PRODUCT MONOGRAPH

HUMULIN®
(insulin, human biosynthetic)
Solution for Injection

THERAPEUTIC CLASSIFICATION
Anti-Diabetic Agent

3650 Danforth Avenue
Toronto, ONTARIO
M1N 2E8

Control No. 142345, 142347

Date of Approval:
February 1, 2011

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CLINICAL PHARMACOLOGY

Insulin, human biosynthetic is a polypeptide hormone consisting of a 21 amino acid A-chain and a 30 amino acid B-chain linked by two disulfide bonds[6]. HUMULIN (insulin, human biosynthetic) is found to be chemically, physically, biologically and immunologically equivalent to pancreatic human insulin which differs slightly from porcine or bovine insulin in amino acid composition[5,10,11].

Studies indicate that immunogenicity problems with biosynthetic human insulin (BHI) produced by recombinant DNA technology are less likely than with insulin that is derived from animal origin[4,18,19,40,47,51]. Biosynthetic human insulin is devoid of all protein contaminants of pancreatic origin normally present in trace amounts in all insulins of pancreatic origin[50]. The purification procedures used in the manufacture of biosynthetic human insulin result in a product which contains an insufficient quantity of E. coli polypeptides to be antigenic in deliberately sensitized animals[2,33]. No antibodies to E. coli polypeptides have been detected in specifically designed radioimmunoassay methods examining patient serum samples[57].

The administration of suitable doses of insulin to patients with diabetes mellitus, along with controlled diet and exercise, temporarily restores their ability to metabolize carbohydrates, fats and proteins; to store glycogen in the liver; and to convert glucose to fat. When given in suitable doses at regular intervals to a patient with diabetes mellitus, the blood sugar is maintained within a reasonable range, the urine remains relatively free of sugar and ketone bodies, and diabetic acidosis and coma are prevented.

Insulin preparations differ in onset, peak and duration of action. Individual variations of blood glucose response profiles are dependent upon factors such as the size of dose, site of injection and physical activity of the patient (for all human insulin formulations). The addition of protamine to insulin, in the presence of zinc, produces a stable complex with less intense and more prolonged action, due to its slow dissolution[26].

HUMULIN-R, insulin injection, human biosynthetic (rDNA Origin) REGULAR is a rapidly-acting insulin with a relatively short duration of activity (6 to 8 hours)[24,57].

HUMULIN-N, insulin isophane, human biosynthetic (rDNA Origin) NPH is an intermediate-acting insulin with a slower onset of action than Regular insulin and a

longer duration of activity of up to 24 hours[25].

HUMULIN MIXTURE, insulin injection, insulin isophane, human biosynthetic (rDNA Origin) 30/70 is an intermediate-acting insulin with a more rapid onset of action than NPH alone and a duration of activity of up to 24 hours.

HUMULIN-N may be mixed with HUMULIN-R to meet individual metabolic requirements of the patient as determined by the physician[45,46].

INDICATIONS AND CLINICAL USE

HUMULIN (insulin, human biosynthetic) is indicated for the treatment of insulin requiring diabetic patients.

HUMULIN-R only should be used for the treatment of emergencies such as diabetic coma and pre-coma and in diabetics undergoing surgery, but not HUMULIN-N, or HUMULIN MIXTURES.

In switching patients from animal source insulins to HUMULIN, it is possible that the patients will require a change in dosage; the adjustment may be made with the first dose or over a period of several weeks. Any change of insulin should be made cautiously and only under medical supervision.

Changes in refinement, purity, strength, brand, type and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage.

CONTRAINDICATIONS

Hypoglycemia (for details see SYMPTOMS AND TREATMENT OF OVERDOSAGE)

HUMULIN (insulin, human biosynthetic) is contraindicated in patients with hypersensitivity to human insulin or any of its excipients contained in the formulation (unless used as part of a desensitization program).

HUMULIN-N, HUMULIN MIXTURES, should not be given intravenously or used for treatment of diabetic coma.

WARNINGS

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Under no circumstances should any HUMULIN MIXTURE be given intravenously.

Do not use the HUMULIN-N or HUMULIN MIXTURES if you see lumps that float or that stick to the sides of the vial, or if the contents of the vial are clear and remain clear after the bottle is shaken or rotated. NOTE: The contents of the vial of HUMULIN-R should be clear. Do not use if cloudy.

