CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 29780/S037

Trade Name: HUMULIN R

Generic Name: HUMAN INSULIN (rDNA ORIGIN) INJECTION

Sponsor: LILLY RESEARCH LABORATORIES

Approval Date: 01/11/94

Indication(s): TREATMENT OF DIABETES

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 18780/S037

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Approvable Letter				X
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Medical Review(s)				X
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 18780/S037

APPROVAL LETTER

NDA 18-780/S-037

JAN 1 1 1994

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

APPEARS THIS WAY
ON ORIGINAL

date corrections made on original

Dear Dr. Talbott:

Reference is made to your supplemental new drug application dated March 22, 1991, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humulin R [human insulin (rDNA origin) injection].

The supplement provides for a new vial size, a 1.5 mL glass cartridge for use in an automatic pen injector.

We also refer to your communications dated November 7, 1991; August 8, 1992; January 11, August 5, November 29, and December 17, 1993; and January 6, 1994. The latter four submissions are in response to our not approvable letter dated February 24, 1993. An error in this letter was corrected in our letter of March 9, 1993.

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 (submitted December 15, 1993) to FDA as soon as available. 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 18-780/S-037." 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.

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,

/S/ 1-10-94

APPEARS THIS WAY
ON ORIGINAL

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
HFC-130/JAllen
HFD-80/ draft labeling attached
HFD-230
HFD-240
HFD-333
HFD-500/LRipper/draft labeling attached
HFD-638
HFD-730
HFD-510/YYChiu, EParish, AFleming
HFD-511/JShort 1/6/94/ft/lp/1/10/94/N18780AP.JRS
Concurrence: Parish, Fleming 1/7/Chiu 1/6/94

SUPPLEMENT APPROVAL /S/
1/10/94

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18780/S037

FINAL PRINTED LABELING

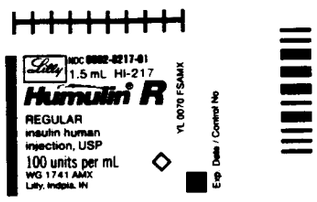
Labeling: SCP-08[illegible]

NDA No: 18758 Rc'd. [illegible]

Reviewed by: [illegible] 5/22/96

APPR[illegible]

APPR[illegible]



APPR[illegible]

APPR[illegible]

Labeling: SCP-03752 Circular
NDA No: 18782 Rc'd. 5/27/96
Reviewed by: /S/ 5/27/96

IMPORTANT-SEE WARNINGS IN ACCOMPANYING CIRCULAR

To open, lift here and pull

Exp. Date/Control No.

5 Cartridges (1.5 mL)

NDC 0002-8217-59
HI-217
100 units per mL

Humulin® R

REGULAR
insulin human
injection USP
(recombinant DNA origin)

U-100

Neutral

FOR USE ONLY IN B-D PEN

Eli Lilly and Company, Indianapolis, Indiana 46285, U.S.A.

1.5 mL **5 x 1.5 mL cartridges**

100 units per mL/U-100 Humulin® R *REGULAR insulin human injection USP (recombinant DNA origin)* U-100

SF 6593 AMS

SF 6593 AMS

N 3 0002-8217-59 7

APPEARS THIS WAY ON ORIGINAL

Labeling: SCP-037-FA Original
NDA No: 18780 Rc'd. 4-6-01
Reviewed by: /S/ 5/23/01

APPROVED
ORIGINAL

U-100

CARTON HAS BEEN OPENED

SH 8581 FSAMS

Keep in a cold place. Avoid freezing.

Warning: Any change of insulin should be made cautiously and only under medical supervision. See enclosed circular.

For subcutaneous or intramuscular use.

As with any drug, if you are pregnant or nursing a baby, seek professional advice when using this product.

Contains m-cresol 0.25% added during manufacture as a preservative.

