adequacy of the sterilization procedures for syringes. As expected. the microbilogist finds the procedures only disinfecting not sterilizing the syringes.

17. CONCLUSION AND RECOMMENDATIONS
The supplement is not approvable. Firm should be informed that the statements in the storage section (p.5) are not acceptable.

b(4)

as cool as possible.

b(4)

b(4)

b(4)

b(4)

b(4)

18. REVIEWER		
NAME	SIGNATURE	DATE COMPLETED
Yuan-yuan Chiu, Ph.D.		8-22-90

DISTRIBUTION: ORIGINAL JACKET REVIEWER DIVISION FILE

S18780.WPS

Conclusion and Recommendation: (continued)

Although the regulations for insulin require a sterilization of the syringes, it is not reasonable to ask patients to "sterilize" them; which can only be achieved by autoclaving, γ-ray or ethylene oxide exposure, not possible to perform in a home setting. Thus, disinfection procedures in the package insert should remain. The CDER is currently revising insulin regulations ...

b(5) b(5) b(5) b(5) b(5) b(5)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-781/S027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

See Chem Rev for comments
J. Chiu 8/22/90

AUG 14 1990

MICROBIOLOGY CONSULT
Division of Anti-Infective Drug Products

Submission No.: NDA 18-781/S-027
and various insulin NDA's

Submitted by: Div. Metabolism & Endocrine Drug Products
HFD 510
John Short 443-3510

Sponsor: Novo-Nordisk

NTFC 8/30/90
Agree w/ Dr. Chiu's Comments & Recommendations

Reasons for Submission: Labelling revision

Dosage Form: Injectable

Name: Trade: Humulin N
Generic: Insulin

Reviewed by: Pandu R. Soprey
Microbiologist, HFD-520

REVIEW:

The probable intent of a resuable syringe is to suggest an alternative for a certain socio-economic group of diabetic consumers. However the benefits gained from the use of reusable syringes should outweigh the consequences of possibly acquired infection if the user cannot properly sterilize/disinfect the device and subsequent cost of the treatment.
Due to an altered or defective immune system, diabetic individuals are susceptible to viral, bacterial, fungal and parasitic infections. In comparison to normal individuals, infections in diabetic patients tend to be severe and more protracted (4). Safety objectives for syringes and needles to be used by the diabetic should be considered as a first priority item and in such a case sterility should be theoretically required rather than desired.

The package insert to be included gives directions to the user to sterilize and then to assemble the sterile syringe and needle. Under this set of directions sterilization is to be achieved either by immersing for 5 minutes in boiling water or in 91 % isopropyl alcohol. Neither boiling water nor alcohol treatment, specified in the package insert is an adequate method of sterilization (1,2,3,8). In addition to killing vegetative cells, the sterilizing agent should posess sporicidal action (3,9). During these two treatments some of the actively growing and vegetative forms of microorganisms will be affected (6,7). Since no data are furnished along with this application, we are unable to establish antimicrobial effectiveness of these two processes.

Antimicrobial action occurs when a physical or chemical agent interacts and denatures macromolecules essential to structure and metabolism (2,3,5). Furthermore, effectiveness of a given antimicrobial treatment for a given task is not constant, but rather depends on the interaction of several physical, chemical and biological variables (5,6).

Application of moist heat is an effective method of thermal destruction of infective agents (2,5). However, the temperature at which water boils is not high enough to cause significant reduction of microorganisms in 5 minutes. Other factors such as mineral content and altitude influence the temperature at which water boils. There are no efficacy data provided by the sponsor that allows us to draw a correlation between the holding time of 5 minutes and the antimicrobial action achieved.

In most instances diluted alcohols are efficient antimicrobial agents (6,8). The most effective concentration of isopropyl alcohol is 70-75 % (8). However, no data were submitted along with this application to support the choice and effectiveness of 91 % alcohol in 5 minutes. Moreover users will have difficulty in obtaining or preparing 91 % alcohol because only 70 % isopropyl alcohol is available over-the-counter. Under these circumstances the users have to prepare 91% alcohol either by following concentration or dilution procedures. Also alcohol,if left behind, would precipitate insulin in the syringe and in the needle.

CONCLUSIONS:

Boiling water or alcohol treatment procedures described in labelling revision are ineffective for sterilizing syringes and needles.
Alcohol treatment could be considered as an antiseptic or disinfectant.
Boiling water could be considered as a disinfectant provided data are available to establish substantial decrease in bacterial numbers as a consequence of the treatment.