PRECAUTIONS

GENERAL:
Visual disturbances in uncontrolled diabetes due to refractive changes are reversed during the early phase of effective management. However, since alteration in osmotic equilibrium between the lens and ocular fluids may not stabilize for a few weeks after initiating therapy, it is wise to postpone prescribing new corrective lenses for 3 to 6 weeks.

Insulin requirements may be increased during illness or emotional disturbances or if the patient is receiving concurrent administration of drugs with hyperglycemic activity, e.g. oral contraceptives, corticosteroids, or thyroid replacement therapy.

Insulin requirements may be decreased in the presence of renal or hepatic impairment or in the presence of agents such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-adrenergic blockers, alcohol, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers.

The number and size of daily doses and the time of administration, as well as diet and exercise, are problems that require direct and continuous medical supervision. Usually, the most satisfactory injection time is before breakfast.

Prompt recognition and appropriate management of the allergic complications of insulin therapy are important for the safe and effective control of diabetes mellitus.

Transferring from Other Insulins -- A small number of patients transferring from insulins of animal source to insulins of recombinant DNA origin may require a reduced dosage, especially if they are tightly controlled and bordering on hypoglycemia. The dosage reduction may occur with the first dose or over a period of several weeks. There is a risk of hypoglycemia if the insulin requirement is decreased, and both the physician and the patient should be aware of this possibility. The risk can be considered to be minimal if the daily dose is less than 40 units.

USE IN OBSTETRICS:
It is essential to maintain good control of the insulin-diabetic patient throughout pregnancy. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters.

NURSING MOTHERS:
Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

DRUG INTERACTIONS:
Hormones that tend to counteract the hypoglycemic effects of insulin include growth hormone, corticotropin, glucocorticoids, thyroid hormone, and glucagon. Epinephrine not only inhibits the secretion of insulin, but also stimulates glycogen breakdown to glucose. Thus, the presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

The hypoglycemic action of insulin may also be antagonized by diphenylhydantoin. Insulin's hypoglycemic action can be increased in some patients by concomitant administration of anabolic steroids, MAO inhibitors, guanethidine, alcohol, propranolol (masking effect), or other drugs affecting beta adrenergic receptors, or by daily doses of 1.5 to 6 g of salicylates.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics. Concomitant administration of oral contraceptives can cause a decrease in glucose tolerance in diabetic women possibly resulting in increased daily insulin requirements.

Insulin plus Thiazolidinediones (TZDs): TZDs, alone or in combination with other antidiabetic agents (including insulin), can cause heart failure and edema. The combination of insulin with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD product monograph Warnings and Precautions information when the use of these drugs in combination with any insulin, including HUMULIN R, HUMULIN N or HUMULIN 30/70 is contemplated.

The physician should be consulted when using other medications in addition to human insulin.

ADVERSE REACTIONS

Since HUMULIN (insulin, human biosynthetic) has been available worldwide, reports of local and systemic allergic reactions in patients receiving it have been received.[1,7,30,52,59] As with all insulins, local inflammatory responses may result from improper cleansing of the skin, contamination of the injection site with alcohol, use of an antiseptic containing impurities or accidental intracutaneous rather than subcutaneous injection. Local reactions that result in skin sensitivity phenomena usually subside spontaneously.

Insulin lipohypertrophy has been reported with HUMULIN. This complication has been ascribed to the local pharmacologic effects of the subcutaneous injection of insulin. A few cases of lipoatrophy and serum sickness have also been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Cause

Hypoglycemia (low blood glucose, also called "insulin reaction") can occur if the patient takes too much insulin, misses meals, exercises or works too hard just before a meal, or has an infection or becomes ill (especially with diarrhea or vomiting) or if the body's need for insulin change for other reasons.

Symptoms and Treatment

Hypoglycemia may occur in any patient receiving insulin and is most commonly manifested by hunger, nervousness, warmth and sweating, and palpitations. Patients also may experience headache, confusion, drowsiness, fatigue, anxiety, blurred vision, diplopia, or numbness of the lips, nose, or fingers. The clinical manifestations of hypoglycemia can be masked by the concomitant administration of propranolol or other beta adrenergic blockers.

Symptoms are likely to appear anytime when the blood sugar concentration falls below 2.2 mmol/L (40 mg/100 mL) but may occur with a sudden drop in blood glucose even when the value remains above 2.2 mmol/L (40 mg/100 mL).