REGULAR
insulin human
injection USP
(recombinant DNA origin)

Humulin® R

Lilly 100 units per mL/U-100

Labeling: SCP-037-FA Original
NDA No: 18-792 Rc'd. 6690
Reviewed by: /S/ 5/23/96

PA 0631 AMP PA 9051 FSAMP

INFORMATION FOR THE PATIENT
CARTRIDGE
HUMULIN® R
REGULAR
INSULIN HUMAN INJECTION, USP
(RECOMBINANT DNA ORIGIN)

FOR USE ONLY IN B-D PEN

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 REFINEMENT, 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.

INSULIN AND 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 exactly 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.

REGULAR HUMAN INSULIN

Description

Humulin is synthesized in a non-disease-producing special laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the human gene for insulin production. Humulin® R consists of zinc-insulin crystals dissolved in a clear fluid. Humulin R has had nothing added to change the speed or length of its action. It takes effect rapidly and has a relatively short duration of activity (4 to 12 hours) as compared with other insulins. 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 R is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Humulin R is a sterile solution and is for subcutaneous injection. It should not be used intramuscularly. The concentration of Humulin R in cartridges is 100 units/mL (U-100).

Identification

Cartridges of Humulin manufactured by Eli Lilly and Company are available in 3 formulations—Regular, NPH, and 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.**

Cartridges of Humulin R, 1.5 mL, are available in boxes of 5.

INSTRUCTIONS FOR USE

Preparing a Cartridge of Humulin R for Insertion in a Pen

1. Wash your hands.
2. Before inserting it in the pen, inspect the cartridge to make sure the contents look clear and colorless. Do not use a cartridge of Humulin R if it appears cloudy, thickened, or slightly colored or if solid particles are visible.
3. Follow the pen manufacturer's directions carefully for loading the cartridge into the pen.

Injecting the Dose

1. Wash your hands.
2. Use an alcohol swab to wipe the exposed rubber surface on the metal cap end of the cartridge.
3. Inspect the insulin. Humulin R should look clear and colorless. Do not use Humulin R if it appears cloudy, thickened, or slightly colored or if solid particles are visible.
4. Follow pen manufacturer's directions for attaching needle.
5. Hold the pen with needle pointing straight up. If there are large bubbles, tap the side of the pen until they float to the top. Remove the bubbles and the air in the needle by setting the pen to a 2-unit dose and depressing the plunger. Repeat this step if necessary until a drop of insulin appears at the end of the needle.
6. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the previous site.
7. Cleanse the skin with alcohol where the injection is to be made.
8. With 1 hand, stabilize the skin by spreading it or pinching up a large area.
9. Insert the needle as instructed by your doctor.
10. To inject the insulin, follow the pen manufacturer's instructions.
11. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.**
12. Immediately after an injection, remove the needle from the pen. This will ensure sterility and prevent leakage, reentry of air, and potential needle clogs. **Dispose of the needle in a responsible manner. Do not reuse needle. NEEDLES, CARTRIDGES, AND PENS MUST NOT BE SHARED.**
13. Once the cartridge is in use, do not continue to use it if the leading edge of the plunger is beyond the black band in the barrel of the pen. If a dose is initiated when the leading edge of the plunger is beyond the black band, an appropriate dose may not be delivered. Use the gauge on the side of the cartridge to help you judge how much insulin remains. The distance between each mark is about 10 units.

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 accommodate exercise.

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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 exactly 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.

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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.**

Cartridges of Humulin R, 1.5 mL, are available in boxes of 5. Humulin cartridges are designed for use only in the Becton Dickinson pen injection device (B-D Pen). The cartridge containing Humulin R is not designed to allow any other insulin to be mixed in the cartridge.

Always examine the appearance of a cartridge of insulin before administering a dose. Humulin R is a clear and colorless liquid with a water-like appearance and consistency. Do not use if it appears cloudy, thickened, or slightly colored or if solid particles are visible.

Always check the appearance of the cartridge before using, and if you note anything unusual in the appearance of your insulin or notice your insulin requirements changing markedly, consult your doctor.