LITERATURE CITED:

1. Borick,P.M. 1970 Chemical Sterlizers. In P,M.Borick (ed.),Chemical Sterlization. Bowden, Hutchinson & Ross Inc. Stroudsburg, Pa.
2. Ernst,R.R. 1980 Sterilization by Heat. In S,S.Block (ed.), Disinfection, Sterilization and Preservation. Lea & Febiger, Philadelphia Pa
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Pandu R. Soprey
Date Review Completed
June 29,1990

CC: HFD-520/Micro/PRS #PD 630
HFD-520/Micro/AS ATS 7/30/90
HFD-510/John Short

8/11/90

Micro ltr. 4/5/90

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

REQUEST FOR CONSULTATION

(Division/Office)		FROM:		
HFD-520		HFD-570		
DATE: 4/4/90	IND NO.: —	NDA NO.: 18-781 plus Various Insulin NDAs	TYPE OF DOCUMENT: Labeling supplement	DATE OF DOCUMENT: NDA 18-781 2/6/90 (Humulin N)
NAME OF DRUG: All Insulins		PRIORITY CONSIDERATION: —	CLASSIFICATION OF DRUG: [redacted] Hypoglycemic agent	DESIRED COMPLETION DATE: 5/4/90
NAME OF FIRM: Lilly, 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	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY 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 ASSESSEMENT 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 *(Attach additional sheets if necessary)*

The attached labeling is a portion of the patient package insert used with Humulin N, indicating how to cleanse reusable syringes and needles. The same text is used for all insulins on the U.S. market. It has been brought to our attention by the Device people that "sterilization" cannot be accomplished by the methods described on page 6 (see attached memo dated 12/22/89 from Timothy A. Ulatowski from HFZ-420). b(5) b(5) We would like your input to help us to make this decision. Please answer the following questions:

1) Will the procedures described under "Boiling" and "Isopropyl Alcohol" sterilize reusable syringes and needles?

2) Assuming that the answer to question #1 is "No," would either of the procedures disinfect the reusable syringes and needles?

SIGNATURE OF REQUESTER		METHOD OF DELIVERY *(Check one)*
John M. Short 443-3570		☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER
N. Blair		

FORM FDA 3291 (7/83)

___/___ Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

___X___ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 18-781
5027

To Dr. Fleming + Dr. Chin

December 22, 1989

FROM: Chief, General Hospital and Personal Use Device Branch (HFZ-420)

THRU: Director, Div. of Product Surveillance (HFZ-340) LWH 12/26/89

TO: Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

John, please file this and set up a meeting to address this and any other labeling issues. Could probably wait until after Advisory meeting AJ 1/10/90

SUBJECT: Insulin Labeling Regulation 21 CFR 429.11(c)(3)

I called your office on December 18 to obtain clarification on the above referenced regulation. The regulation provides that insulin labeling shall indicate a method for sterilizing reusable syringes and needles between use.

As implemented in insulin labeling, e.g., Humulin, there are directions to the user to sterilize syringes and needles in (1) boiling water for 5 minutes, or (2) 91% isopropanol. We believe that neither of these two methods actually sterilize syringes or needles. EPA, CDC, and CDRH rely upon a common microbiological understanding of the term "sterilization" to mean the complete destruction of all contamination. It is commonly understood by the three groups that a sterilizing procedure must be sporicidal.

Demonstrating sterilization is an exercise in probabilities since absolute sterilization is not possible. In our evaluation of sterilizers and disinfectants in CDRH we apply a sterility assurance level of a probability of only 1 in 1 million survivors to a claim of sterilization.

The literature indicates that boiling water immersion cannot eliminate all bacterial spores thus rendering the method as ineffective as a sterilizing procedure. There are no data on the 91% isopropanol showing effectiveness as a sterilant. Isopropanol is not EPA registered as a sterilant.

Ok so. John 1/22/90

b(5) [redacted] b(5)

b(5) [redacted] The boiling water matter remains. I recognize that the term "sterilization" in this instance has been applied loosely, and in fact the method has its merits. Since the risk of infection of one reusing their own syringes is relatively low, boiling water or even 91% isopropanol may be sufficiently effective as a between use treatment. It is certainly economical.

May I recommend that the drug labeling regulation be modified to [redacted] indicate [redacted] sterilization, and [redacted] the drug labeling be so revised.

b(5) b(5) b(5) b(5) b(5)

[redacted] sterilization. Even 91% isopropanol may survive under this

revision, given some data.

Please provide your opinions and intentions in response so that we may further direct those wishing to market insulin syringe and needle treatment devices.

Thank you for your staff's expeditious response to my previous telephone calls.