If a patient is unable to take soluble carbohydrate or fruit juice orally, hypoglycemia is treated with 10 to 20 g of dextrose intravenously or glucagon may be given subcutaneously or intramuscularly.

DOSAGE AND ADMINISTRATION

The dosage should be determined by the physician, according to the requirements of the patient.[41]

New Patients

Patients receiving insulin for the first time can be started on HUMULIN (insulin, human biosynthetic) in the same manner as they would be on animal-source insulin.

Patients should be monitored closely during the adjustment period.[47]

Transfer Patients

When transferring patients from animal-source insulin to HUMULIN, use the same dose and dosage schedule.

Some patients transferring to HUMULIN will require a change in dosage from that used with animal-source insulin.[47] If an adjustment is needed, it may be made with the first dose or over a period of several weeks.

Changes in total daily dosage, the number of injections per day, and/or timing of injections may be necessary to achieve maximum glycemic control.

When a patient on high doses of animal insulin is switched to HUMULIN, it may be appropriate to reduce the starting dosage and monitor the patient carefully.

Patients who have systemic allergy to pork or beef insulin may also react to human insulin.[48,49] In such patients, appropriate procedures (intradermal testing and, if necessary, desensitization) should be undertaken before therapeutic doses of human insulin are administered.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that the early warning symptoms, i.e., nervousness, sweating, and palpitations, were less pronounced than they were with animal-source insulin.[49]

Formulations of HUMULIN appear to produce a slightly faster onset and slightly shorter duration of action than the corresponding forms of animal-source insulins.[9,26,56,57]

HUMULIN-R is a clear, colorless solution. It may be administered by subcutaneous, intra-muscular or intravenous injection.

HUMULIN-N and HUMULIN MIXTURES are suspensions. They should be administered by subcutaneous injection only.

Subcutaneous administration, preferably by the patient, should be in the upper arms, thighs, buttocks or abdomen. Injection sites should be rotated so that the same site is not used more than approximately once a month.

Care should be taken to ensure that a blood vessel has not been entered. The injection site should not be massaged.

<u>Mixing Instructions:</u>

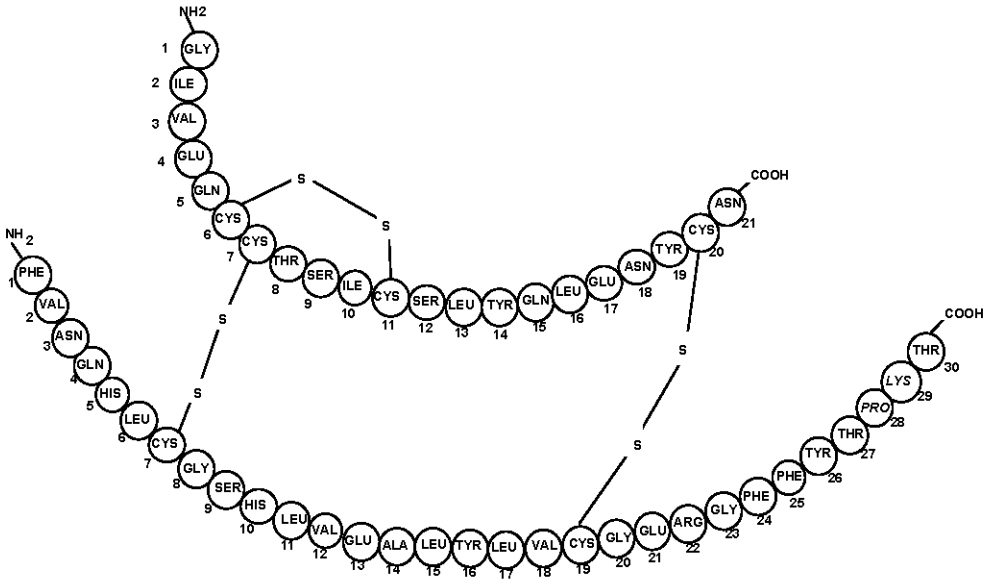
The rapid action of HUMULIN-R is preserved when mixed with HUMULIN-N; independent of the time lag between mixing and administration, and independent of the proportion of regular insulin incorporated in the mixture.

The effects of mixing HUMULIN with animal-source insulins have not been studied. This practice is not recommended.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:
HUMULIN (insulin, human biosynthetic) is a polypeptide hormone consisting of a 21 amino acid A-chain and a 30 amino acid B-chain linked by two disulfide bonds. It is synthesized in a non-disease-producing special laboratory strain of E. coli that has been genetically altered by the addition of the human gene for insulin production.