Storage

Insulin cartridges should be stored in a refrigerator but not in the freezer. The pen and cartridge of insulin that you are currently using should not be refrigerated but should be 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. Unrefrigerated cartridges **must be discarded after 1 month**, even if they still contain insulin. Do not use a cartridge of insulin after the expiration date stamped on the label.

barrel of the pen. If a dose is initiated when the leading edge of the plunger is beyond the black band, an appropriate dose may not be delivered. Use the gauge on the side of the cartridge to help you judge how much insulin remains. The distance between each mark is about 10 units.

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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.

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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 [illegible] to insulin, which may cause rash over the whole

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.

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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 on 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 issued December 7, 1993

ELI LILLY AND COMPANY • Indianapolis, IN 46285, USA

PA 0631 AMP PA 9051 FSAMP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18780/S037

CHEMISTRY REVIEW(S)

ORIGINAL

JAN 6 1993

CHEMIST'S REVIEW	1. ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER 18-780
3. NAME AND ADDRESS OF APPLICANT Lilly Research Lab. Indianapolis, IN 46285		4. SUPPLEMENT NUMBER, DATE S037 ✓ 3-22-91
6. NAME OF THE DRUG human insulin injection (rDNA origin)	7. NONPROPERIETARY NAME Humulin R	9. AMENDMENTS/ DATE. 11-7-91 8-8-92
8. REPORT PROVIDES FOR: an additional presentation of Humaulin R in the form of a 1.5 mL glass cartridge.		
10. PHARMACOLOGICAL CATEGORY antihyperglycemia	11.HOW DISPENSED OTC	12. RELATED IND/NDA/DMF.
13. DOSAGE FORM Injection	14. POTENCY 100U/ml	

15. CHEMICAL NAME AND STRUCTURE
human insulin (two-chain polypeptide hormone)

16. COMMENTS
Firm submitted on May 29, 1987 a supplement (S025) for the 1.5 mL Humulin R cartridge to be used with NovoPen designed for Novo's human insulin products. This supplement was not approved (5-27-88) due to the inadequate compatibility between Lilly's cartridge and Novo's device as concluded by CDRH, and deficiencies in chemistry and manufacturing of the cartriges.

17. CONCLUSION AND RECOMMENDATIONS
This supplement is deficient and can not be approved. Additionally, cGMP clearance (EER) has not been received. Labeling should be reviewed by Medical Officer too.

18. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Yuan-yuan Chiu, Ph.D.	/S/	1-6-93

DISTRIBUTION: ORIGINAL JACKET REVIEWER DIVISION FILE

S18780.WPS

See ~~above~~ subsequent chem Review dated 1/26/93. (in front of 1/11/93 sub)
/S/
2/4/93

Comments: (Continued)
Lilly now submitted this new supplement for Humulin R cartridges to be used with its own delivery pen
Novo's NovoPen and NovoPen II devices. The 8-8-92 amendmet provided additional manufacturing information. The 11-7-91 amendment provided addresses of the manufacturing sites.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

JAN 26 1993

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15. CHEMICAL NAME AND STRUCTURE human insulin (two-chain polypeptide hormone)		
16. COMMENTS		
17. CONCLUSION AND RECOMMENDATIONS This supplement is still deficient and can not be approved. Firm should also be told (1) to resubmit the supplement after the removal of celphalosporin manufacturing operations from the cartridge maunfacturing facility as planned by Lilly and		

18. REVIEWER		
NAME	SIGNATURE	DATE COMPLETED
Yuan-yuan Chiu, Ph.D.	/S/	1-26-93

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S18780.WPS

DEC 21 1993

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16. COMMENTS

17. CONCLUSION AND RECOMMENDATIONS

This supplement is approvable. A minor revision of the is needed. First, the cover page must include the statement "For Use Only with Humulin R, Humulin N, and Humulin 70/30 Cartridges." Second, throughout the text, the term "insulin carteidges" should be changed to "Humulin cartridges." These requiremets can be included in the approval letter. The reviewing MO also needs to evaluate the P-D Pen insert.

18. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Yuan-yuan Chiu, Ph.D.	/S/	12-21-93

DISTRIBUTION: ORIGINAL JACKET REVIEWER DIVISION FILE

S18780.WPS

12-28-93
Concur!. See below
/S/

12-28-93 Telecon c̄ Dr. P Gesellchen of Lilly Cartridge insert which recommends using 2 unit dose to remove bubbles, and, — which recommends starting c̄ 4 unit dose (new cartridge) and 1 unit dose in a previously used cartridge. I told him that this would probably be confusing to patients and would recommend that both inserts be consistent in their explanation. He said he would discuss this with the Company and I would discuss c̄ Dr. Chiu.

Awaiting final revisions. /S/

OK /S/ 12/30/93

Would prefer that these two instructions be reconciled. Alternatively, an asterisked foot note in the Lilly patient information could point out the difference and suggest that the Lilly instruction be used. /S/ 1/3/94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18780/S037

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date October 29, 1993

From Mathematical Statistician (J. Chen) HFZ-162
Statistics Branch, Division of Biometric Sciences, OSB

Subject Statistical Comment on the Supplemental New Drug Applications (SNDA) Submitted as NDA 18-780 (S-037), 18-781 (S-031) and 19-717 (S-006) for Humulin R, Humulin N and Humulin 70/30 Amendments, Lilly Research Laboratories

To Eugene Berk, HFZ-402
Program Operations Staff, ODE

/S/

Through: Director, Division of Biometric Sciences, OSB
Through: Chief, Statistics Branch, DBS, OSB /S/

I have reviewed the sponsor's response to FDA's request for a statistical justification of their proposed cartridge (injector) sample size of 3000 vs 24. I found sponsor's sample size estimates of 4 pens per cartridge manufacturer (based on a standard deviation in dose of 0.04 to 0.14 units) can not be statistically justified since the statistical tests (binomial and t) that the sponsor implicitly used do not adequately account for the actual experimental situation. Further, no statistical models, parameters or hypotheses were specified.

Since the sample size may be inadequate to detect a clinically important difference, alternative descriptive statistical approaches, such as confidence interval, may be useful. If you have any questions concerning this memorandum, please contact me at 594-0624.

/S/

Judy Chen

cc: PMS Group (HFZ-402)
DCC (HFZ-401)
Medical Device File
Board File

MEMORANDUM OF CONSULTATION

DATE: November 29, 1993

BETWEEN: Yuan Yuan Chiu (HFD-510)

AND: Daniel N. Marticello (HFD-713)

APPEARS THIS WAY
ON ORIGINAL

SUBJECT: NDA 18-781, 5-C31 Humulin N submission dated November 29, 1993

As we discussed, I am in agreement with the confidence interval approach recommended by Judy Chen (HFZ-162) in a memorandum dated October 29, 1993.

The sponsor has complied with our request for between-treatment and within-treatment confidence intervals. Their current submission includes the information that was sent directly to me via fax on November 19 and 23, 1993 respectively.

In examining the sponsor's submission we are in agreement that the confidence intervals support the comparability of the Lilly and Novo cartridges and that the dosage weight did not change by a meaningful amount over the 5 years of simulated use for the Lilly and Novo cartridges.

/S/

APPEARS THIS WAY
ON ORIGINAL

Daniel N. Marticello
Mathematical Statistician

cc:
Orig. NDA#: 18-781
HFD-510
HFD-510/Dr. Sobel
✓HFD-510/Dr. Chiu
HFD-510/Ms. Galliers
HFD-510/Mr. Short
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Group 2 File
HFD-713/Mr. Marticello

APPEARS THIS WAY
ON ORIGINAL

This memorandum consists of 1 page of text

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18780/S037

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date April 2, 1991

NDA No. 18-780

Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, Indiana 46285

APPEARS THIS WAY
ON ORIGINAL

Attention: M.W.Talbott,Ph.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Humulin R

NDA Number: 18-780

Supplement Number: S-037

APPEARS THIS WAY
ON ORIGINAL

Date of Supplement: March 22, 1991

Date of Receipt: March 25, 1991

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation & Research HFD-510
~~National Center for Drugs and Biologics (HFN-150)~~
Attention: Document Control Room ~~7B-20~~ 14B-03
5600 Fishers Lane
Rockville, MD 20857