Timothy A. Ulatowski

NDA 18-781/S-027

JUL 5 1991

Lilly Research Laboratories
Attention: M. W. Talbott, Ph.D.
Director, Medical Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Talbott:

Reference is made to your supplemental new drug application dated February 6, 1990, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humulin N [human insulin (rDNA origin) isophane suspension].

The supplement provides for revisions in the patient package insert.

We also acknowledge receipt of your communication dated May 22, 1991, enclosing final printed labelling as requested in our supplement approval letter dated April 3, 1991.

The final printed labelling is being retained for our files.

Sincerely yours,

7/5/91

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

LUB 7/5/91

cc: NDA Arch
HFD-510
HFD-80 w/labelling
HFC-130/JAllen
HFD-333 w/ labelling
HFD-500/LRipper w/labelling
HFD-638 w/ labelling
HFD-735 w/ labelling
HFD-510/SShen/AFleming/YYChiu/AJordan
HFD-511/LBraithwaite/06.20.91/FT/MMM/7/3/91/N18781AR.S27
Concurrence:JShort/6/25/SShen/AFleming/7/1/YYChiu/AJordan/7/2/91

ACKNOWLEDGE & RETAIN

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date 2-9-90

NDA No. 18-981

ELLY RESEARCH LABORATORIES
LILLY CORPORATE CENTER
INDIANAPOLIS, INDIANA 46285

Attention: M. W. TALBOTT, PH.D

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: HUMULIN N/ NPH (human INSULIN, rDNA ORGIN)

NDA Number: 18-981

Supplement Number: 027

Date of Supplement: February 8, 1990

Date of Receipt: February 7, 1990

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research HFD-510
Center for Drugs and Biologics, HFN-810
Attention: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857

Audrey Gamble

Supervisory Consumer Safety Officer
Division of Metabolism and Endocrine Drug Products
Center for Drugs and Biologics

cc:
NDA-File
HFN-810 File
CSO File

FORM FDA 3217c (7/84)

U.S. GOVERNMENT PRINTING OFFICE-1984-450-520/7433

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

AJ 6/18/9

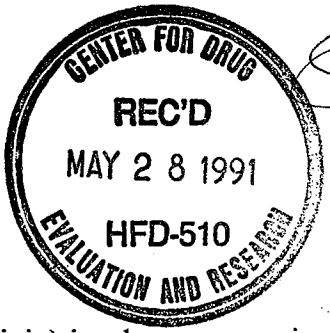
May 22, 1991

NDA SUPPL AMENDMENT
CR/FA
S-027

NTed
6/17/9

Acceptable

Noted
6/18/91



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18,781Humulin N [human insulin (rDNA origin) isophane suspension]
FPL for Approved NDA 18-781/S-027

Please refer to your letter of April 3, 1991 in which final approval was granted for our supplemental new drug application, dated February 6, 1990 (and amended March 8, 1991). Pursuant to your request we are submitting twelve (12) copies of the final printed labeling (FPL) which is identical to the approved draft labeling. The labeling is dated April 12, 1991 and is identified as PA 6341 AMP.

Please call me at (317) 276-2574 or Dr. Paul D. Gesellchen at (317) 276-4306 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

M. W. Talbott, Ph.D.
Director
Medical Regulatory Affairs

Enclosures - PA 6341 AMP

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER ☐ N.A.I.

LETTER ISSUED 7/5/91

UB 7/6/91
CSO INITIALS DATE

ORIGINAL

Lilly

REVIEWS COMPLETED

Lilly Research Laboratories
A Division of Eli Lilly and Company

CSO ACTION:
☑ LETTER ☐ N.A.I.
LIB 4/4/91
CSO INITIALS DATE

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

March 8, 1991

NDA SUPPL AMENDMENT

SLR/027/AL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 12 1991
HFD-510

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-781 (S-027) Humulin N [human insulin (rDNA origin) isophane suspension].

Please refer to the referenced supplemental new drug application dated February 6, 1990 which provides for an extensive revision of the "Information for the Patient" insert. Please also refer to your letter of October 11, 1990 which informed us that the referenced application was not approvable. Reference is also made to our letter dated October 26, 1990 in which we advised you of our intent to file an amendment to the referenced supplemental new drug application.

Pursuant to 21 CFR §314.70(b) we are now submitting the amendment to the referenced supplemental new drug application. For your convenience the draft copy of the current labeling contains any additions highlighted by bold text in blue and any deletions highlighted by bold strikethroughs in red. In addition, we have also enumerated all changes below.