Structural Formula:



Molecular formula: $C_{257}H_{383}N_{65}O_{77}S_{6}$

Molecular weight: 5807.72.

STABILITY AND STORAGE:
Prior to first use insulin should be stored in a cold place (2-8°C), preferably in a refrigerator, but not in a freezer. Do not let it freeze or leave it in direct sunlight. Expiration dates are stated on the labels.

When in current use, vials and cartridges and prefilled pens should be stored at room temperature and discarded after 28 days.

AVAILABILITY OF DOSAGE FORMS

HUMULIN (insulin, human biosynthetic) is available in the following presentations:

HUMULIN R, insulin injection, human biosynthetic (rDNA Origin) REGULAR:
Vial HI-210, 10 mL, 100 units/mL.
Vial HI-213, 3 mL, 100 units/mL.
Cartridge HI-219, 3.0 mL, 100 units/mL, 5 cartridges/box.

HUMULIN N, insulin isophane, human biosynthetic (rDNA Origin) NPH:
Vial HI-310, 10 mL, 100 units/mL.
Vial HI-313, 3 mL, 100 units/mL.
Cartridge HI-319, 3.0 mL, 100 units /mL, 5 cartridges/box.

HUMULIN N Pen, insulin isophane, human biosynthetic (rDNA Origin) NPH:
Cartridge and Pen HP-8730, 3.0 mL prefilled pen, 100 units/mL, 5 pens/box.

HUMULIN N KwikPen™, insulin isophane, human biosynthetic (rDNA Origin) NPH:
Cartridge and Pen HP-8805, 3.0 mL prefilled pen, 100 units/mL, 5 pens/box.

HUMULIN 30/70, 30% insulin injection, 70% insulin isophane, human biosynthetic (rDNA Origin):
Vial HI-710, 10 mL, 100 units/mL.
Cartridge HI-719, 3.0 mL, 100 units /mL, 5 cartridges/box.

HUMULIN cartridges are designed for use with Lilly injector systems.

Not all pack sizes and presentations may be marketed.

INFORMATION FOR THE PATIENT

HUMULIN® (insulin, human biosynthetic) VIALS, CARTRIDGES AND PRE-FILLED PENS

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, ETC.), SPECIES (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® WILL REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH ANIMAL-SOURCE INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY BE MADE WITH THE FIRST DOSE OR OVER A PERIOD OF SEVERAL WEEKS.

THE USE OF THIAZOLIDINEDIONES (SUCH AS ROSIGLITAZONE AND PIOGLITAZONE), ALONE OR IN COMBINATION WITH OTHER ANTIDIABETIC AGENTS (INCLUDING INSULIN), HAS BEEN ASSOCIATED WITH HEART FAILURE AND SWELLING OF THE LOWER EXTREMITIES. PLEASE CONTACT YOUR PHYSICIAN IMMEDIATELY IF YOU DEVELOP SYMPTOMS OF SHORTNESS OF BREATH, FATIGUE, EXERCISE INTOLERANCE, OR SWELLING OF THE LOWER EXTREMITIES WHILE YOU ARE ON THESE AGENTS.

INSULIN AND DIABETES

Your doctor has explained that you have diabetes. You have learned that the treatment of your diabetes requires injections of insulin.

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 sugar at a nearly normal level and to keep your urine as free of sugar as possible. Each case of diabetes is different. Your doctor has told you which insulin to use, how much, and when and how often to inject it. This schedule has been individualized for you. 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 by your doctor.

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

If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your blood and/or urine and notify your doctor at once.

Always keep an extra supply of insulin. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

USE THE PROPER TYPE OF INSULIN

This insulin, manufactured by Eli Lilly and Company, has the trademark Humulin®, insulin, human biosynthetic (rDNA Origin) - Lilly, and is available in several formulations.

These products can be identified by the large letter(s) or numbers that appear on the carton and vial, cartridge or prefilled pen label following the name Humulin: i.e. Humulin R (Regular), Humulin N (NPH), and Humulin 30/70 (30% Regular/70% NPH).

These types of insulin differ mainly in the time they require to take effect and in the length of time their action lasts. Your doctor has prescribed the type of insulin that he/she believes is best for you. DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION.

When you receive your insulin from the pharmacy, always check to see that:

1. The name Humulin appears on the carton and vial, cartridge or prefilled pen label and is followed by the proper letter designation and name for the insulin formulation: R-Regular; N-NPH; and 30/70-30% Regular/70% NPH.