/S/

APPEARS THIS WAY
ON ORIGINAL

Peter Smith
Supervisory Consumer Safety Officer
~~Division of Oncology and Radiopharmaceutical~~
~~Drug Products~~
~~National Center for Drugs and Biologics~~

Division of Metabolism and
Endocrine Drug Products

FORM FDA 3217e (6/83)

☆ GPO : 1983 O - 408-424

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

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

March 22, 1991

NDA NO. 18-780 REF. NO. S-037
NDA SUPPL FOR SCP

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

APPEARS THIS WAY
ON ORIGINAL

Re: NDA 18-780 Humulin® R [human insulin injection, (rDNA origin)]

Pursuant to 21 CFR §314.70(b) we are submitting herewith, to the referenced NDA, a supplement to provide for a new vial size for Humulin R, 100 U/mL. The new vial is a 1.5 mL glass cartridge for use in an automatic pen injector such as that provided by Becton Dickinson.

The Humulin R formulation in the cartridges remains the same as that currently approved and marketed in our 10 mL vial of Humulin R. The filled cartridges will continue to meet the specifications of the referenced NDA and the USP.

The archival copy of this application consists of one volume including development and control information, draft product labels and draft package literature.

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,

APPEARS THIS WAY
ON ORIGINAL

ELI LILLY AND COMPANY

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

REVIEWS COMPLETED

CSO ACTION:

☒ LETTER ☐ N.A.I.

Issued 3/24/93 /S/ 3/24/93

CSO INITIALS DATE

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

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

[redacted]

NDA 18-780/S037

CP
S037 BC

November 7, 1991

CENTER FOR DRUG
REC'D
NOV 8 1991
HFD-510
EVALUATION AND RESEARCH

Dr. Y. Y. Chiu
Food and Drug Administration
Center for Drugs and Biologicals
HFD-510, Room 14B26
5600 Fishers Lane
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Chiu,

Attached is the information regarding our Humulin® cartridge supplements which you requested in your telephone conversation with Dr. David Miner on November 1. Please contact me at (317)-276-4248 or Dr. Miner at (317)-276-4509 if you have any further questions.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

ELI LILLY AND COMPANY

Richard A. Raths

Richard A. Raths, Ph.D.
Head, Pharmaceutical Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☒ LETTER ☐ N.A.I.

Issued 2/24/93 /S/ 2/26/93

CSO INITIALS DATE

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

1-22-93 Note /S/

January 11, 1993

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, MD 20857-1706

NDA SUPPL AMEND
SCP-037
BC

Re: NDA 18-780 (S-037) Humulin®R (human insulin injection, rDNA origin)
NDA 18-781 (S-031) Humulin®N (human insulin isophane injection, rDNA origin)
NDA 19-717 (S-006) Humulin®70/30 (70% human insulin isophane suspension and 30% human insulin injection, rDNA origin)

APPEARS THIS WAY
ON ORIGINAL

Reference is made to the supplemental New Drug Applications (SNDA) submitted on March 22, 1991, to the referenced NDAs. The SNDAs provided for a new container system (cartridges) for the referenced drug products.

APPEARS THIS WAY
ON ORIGINAL

We are hereby amending NDA 18-780

APPEARS THIS WAY
ON ORIGINAL

Please note that the data are being submitted only to NDA 18-780. We request that you incorporate the information from this report into the remaining NDA files by reference.

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

Sincerely,

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

enclosure

cc: Dr. Y. Y. Chiu

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I.
Issued 2/24/93 /S/ 2/26/93
CSO INITIALS DATE

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

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

March 4, 1993

SUPPL NEW CORRESP

SNC- 037

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, MD 20857-1706

Re: NDA 18-780, Humulin® R (human insulin injection, rDNA origin)

Reference is made to your letter of February 24, 1993 (received March 1, 1993). In this letter, the Lilly supplemental New Drug Application (March 22, 1992, S-037), which provided for a new vial size, a 1.5 mL glass cartridge for use in an automatic pen injector, was deemed to be "not approvable".

