DRUG FACTS

ctive ingredient(s)	Purpose
scherichia coli	

Use(s)

Humulin R U-100 is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus

Humulin R U-100 may be administered intravenously under proper medical supervision in a clinical setting for glycemic control (see DOSAGE AND ADMINISTRATION and Storage).

Warnings

Any change in insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog, etc.), species, or method of administration may result in the need for a change in dosage.

Do not use

Ask a doctor before use if you have

Ask a doctor or pharmacist before use if you are

When using this product

Stop use and ask a doctor if

If pregnant or breast-feeding

Pregnancy Category B. All pregnancies have a background risk of birth defects, miscarriage, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and is decreased with good glucose control. It is important for patients to maintain good control of diabetes before conception and during pregnancy. Special attention should be paid to diet, exercise and sulin regimens. Insulin requirements may decrease during the first trimester, usually increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring is essential in these patients. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant.

Studies show that endogenous insulin only crosses the placenta in minimal amounts. While there are no adequate and well-controlled studies in pregnant women, an extensive body of published literature demonstrates the maternal and fetal benefits of insulin treatment in patients with diabetes during pregnancy. Humulin R is a recombinant human insulin that is identical to the endogenous hormone; therefore, reproduction and fertility studies were not performed in animals.

Keep out of reach of children

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Directions

Humulin R U-100, when used subcutaneously, is usually given three or more times daily before meals. The dosage and timing of Humulin R U-100 should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. Humulin R U-100 may also be used in combination with oral antihyperglycemic agents or longer-acting insulin products to suit the needs of the individual patients with diabetes. The injection of Humulin R U-100 should be followed by a meal within approximately 30 minutes of administration.

The average range of total daily insulin requirement for maintenance therapy in insulin-treated patients without severe insulin resistance lies between 0.5 and 1 unit/kg/day. However, in pre-pubertal children it usually varies from 0.7 to 1 unit/kg/day, but can be much lower during the period of partial remission. In situations of insulin resistance, e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher. Initial dosages for patients with diabetes are often lower, e.g., 0.2 to 0.4 units/kg/day.

Humulin R U-100 may be administered by subcutaneous injection in the abdominal wall, the thigh, the gluteal region or in the upper arm. Subcutaneous injection into the abdominal wall ensures a faster absorption

than from other injection sites. Injection into a lifted skin fold minimizes the risk of intramuscular injection. Injection sites should be rotated within the same region. As with all insulin, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

Intravenous administration of Humulin R U-100 is possible under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia.

For intravenous use, Humulin R U-100 should be used at concentrations from 0.1 unit/mL to 1 unit/mL in infusion systems with the infusion fluids 0.9% sodium chloride using polyvinyl chloride infusion bags. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use Humulin R U-100 if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. Humulin R U-100 should not be used after the printed expiration date.

Other information

 $HUMULIN^{\circledR} \ R$ REGULAR INSULIN HUMAN INJECTION, USP (rDNA ORIGIN)

100 UNITS PER ML (U-100)

A 48-month multicenter, open-label, single-arm study was conducted in insulin-naive patients with type 1 or type 2 diabetes (N=129) to assess the safety and efficacy of Humulin R U-100. Humulin R U-100 and

Humulin (R) N (alone or in combination) were administered by subcutaneous injection. Eighty-four percent of patients were Caucasian. Fifty-seven percent of the patients were male. The mean age was 45 years (range: 4 to 83 years). The average weight was 72 kg.

Total mean (± SD) glycohemoglobin improved from baseline to endpoint (baseline: 14.3 ± 3.1%, endpoint: 10.1 ± 2.8%). Hemoglobin A_{1C} was not measured in this study. At baseline, patients weighed 72 ± 23 kg; at endpoint mean weight was 80 ± 22 kg. At endpoint, mean (\pm SD) total daily insulin doses for Humulin R U-100 were 0.18 ± 0.17 units/kg. At 48 months, 16 patients (21%) reported hypoglycemia. During the study, 4 patients experienced diabetic ketoacidosis.

The intravenous administration of Humulin R U-100 was tested in 21 patients with type 1 diabetes. The patients' usual doses of insulin were temporarily held, and blood glucose concentrations were maintained at a range of 200 - 260 mg/dL for one to three hours during a run-in phase of intravenous Humulin R U-100 followed by a 6-hour assessment phase. During the assessment phase patients received intravenous Humulin R at an initial dose of 0.5 U/h, adjusted to maintain blood glucose concentrations near normoglycemia (100 to 160 mg/dL).