2. The carton and the vial, cartridge or prefilled pen label is correct for your type of insulin.
3. The human insulin is of rDNA origin.
4. The insulin strength is U-100.
5. The expiration date on the package will allow you to use the insulin before that date.

INSULIN, HUMAN BIOSYNTHETIC

Humulin has been produced by recombinant DNA processes. Humulin mixtures are fixed mixtures of Humulin R (insulin injection, human biosynthetic) and Humulin N (insulin isophane, human biosynthetic). They are intermediate-acting insulins with a more rapid onset of action than NPH insulin alone. The duration of activity may last up to 24 hours following injection.

Humulin is for subcutaneous use only.

WARNINGS: (SEE ADDITIONAL WARNINGS ABOVE)

Humulin mixtures should be used only if your doctor has prescribed insulins mixed in a specific ratio of REGULAR and NPH. You should not attempt to change the ratio of these products by adding additional NPH or REGULAR insulin to this bottle. If Humulin N and Humulin R mixtures are prescribed in a different proportion, the individual insulins should be mixed as instructed in the amounts recommended by your doctor or purchased as mixtures in the ratio recommended if available.

USAGE IN PREGNANCY

Control of the blood sugar is vital to assure the birth of a healthy child. Normalization of the blood sugar should have occurred before conception and should continue throughout the pregnancy. Since pregnancy may make diabetes worse and because of the importance of good diabetic control, patients who contemplate pregnancy or who are pregnant should seek expert medical advice.

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

INSULIN REACTION AND SHOCK

Cause:

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about by:

1. Taking too much insulin
2. Missing or delaying meals
3. Exercising or working too hard just before a meal
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin

Dietary Implications:
If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Symptoms and Treatment:
The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or "shakiness", rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention.

A few patients who experienced hypoglycemic reactions after being transferred to Humulin have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a diabetic becomes delirious or mentally confused, or suffers from loss of memory or delusions, corn syrup diluted or orange juice with sugar should be administered by mouth. In severe reactions, it may be desirable for your doctor to administer intravenously from 15 to 20 grams of dextrose (d-glucose) in sterile solution. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

DIABETIC ACIDOSIS AND COMA

Diabetic acidosis may develop if your body has too little insulin. (This is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

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, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

ALLERGY TO INSULIN

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. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

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. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

IMPORTANT NOTES

1. Never change from the insulin that has been prescribed for you to another insulin without instructions from your doctor. Changing the type, strength, source, or manufacturer of insulin can cause problems with your diabetes.

2. Your doctor will tell you what to do if you miss a dose of insulin or miss a meal because of illness.

Always keep on hand an extra supply of insulin, as well as a spare needle. If you miss a meal, as a substitute use sugar, sugar-sweetened candy, fruit juice, or sugar-sweetened beverage according to your doctor's instructions. If a shortage of insulin appears inevitable, a temporary reduction in the size of dose may be made, accompanied by limitation of food to two-thirds its usual quantity and a liberal increase in fluids of little or no food value, such as water, tea, coffee, broths, or clear soups.

3. If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your urine and/or blood and notify your doctor at once.

4. Consult your doctor if you notice anything unusual or have doubts about your condition or your use of insulin.

5. Consult your doctor concerning adjustments in your insulin schedule if you travel across more than 2 time zones.

6. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

7. Understand how to manage your diabetes so that your life can be active and healthy.

INSTRUCTIONS FOR USE FOR VIALS

Humulin should be used only if it has been prescribed by your doctor. Humulin is for subcutaneous use only. Do not inject into a vein.

Vial (Bottle) Inspection:
DO NOT USE AFTER EXPIRY DATE.
DO NOT USE a bottle of Humulin if after resuspending there are clumps floating in the insulin or if solid white particles stick to the bottom or wall of the bottle giving it a frosted appearance. (Resuspend the insulin by following instruction 2 under Preparing the Dose). A bottle that appears frosted or contains clumps should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your doctor.

Storage:
Your unused Humulin bottles should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The bottle of insulin currently in use does not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. Bottles in use or not refrigerated should be discarded after 28 days even if they contain insulin.

INJECTION PROCEDURES FOR VIALS

Correct Syringe
Doses of insulin are measured in units. U-100 insulin contains 100 units/mL. 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**.