As per your February 24 letter and as per 21 CFR §314.120(a) we hereby give notice that we intend to amend the supplemental NDA.

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

Sincerely,

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I.

/S/ 3/11/93

CSO INITIALS DATE

BL
SCP-037

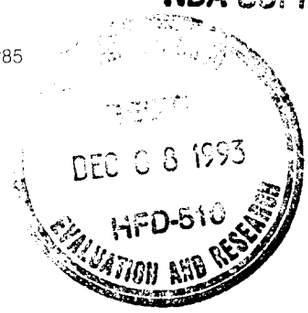
Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

NDA SUPPL AMEND

December 7, 1993

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



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, MD 20857-1706

Re: NDA 18-780 (S-037) Humulin® R (human insulin injection, rDNA origin), AMENDMENT

Reference is made to the supplemental New Drug Application (SNDA) submitted on March 22, 1991, to the referenced NDA which provided for a new container system (cartridges) for the referenced drug product. Reference is also made to your letter (dated February 24, 1993) in which we were notified that the SNDA was not approvable. Please also refer to our supplement amendment (August 5, 1993) in response to your not approvable letter.

We are hereby amending the SNDA to provide for minor editorial changes in the draft labeling.

Package Insert:

APPEARS THIS WAY
ON ORIGINAL

The words "PRINTED IN USA" have been removed as we have changed our printing location and now will print the labeling at our manufacturing site

Cartridge Labels:

APPEARS THIS WAY
ON ORIGINAL

The label has been modified by addition of the a new US item code (WG 1741 AMX) and a different barcode used for printing control purposes.

Cartridge Cartons:

APPEARS THIS WAY
ON ORIGINAL

The carton has been modified by additions of the a revised US item code (SF 6593 AMS), and a barcode and identifier bars to function as printing controls.

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

Sincerely,

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

enclosures

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

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

November 29, 1993

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

NDA SUPPL AMENDMENT

Re: NDA 18-780 - Humulin® R (human insulin injection, rDNA origin)

Reference is made to the Lilly supplemental New Drug Application (March 22, 1992, S-037), which provided for a new vial size, a 1.5 mL glass cartridge, for use in automatic pen injector. Reference is also made to your letter of February 24, 1993 (received March 1, 1993) in which the SNDA was deemed to be non-approvable. We also refer you to the subsequent supplement amendment submission (August 5, 1993) in which we provided responses to the questions posed in the non-approvable letter.

In phone conversations (November 19 and 23, 1993) between John Short and Dan Matricello (FDA) and Paul Geselchen (Lilly) additional information was requested by the FDA to supplement the tabular statistical information that was submitted in the original SNDA.

We are hereby officially amending the referenced SNDA with exact copies of the information that was originally Faxed to Mr. Marticello.

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

Sincerely,

ELI LILLY AND COMPANY

Michael E Hanson

(Mike Hanson signing in Max Talbott's absence)
M. W. Talbott, Ph.D.
Director
Worldwide Regulatory Affairs

Michael E. Hanson
Vice President
Lilly Research Laboratories

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I.
Faxed 1/19/94 /S/ 1/19/94
CSO INITIALS DATE

Enclosure

Lilly ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

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

August 5, 1993

SUP-037

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, MD 20857-1706

EXPEDITED REVIEW
REQUESTED

Re: NDA 18-780 (S-037) Humulin® R (human insulin injection, rDNA origin), AMENDMENT

Reference is made to the supplemental New Drug Applications (SNDA) submitted on March 22, 1991, to the referenced NDA. The SNDA provided for a new container system (cartridges) for the referenced drug product. Reference is also made to your letter (dated February 24, 1993) in which we were notified that the SNDA was not approvable. Please also refer to your letter of March 9, 1993, in which you corrected an error in the not-approvable letter.