The mean blood glucose levels during the assessment phase for patients on Humulin R U-100 therapy are summarized below in Table 1. All patients achieved near normoglycemia during the 6-hour assessment phase. At the endpoint, blood glucose was within the target range (100 to 160 mg/dL) for 20 of 21 patients treated with Humulin R U-100. The average time (± SE) required to attain near normoglycemia was 161 ± 14 minutes for

centrations (mg/dL) during Intravenous Infusions of Humulin P. U. 100

Table 1: Mean Blood Glucose Concentrations (mg/dL) during intravenous infusions of Humulin R U-100		
Time from Start of Infusion (min)	Mean Blood Glucose (mg/dL) Intravenous ^a	
0	220 ± 11	
30	204 ± 17	
60	193 ± 18	
120	172 ± 28	
180	153 ± 30	
240	139 ± 24	
300	131 ± 22	
360	128 ± 18	

a Results shown as mean \pm Standard Deviation.

Hypoglycemia is the most common adverse reaction of all insulin therapies, including Humulin R U-100. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with Humulin R U-100.

As with all insulin preparations, the time course of Humulin R U-100 action may vary in different individuals or at different times in the same individual and is dependent on dose, site of injection, blood supply, temperature, and physical activity

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

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia (see PRECAUTIONS, Drug Interactions).

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The atient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery Hyperglycemia, diabetic ketoacidosis, or hyperosmolar coma may develop if the patient takes less Humulin R U-100 than needed to control blood glucose levels. This could be due to increases in insulin demand during illness or infection, neglect of diet, omission or improper administration of prescribed insulin doses or use of drugs that affect glucose metabolism or insulin sensitivity. Early signs of diabetic ketoacidosis include glycosuria and ketonuria. Polydipsia, polyuria, loss of appetite, fatigue, dry skin, abdominal pain, nausea and vomiting and compensatory tachypnea come on gradually, usually over a period of some hours or days, in conjunction with hyperglycemia and ketonemia. Severe sustained hyperglycemia may result in hyperosmolar coma or death.

Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia, that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Since intravenously administered insulin has a rapid onset of action, increased attention to hypokalemia is necessary. Therefore, potassium levels must be monitored closely when Humulin R U-100 or any other insulin is administered intravenously. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Humulin R U-100 (see ADVERSE REACTIONS).

Localized reactions and generalized myalgias have been reported with the use of metacresol as an injectable excipient.

Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment

Some medications may alter insulin requirements and the risk for hypoglycemia and hyperglycemia (see ADVERSE REACTIONS, Drug Interactions).

Hypoglycemia is one of the most frequent adverse events experienced by insulin users. Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

Symptoms of finite to moderate hypogrycenna may occur suddenly and can include:	
sweating	• drowsiness
• dizziness	sleep disturbances
• palpitation	• anxiety
• tremor	blurred vision
• hunger	slurred speech
• restlessness	depressed mood
tingling in the hands, feet, lips, or tongue	• irritability
lightheadedness	abnormal behavior
inability to concentrate	unsteady movement
headache	personality changes
Signs of severe hypoglycemia can include:	
disorientation	• seizures
unconsciousness	• coma
• death	

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

Without recognition of early warning symptoms, the patient may not be able to take steps to avoid more serious hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose more frequently, especially prior to activities such as driving. Mild to moderate hypoglycemia may be treated by eating foods or taking drinks that contain sugar. Patients should always carry a quick source of sugar, such as hard candy, non-diet carbohydrate-containing drinks or glucose tablets. See Precautions

Administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue).

Local Allergy - Patients occasionally experience crythema, local edema, and pruritus at the site of injection. This condition usually is self-limiting. 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.

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 (anaphylaxis) may be life threatening.

Weight gain can occur with some insulin therapies and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy

- Humulin R U-100 should only be mixed as directed by the physician.
- Humulin R U-100 is short-acting and is often used in combination with intermediate- or long-acting insulins.
- The order of mixing and brand or model of syringe should be specified by the physician. A U-100 insulin syringe should always be used. Failure to use the correct syringe can lead to dosage errors
- In general, when an intermediate-acting insulin (e.g., NPH insulin isophane suspension) is mixed with short-acting soluble insulin (e.g., regular), the short-acting insulin should be drawn into the syringe first. Not in-use (unopened): Humulin R U-100 vials not in-use should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the freezer.

In-use (opened): The Humulin R U-100 vial currently in-use can be kept unrefrigerated as long as it is kept as cool as possible [below 30°C (86°F)] away from heat and light. In-use vials must be used within 31 days or be discarded, even if they still contain Humulin R U-100.

Admixture: Infusion bags prepared with Humulin R U-100 as indicated under DOSAGE AND ADMINISTRATION are stable when stored in a refrigerator (2° to 8°C [36° to 46°F]) for 48 hours and then may be used at room temperature for up to an additional 48 hours.

Do not use Humulin R U-100 after the expiration date stamped on the label or if it has been frozen.

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Inactive ingredients

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