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. Except for Humulin R, all other Humulin products 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. Wipe the top of the bottle with an alcohol swab.

5. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the insulin bottle and inject the air into the bottle.

6. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in 1 hand.

7. Making sure the tip of the needle is in the insulin, withdraw the correct dose of insulin into the syringe.

8. 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 needle up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.

9. Remove the needle from the bottle and lay the syringe down so that the needle **does not touch anything**.

Injecting The Dose:

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 1.5 cm (0.5 inches) from the previous site.

INSTRUCTIONS FOR USE FOR CARTRIDGES

Humulin cartridges are designed for use with Lilly injector systems.

Humulin cartridges and prefilled pens are not designed to allow any other insulin to be mixed in the cartridge. Humulin cartridges and prefilled pens MUST NOT be refilled and are not designed for use with a traditional syringe. However, it is recommended that you carry a syringe or prefilled pen for a single use. This cartridge or prefilled pen should not be reused.

For guidance on the use of the Pen (prefilled, disposable human insulin injector), please refer to the separate Instructions for Use enclosed within the packaging.

Humulin should be used only if it has been prescribed by your doctor. Humulin cartridges and prefilled pens are for subcutaneous use only. Do not inject into a vein.

Cartridge Inspection:
DO NOT USE AFTER EXPIRY DATE.
DO NOT USE a cartridge of Humulin if after resuspending there are clumps floating in the insulin or if solid white particles stick to the bottom or wall of the cartridge giving it a frosted appearance. (Resuspend the insulin by following instruction 2 under Preparing the Dose). A cartridge that appears frosted or contains clumps should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your doctor.

Storage:
Your unused Humulin cartridges or prefilled pens should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The cartridge of insulin currently in use should be left in the pen and may be carried with you. The pen and cartridge do not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. Cartridges or prefilled pens in use or not refrigerated should be discarded after 28 days even if they contain insulin.

Preparing The Dose:

1. Wash your hands.

2. Always examine the cartridge of Humulin after removing from the box. Resuspend the insulin by rolling the cartridge or pre-filled pen between the palms 10 times and inverting it 180° 10 times. Inspect the cartridge for uniform resuspension; if the Humulin does not look uniformly cloudy or milky (except for Humulin R which is a clear solution), repeat the resuspension procedure as often as necessary. DO NOT USE if the white insulin particles stick to the bottom or sides of the cartridge or if there are clumps floating in the insulin.

3. Carefully load the cartridge into the reusable pen following the manufacturers directions.

4. Wipe the exposed rubber membrane on the metal cap end of the cartridge or prefilled pen with an alcohol swab and attach the needle.

5. Carefully resuspend the Humulin by rolling the cartridge and pen in your hands 10 times and inverting it 180° 10 times. This must be performed each time before you give yourself an injection even after just loading the pen.

6. Prime the pen as directed by the manufacturer. If air bubbles are present, hold the pen with the needle pointing up and tap the side of the pen until the bubbles float to the top. With the pen still vertical, purge the needle with a 2 unit dose setting of the pen. Repeat until an insulin drop appears at the end of the needle. There may be small bubbles left; the air is harmless but too large an air bubble will affect the accuracy of the insulin dose administered.

7. Set the dose as instructed by your doctor. A gauge has been provided on the side of the cartridge to help you judge the amount of insulin remaining. The distance between each mark represents approximately 10 units for 1.5 mL cartridges and 20 units for 3.0 mL cartridges or prefilled pens.

Injecting The Dose:

1. Cleanse the skin with alcohol where the injection is to be made. To avoid tissue damage, always change the site for each injection by at least 1.5 cm (0.5 inches) from the previous site, rotating sites on the body.

2. With one hand stabilize the skin by pinching up a large area.

3. Insert the needle as instructed by your doctor or nurse.

4. To inject the insulin, follow the instructions of the pen's manufacturer.

5. Pull the needle out and apply gentle pressure over the injection site for several seconds. DO NOT RUB THE AREA.

6. Immediately after injection, remove the needle from the pen. This will ensure sterility and prevent leakage, re-entry of air and potential needle clogs.

