HIGHLIGHTS OF PREScribing INFORMATION

These highlights do not include all the information needed to use HUMULIN® R safely and effectively. See full prescribing information for HUMULIN® R.

HUMULIN® R (insulin human injection), for subcutaneous or intravenous use

Initial U.S. Approval: 1982

INDICATIONS AND USAGE

HUMULIN® R is a short-acting human insulin indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus. (1)

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for important administration instructions. (2.1)
- Subcutaneous injection: inject subcutaneously 30 minutes before a meal. Rotate injection sites to reduce the risk of lipodystrophy. (2.2)
- Intravenous infusion: administer intravenously ONLY under medical supervision at concentrations from 0.1 unit/mL to 1 unit/mL in infusion systems containing 0.9% sodium chloride. (2.2)
- Individualize dose based on route of administration, metabolic needs, blood glucose monitoring results and glycemic control goal. (2.3)
- HUMULIN® R given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin. (2.3)
- Do not mix with insulin preparations other than HUMULIN® N. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection: HUMULIN® R 100 units per mL (U-100) is available as:
- 10 mL vials (3)
- 3 mL vials (3)

CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia. (4)
- Do not use in patients with hypersensitivity to HUMULIN® R or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

- Never share needles or syringes with another person. (5.1)
- Hyper- or Hypoglycemia with Changes in Insulin Regimen: Carry out under close medical supervision and increase frequency of blood glucose monitoring. (5.2)
- Hypoglycemia: May be life-threatening. Increase frequency of blood glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment or with hypoglycemia unawareness. (5.3)
- Hypoglycemia Due to Medication Errors: Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)
- Hypersensitivity and Allergic Reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue HUMULIN® R, monitor, and treat if indicated. (5.5)
- Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated. (5.6)
- Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.7)

ADVERSE REACTIONS

Adverse reactions observed with HUMULIN® R include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, weight gain, edema, pruritus, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that may increase the risk of hypoglycemia: anti-diabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics (7)
- Drugs that may decrease the blood glucose lowering effect: atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones (7)
- Drugs that may increase or decrease the blood glucose lowering effect: Alcohol, beta-blockers, clonidine, lithium salts, and pentamidine (7)
- Drugs that may blunt the signs and symptoms of hypoglycemia: beta-blockers, clonidine, guanethidine, and reserpine (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 05/2018
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
HUMULIN R is indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
• Always check the insulin label before administration to confirm the correct insulin product is being used [see Warnings and Precautions (5.4)].
• Inspect HUMULIN R visually before use. It should appear clear and colorless. Do not use HUMULIN R if particulate matter or coloration is seen.

2.2 Route of Administration
Subcutaneous Injection
• Inject HUMULIN R subcutaneously approximately 30 minutes before meals into the thigh, upper arm, abdomen, or buttocks.
• Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy [see Adverse Reactions (6)].

Intravenous Administration
• Administer HUMULIN R intravenously ONLY under medical supervision with close monitoring of blood glucose and potassium levels to reduce the risk of hypoglycemia and hypokalemia [see Warnings and Precautions (5.3, 5.6), How Supplied/Storage and Handling (16.3)].
• For intravenous use, HUMULIN R should be used at concentrations from 0.1 unit/mL to 1 unit/mL in infusion systems containing 0.9% sodium chloride.

2.3 Dosing Instructions
• Individualize and adjust the dosage of HUMULIN R based on the route of administration, the patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal.
• HUMULIN R given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.
• Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (e.g., macronutrient content or timing of food intake), changes in renal or hepatic function, or during acute illness [see Warnings and Precautions (5.2, 5.3), Use in Specific Populations (8.6, 8.7)].
• Dosage adjustment may be needed when switching from another insulin to HUMULIN R [see Warnings and Precautions (5.2)].

2.4 Dosage Adjustment due to Drug Interactions
• Dosage adjustment may be needed when HUMULIN R is co-administered with certain drugs [see Drug Interactions (7)].

2.5 Instructions for Mixing with Other Insulins for Subcutaneous Injection
• Do not mix HUMULIN R with insulin preparations other than HUMULIN N.
• To mix HUMULIN R and HUMULIN N, draw HUMULIN R into the syringe first. Inject immediately after mixing.