The following changes have been made in response to your "not approvable" letter of 10/11/90:

1. In the WARNINGS section (page 2), the last sentence has been revised by replacing "1ST" with the word FIRST.

2. In the "Syringe Use" subsection of the INJECTION PROCEDURES section (page 6), the sentence "NEEDLES AND SYRINGES MUST NOT BE SHARED." ———— b(4)
———— b(4) . capitalized bold-faced print.

3. In the "Storage" subsection of the NPH HUMAN INSULIN section (page 5), the word "[redacted]

"... kept as cool as possible (below 86°F[30°C]) and away from heat and light."

4. In the "Storage" subsection of the NPH Human Insulin section (page 5), [redacted] has been deleted. You had requested that "... we

5. In the "Hypoglycemia (Insulin Reaction)" subsection of the COMMON PROBLEMS OF DIABETES section, the sentence on page 13 starting with the words "A few patients have experienced hypoglycemic reactions ..." has been changed to bold-faced print.

In addition to the above changes requested in your letter of October 11, 1990 we have made several additional changes to the original supplement some of which are are editorial in nature. Several changes were made to reduce any potential for confusion by the patient and one item (number 14 in the following list) arose as a direct result of the FDA Advisory Committee meeting on Hypoglycemia Unawareness held on March 27, 1990.

The additional changes are listed as follows with specific references to the page and section or subsection name where appropriate:

1. In the "Description" subsection of the NPH HUMAN INSULIN section (page 2-3), the second and third sentences in the first paragraph have been modified [redacted] The result is ..." and insertion of the words "... crystalline suspension of human insulin with protamine and zinc providing ...". The net result is creation of one clear sentence "Humulin N is a crystalline suspension of human insulin with protamine and zinc providing an intermediate-acting insulin with a slower onset of action and a longer duration of activity (up to 24 hours) than that of regular insulin.", out of two somewhat redundant sentences.

2. In the "Identification" subsection of the NPH HUMAN INSULIN section, the trade mark symbol next to the word Lente in the first sentence on page 3 has been removed since it has previously been identified as a trademark item in the WARNINGS section (page 1).

3. In the "Identification" subsection of the NPH HUMAN INSULIN section, the word [redacted] has been deleted from the fifth sentence of the third paragraph (page 4) since clumps may be present [redacted]

4. In the "Identification" subsection of the NPH HUMAN INSULIN section, the seventh sentence on page 4 which formerly stated that [redacted] has been reworded for clarity. The new sentence reads, "Always check the appearance of your bottle of insulin before using, and if you note anything unusual in the appearance of your insulin or notice your insulin requirements changing markedly, consult your doctor.".

5. In the [redacted] the last sentence of the section (page 5) which begins "Do not use ..." has been moved to the last sentence in the "Storage" subsection (page 5).

6. In the "Identification" subsection of the NPH HUMAN INSULIN section, (Fig. 1, page 5) the words [redacted] have been removed from the figure legend after the word "clumps" and the words "... there are ..." have been inserted immediately before the word "clumps". This brings the directions in accordance with the change specified in point 3 above.

7. In the "Correct Syringe" subsection of the INJECTION PROCEDURES section (page 6), a comma has been inserted after "With Humulin N" in the second sentence.

8. In the "Preparing the Dose" subsection of the INJECTION PROCEDURES section (page 7, step 4., sentence one and sentence two), the word ⟵ has been replace by the word "bottle". Correction of this inconsistency brings the terminology into uniformity throughout the document. b(4)

9. In the "Medication" subsection of the DOSAGE section (pages 10-11, the first two sentences), the abbreviation "eg," has been replaced with the more recognizable phrases "such as" and "for example,".

10. In the "Medication" subsection of the DOSAGE section (pages 10-11), a comma "," has been added after the words "... with hypoglycemic activity" in the second sentence and the word ⟋ has been deleted from in front of the words "sulfa antibiotics, ..." later in that same sentence. b(4)

11. In the "Exercise" subsection of the DOSAGE section (page 11), the abbreviation "eg," has been replaced with the more recognizable phrase "for example," in the second sentence.

12. In the "Hypoglycemia (Insulin Reaction)" subsection of the COMMON PROBLEMS OF DIABETES section (part 7. on page 12), the word ⟵ has been deleted from in front of the words "sulfa antibiotics, ..." and the words "and certain antidepressants" have been added at the end of the statement. This statement now matches the wording in the penultimate sentence in the paragraph under the "Medication" subsection of the DOSAGE section on page 11. b(4)

13. In the "Hypoglycemia (Insulin Reaction)" subsection of the COMMON PROBLEMS OF DIABETES section (pages 12-13), the parenthetical phrase "(3 or more insulin injections per day)" has been added to the sentence which begins "Early warning symptoms of hypoglycemia ..." as an example of the terminology "intensified control".