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PHARMACOLOGY

Pre-Clinical Pharmacology

Biosynthetic human insulin, or BHI, has been studied extensively by several investigators.[8,22,24,31,32,35,36,44] In nearly all the studies, BHI was compared with native pancreatic human insulin as well as with purified pork insulin. The resulting data clearly indicate that BHI is chemically, physically, biologically and immunologically equivalent to the appropriate pancreatic insulin standards.[10] BHI is prepared by the proinsulin route, starting with an E. coli fermentation using recombinant DNA-containing plasmids. The amino acid sequences of the insulin chains were found to be correct and the disulfide bonds were shown to be in the proper configuration. Additional chemical and physical studies verified that the normal structure of the human insulin molecule was integrally formed by the proinsulin process.[11,13,33]

Further confirmation that BHI is structurally identical to pancreatic human insulin was provided by radioimmunochemical assays for insulin. BHI and pancreatic human insulin reacted identically in the insulin radioimmunoassay, a method that is sensitive to minor structural variations within the insulin molecule.[10,37,38,58]

The biological activity of BHI was evaluated by a wide variety of in vitro techniques, all of which demonstrated that BHI and pancreatic human insulin are equivalent within experimental error.[15,17,21,29,53,60] In addition, BHI was found to have a hypoglycemic potency equivalent to purified pancreatic insulins as determined by the USP rabbit assay.[10,39,51]

BHI did not elicit an antigenic response when administered to E. coli polypeptide-sensitized rats and guinea pigs.[33] In a clinical experiment, it was demonstrated that the anti-E.coli polypeptide antibody levels in 20 new diabetic patients were the same regardless of whether the treatment was with BHI or purified pork insulin.[3,12,23]

No antibodies specific to E.coli polypeptide have been detected in patient serum samples from over 1,350 patients.

Clinical Pharmacology

Clinical pharmacologic studies with insulin, human biosynthetic (rDNA) (BHI) demonstrate that generally the pharmacokinetics and pharmacodynamics of BHI and purified pork insulin (PPI) are the same.[24,32,39,44] However, serum concentrations after BHI is administered subcutaneously may be higher or occur sooner than after PPI.[9,24,26,27] These differences are generally ascribed to the greater solubility of BHI, which apparently is related to the presence of threonine instead of alanine on the B_{-30} position of the molecule.[28]

A 30/70 Regular: NPH mixture produced the same effect as equivalent doses of the two formulations administered separately. Mixtures of NPH and Regular BHI have demonstrated a slight excess of protamine in NPH BHI which binds to added Regular

insulin, and that this binding delays slightly the occurrence of the peak serum concentration.[26] Effects of BHI on substrates and other non-insulin and glucose parameters have been studied.[43,46] Most investigators have reported that the suppression of endogenous insulin as indicated by serum C-peptide values was equivalent for BHI and PPI.[57]

Growth hormone (GH) increase was also equivalent or slightly less with BHI. Prolactin response was less after BHI than with PPI, while the cortisol response to insulin hypoglycemia may be greater with BHI than with PPI. There was no difference in non-esterified fatty acid lowering or blood glycerol, lactate, or 3-hydroxybutyrate levels between BHI and PPI.[16,42,51]

While the effects of BHI on suppression of human C-peptide usually are the same as those for PPI, BHI may affect other variables differently than PPI.[55] Further studies will be needed to determine the significance of differences between BHI and PPI on prolactin, GH, and glucagon concentrations.

Clinical Experience

New Patient Studies:

129 insulin naive patients were treated for one year.[28] Dramatic, albeit expected, improvement of metabolic control followed institution of BHI. Insulin antibody binding was measured and compared with results obtained from a well-matched group of historical controls on animal insulins. BHI was less immunogenic than modified beef pork (MBP) or PPI.[19] (The possible reasons that BHI is ever immunogenic in humans are (1) the fact that BHI is given subcutaneously and (2) the presence of insulin aggregates.)[34]

Transfer Patient Studies:

In a double-blind, double-crossover study, patients were switched from beef-insulin to PPI or BHI and then back again; patients on BHI had modestly higher fasting blood sugars. Moreover, the A.M. dose of BHI could be administered closer to breakfast than was possible with animal-sourced insulins.[14]

In another double-blind study,[25,28] patients were switched either to BHI or maintained on their PPI or MBP insulin. Patients switched from MBP or PPI to BHI had slightly higher fasting and/or postprandial blood sugars than control groups which were maintained on their prestudy animal insulin programs. Patients switched from MBP to BHI demonstrated clear reductions in their serum insulin antibody binding. Patients switched from PPI to BHI demonstrated significantly less insulin binding at six months after transfer; at 24 months, bound insulin was essentially the same for both groups.[67]

The immune responses of a subset of 142 of 427 transfer patients have been statistically analyzed by Fineberg, et al.[20] These patients had been randomly allocated to treatment

with BHI, PPI or MBP. Taking type of diabetes into account, this study confirmed that BHI was the least immunogenic.