This supplement amendment also provides for several editorial changes in the draft labeling and responds to the request (April 24, 1993) from Dr. Y.-Y. Chiu (FDA) for a dose accuracy test for cartridge release. The specifications for Cartridges Humulin R Regular Insulin Injection will be revised to include this test and are restated in their entirety in this submission for the convenience of the reviewer.

As noted above, the original SNDA submission seeking approval of Humulin R in cartridges was made on March 22, 1991.

This insulin injection device is intended to be used with the Lilly Humulin cartridges.

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

Sincerely,

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

enclosure

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

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

January 6, 1994

NDA SUPPL AMENDMENT
Scp-037 BL

Approval of this letter is circulating in place of signed original

/S/ 1/11/94

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, MD 20857-1706

Re: NDA 18-780, Humulin® R (human insulin injection, rDNA origin), S-037
NDA 18-781, Humulin® N (human insulin isophane injection, rDNA origin), S-031
NDA 19-717, Humulin® 70/30 (70% human insulin isophane suspension and 30% human insulin injection, rDNA origin), S-006

Reference is made to the Lilly supplemental New Drug Applications (March 22, 1991), which provided for a new vial size, a 1.5 mL glass cartridge for use in an automatic pen injector. Reference is also made to the phone conversation between Dr. Y.-Y. Chiu (FDA) and Dr. Paul Gesellchen (Lilly) on January 4, 1993.

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I.
Issued 1/11/94 /S/ 1/14/94
CSO INITIALS DATE

We are submitting a revision of the two pages (cover page and introduction page) in the draft which highlights the proposed changes.

Cover Page: will add the sentence "For use with 1.5 mL Humulin® cartridges". The actual location of this sentence will be determined

Introduction Page: The second sentence in the first paragraph has been revised to read:

> "It is used with 1.5 mL cartridges containing 150 units of Humulin® insulin instead of vials containing 1000 units of insulin that are used with syringes."

In addition, has agreed to revise the text on the carton from "For use with 1.5 mL cartridges" to state "For use with 1.5 mL Humulin® cartridges".

Reference is also made to a phone conversation (December 28, 1993) between Dr. Eileen Parrish (FDA) and Paul Gesellchen in which Dr. Parrish requested that either the the Lilly Patient Package Insert be modified to address a difference between the two sets of instructions which she believed could lead to patient confusion.

Dr. Parrish noted that the Lilly insert advised patients to dial up a 2 unit dose on the pen to express air bubbles (repeating the process if necessary) while the manual suggested that the patient should use 4 units with new cartridges and 1 unit with started cartridges for the purpose of expressing air. After discussions between has made the commitment to modify the manual to indicate that patients should use 2 units in all cases (repeating the step as necessary). We are submitting a revision of the two pages (pages 12 and 13) in the draft which highlight the proposed changes.

Page 12: The first sentence now reads:

> "If you are using a new cartridge, dial the dose knob so the arrow lines up with the 2 on the dose scale."

Page 13: The first, second and fourth sentences have been modified to read as follows:

> "If not, dial up 2 more units, press in the grey button, and check for a drop of insulin."
> "Continue to dial up 2 units and press the grey button, until you see a drop of insulin."
> "When you are using a started cartridge, you will usually only have to dial 2 units to check the flow."

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

Sincerely,

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

enclosure

cc: Dr. Y.-Y. Chiu, Dr. E. Parrish, Mr. John Short

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

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

June 1, 1994

ORIGINAL

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, MD 20857-1706

FPL for Approved NDA
18-780/S-037

APPEARS THIS WAY
ON ORIGINAL

Re: NDA 18-780, Humulin® R (human insulin injection, rDNA origin)

APPEARS THIS WAY
ON ORIGINAL

Reference is made to your letter of January 11, 1994. In this letter, the Lilly supplemental New Drug Application (March 22, 1992, S-037), which provided for a new vial size, a 1.5 mL glass cartridge for use in an automatic pen injector, was approved. In that letter you requested twelve (12) copies of the final printed labeling (FPL).

We are herewith submitting the requested FPL, seven of which have been mounted on heavy weight paper.

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:

/S/ 5/31/94

CSO INITIALS DATE