14. In the "Hypoglycemia (Insulin Reaction)" subsection of the COMMON PROBLEMS OF DIABETES section, the following sentence has been inserted between the first and second sentences of the third paragraph on page 13: "Patients should always carry a quick source of sugar, such as candy mints or glucose tablets." This

statement has been added as a result of the Division of Metabolism and Endocrine Drug Products' Advisory Committee Meeting on Hypoglycemia Unawareness held on March 27, 1990 at the FDA.

15. In the "Hypoglycemia (Insulin Reaction)" subsection of the COMMON PROBLEMS OF DIABETES section, the two commas in the fourth sentence of the third paragraph on page 13 have been deleted as unnecessary.

16. In the "Hypoglycemia (Insulin Reaction)" subsection of the COMMON PROBLEMS OF DIABETES section, the comma in the first sentence of the second paragraph on page 14 in the phrase "... of hypoglycemia, or experience ..." has been deleted as unnecessary.

17. In the "Hyperglycemia and Diabetic Acidosis" subsection of the COMMON PROBLEMS OF DIABETES section (page 14), the wording ' [redacted] has been changed to "... meal plan suggests". b(4)

Please call me at (317) 276-2574 or Dr. Paul D. Gesellchen at (317) 276-4306 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

M. W. Talbott, Ph.D.
Director
Medical Regulatory Affairs

Attachments - PA 6130-B AMP

My comments are written in red on attachment I.
Y. Chiu 2/9/90

Original
NDA NO. 18-781 REF. NO. 027
NDA SUPPL FOR SLR
Noted
Changes Acceptable.
2/20/90

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

February 6, 1990

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn.: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-781, Humulin® N NPH (human insulin, rDNA origin)

Pursuant to the provisions of 21 CFR §314.70(b), we are submitting revised package labeling for the referenced product for your review.

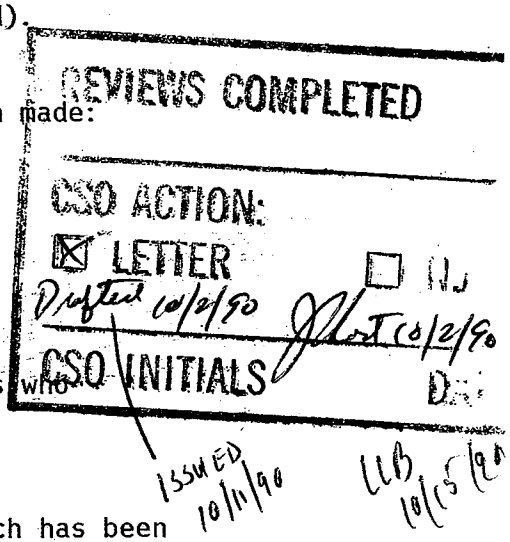
Extensive revisions have been made. In order to facilitate your comprehension of these changes, this submission consists of the following:

1. An unmarked copy of our proposed draft "Information For The Patient". (Attachment I)

2. A copy of our proposed draft "Information For the Patient", with new information which has been added marked in yellow. (Attachment II)

3. A copy of our current "Information For The Patient", with deletions marked in red, and copy which has been moved marked in blue (blue brackets reflect areas that have been reworded as well as moved). (Attachment III)

To clarify further, the following changes have been made:



Major changes -

1. Additional information on hypoglycemia
   - highlights warning symptoms
   - further defines hypoglycemia unawareness
   - lists precautionary measures for patients who have hypoglycemia unawareness
   - expands upon treatment for hypoglycemia

2. Instructs patients to discard any insulin which has been

b(4)

3. Provides more details on procedures for mixing insulins

4. Adds or enhances information on situations that may affect the patient's usual dosage, e.g., illness, pregnancy, medications, exercise, and travel

5. Adds lipodystrophy to the list of common problems of diabetes

Other changes -

1. Emphasizes blood glucose measurements as a measure of glycemic control b(4)

2. b(4) b(4)

3. b(4)

The deletions, additions, and changes in location should make the new document easier to read and understand by:

- removing redundancy
- improving flow of the information
- simplifying instructions

Subsequent to mutual agreement on the wording and format in this Humulin N draft labeling, we will apply the agreed upon wording and format to other Humulins and Iletins, with appropriate modification for species and formulation.

Please call me at (317) 276-2574 or Dr. Al Webber at (317) 276-4255 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

M. W. Talbott, Ph.D.
Director
Medical Regulatory Affairs

Enc. - PA 6130-A AMP

cc: Mr. John Short (4)