Use of BHI in Patients with the Complications of Insulin Therapy:

In isolated instances where patients were experiencing insulin allergy or resistance to insulin therapy, BHI has been used with limited success.[54,61-66]

There are isolated case reports in which patients with the complications of insulin therapy, principally lipoatrophy, insulin allergy and insulin resistance, have been treated with BHI.

Overall, the clinical studies indicate that BHI is an effective, safe insulin both in patients receiving insulin for the first time and in patients being switched from animal insulin. However, BHI appears to be shorter acting than animal insulin. The data from these studies are not sufficient to determine whether BHI is superior to PPI in the prevention or treatment of complications of insulin therapy. However, HUMULIN (insulin, human biosynthetic) was shown to be less immunogenic than mixed beef-pork insulin or purified pork insulin.

TOXICOLOGY

As with pork insulin, biosynthetic human insulin will be mainly used by subcutaneous injection in humans and, therefore, the majority of studies in animals have been performed using this route of administration. However, acute toxicity studies in monkeys and a subchronic study in dogs were performed using intravenous administration. The experiments for acute toxicity are presented in Table 1 and for sub-acute toxicity in Table 2 and are summarized as follows:

1. The selection of dose levels of human insulin for the single and multiple dose studies in animals was restricted by the potent hypoglycemic activity of this compound. The pharmacological effects of insulin are well-known from many years of human therapy and therefore the toxicological studies were designed to evaluate adverse effects of possible impurities such as E. coli polypeptides.

2. The minimal lethal subcutaneous dose of biosynthetic human insulin in rats and mice was greater than 10 units/kg. This dose was a large multiple of the initial human clinical trial dose and also much greater than the average daily therapeutic dose of insulin (0.6 units/kg/day).

3. Dogs given a single subcutaneous dose of 2 units/kg or an intravenous dose of 0.1 unit/kg of human insulin evidenced hypoglycemia and related pharmacological effects but no significant toxicity.

4. No compound-related toxic effects were observed when rats were given daily

subcutaneous injections of 2.4 units/kg of biosynthetic human insulin for one month. Similarly, beagle dogs given daily subcutaneous injections of 2 units/kg or intravenous injections of 0.1 unit/kg of human insulin for one month evidenced marked hypoglycemia, but no adverse effects were seen on hematologic or serum chemistry parameters and there were no pathologic changes. There was no evidence of tissue damage or irritation at the site of injection in the rats or dogs.

5. Biosynthetic human insulin gave negative results in the Modified Ames, Rat Hepatocyte, and Chinese Hamster mutagenicity tests.

It can be concluded that injections of pharmacologically effective doses of biosynthetic human insulin in animals did not produce toxic effects. There were no findings that would preclude the use of this compound in humans.

Acute Toxicity - Table 1:

Species	Number Per Dose	Route of Administration	Single Dose	Number of Days' Duration	Observations
Rats	10 females 10 males	SC	10 iu/kg	14	No mortality. Minimum lethal dose > 10 iu/kg.
Mice	10 females 10 males	SC	10 iu/kg	14	No mortality. Alopecia in females on BHI. Minimum lethal dose > 10 iu/kg.
Mice	10 females 10 males	SC	10 iu/kg	14	No mortality. Minimum lethal dose > 10 iu/kg
Rats	10 females 10 males	SC	10 iu/kg	14	Significant tolerance of doses without signs of toxicity.
Dogs	2 females 2 males	SC	2 iu/kg	14	Significant tolerance of doses without signs of toxicity.
Monkeys	2 females 2 males	IV	1 iu/kg	14	Significant tolerance without signs of toxicity. Blood glucose values decreased sharply in all 15-20 minutes post administration.

Subacute Toxity - Table 2

Species	Number Per Dose	Route of Administration	Single Daily Dose	Number of Doses	Observations

Rats	15 females 15 males	SC	2.4 iu/kg /day	30	No toxicologically important changes occurred.
Dogs	3 females 3 males	SC	2.0 iu/kg /day	30	One male on BHI experienced convulsions. Some ataxia and hypoactivity.
Dogs	4 females 4 males	IV	0.1 iu/kg /day	30	Decreased thrombocyte numbers. Minor changes in alanine transaminase activities.

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