3 DOSAGE FORMS AND STRENGTHS
HUMULIN R injection is 100 units per mL (U-100), a clear and colorless solution available as:
• 10 mL vials
• 3 mL vials

4 CONTRAINDICATIONS
HUMULIN R is contraindicated:
• during episodes of hypoglycemia
• in patients with hypersensitivity to HUMULIN R or any of its excipients.
5 WARNINGS AND PRECAUTIONS

5.1 Never Share Needles or Syringes between Patients

Patients using HUMULIN R vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia [see Warnings and Precautions (5.3)] or hyperglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant anti-diabetic medications may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of all insulins, including HUMULIN R. Severe hypoglycemia can cause seizures, may lead to unconsciousness, may be life threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see Drug Interactions (7)], or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of HUMULIN R may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [see Clinical Pharmacology (12.2)].

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see Drug Interactions (7)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see Use in Specific Populations (8.6, 8.7)].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between HUMULIN R and other insulins have been reported. To avoid medication errors between HUMULIN R and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with HUMULIN R [see Adverse Reactions (6)]. If hypersensitivity reactions occur, discontinue HUMULIN R; treat per standard of care and monitor until symptoms and signs resolve. HUMULIN R is contraindicated in patients who have had a hypersensitivity reaction to HUMULIN R or its excipients [see Contraindications (4)].

5.6 Hypokalemia

All insulin products, including HUMULIN R, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including HUMULIN R, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.
ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling:

- Hypoglycemia [see Warnings and Precautions (5.3)]
- Medication Errors [see Warnings and Precautions (5.4)]
- Hypersensitivity [see Warnings and Precautions (5.5)]
- Hypokalemia [see Warnings and Precautions (5.6)]

Adverse Reactions from Clinical Studies or Postmarketing Reports

The following additional adverse reactions have been identified during clinical studies or from postmarketing reports with use of HUMULIN R. Because some of these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Adverse reactions associated with insulin initiation and glucose control intensification

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. Over the long-term, improved glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Hypersensitivity Reactions

Severe allergic reactions may include anaphylaxis, generalized skin reactions, rash, angioedema, bronchospasm, hypotension, and shock.

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in HUMULIN R.

Hypokalemia

HUMULIN R can cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia.

Injection Site Reactions

Injection site reactions may include injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass.

Lipodystrophy

Administration of insulin subcutaneously, including HUMULIN R, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients [see Dosage and Administration (2.2)].

Medication Errors

Medication errors in which other insulins have been accidentally substituted for HUMULIN R have been identified during postapproval use.

Peripheral Edema

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

Weight Gain

Weight gain can occur with insulin therapy, including HUMULIN R, and has been attributed to the anabolic effects of insulin.

Immunogenicity

As with all therapeutic peptides, insulin administration may cause anti-insulin antibodies to form. The incidence of antibody formation with HUMULIN R is unknown.

DRUG INTERACTIONS

Table 1: Clinically Significant Drug Interactions with HUMULIN R

<table>
<thead>
<tr>
<th>Drugs that May Increase the Risk of Hypoglycemia</th>
<th>Drugs:</th>
<th>Intervention:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, pramlintide, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics</td>
<td>Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs that May Decrease the Blood Glucose Lowering Effect of HUMULIN R</th>
<th>Drugs:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Intervention:** Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R is co-administered with these drugs.

### Drugs that May Increase or Decrease the Blood Glucose Lowering Effect of HUMULIN R

**Drugs:** Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

**Intervention:** Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R is co-administered with these drugs.

### Drugs that May Blunt Signs and Symptoms of Hypoglycemia

**Drugs:** Beta-blockers, clonidine, guanethidine, and reserpine

**Intervention:** Increased frequency of glucose monitoring may be required when HUMULIN R is co-administered with these drugs.

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### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Available data from published studies over decades have not established an association with human insulin use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations). Animal reproduction studies were not performed.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7% and has been reported to be as high as 20-25% in women with a HbA1c >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**Clinical Considerations**

**Disease-associated maternal and/or embryo/fetal risk**

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

**Data**

**Human Data**

While available studies cannot definitively establish the absence of risk, published data from retrospective studies, open-label, randomized, parallel studies and meta-analyses over decades have not established an association with human insulin use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. All available studies have methodological limitations, including lack of blinding, unclear methods or randomization, and small sample size.

#### 8.2 Lactation

**Risk Summary**

Available data from published literature suggests that exogenous human insulin products, including HUMULIN R, are transferred into human milk. There are no adverse reactions reported in breastfed infants in the literature. There are no data on the effects of exogenous human insulin products, including HUMULIN R on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMULIN R and any potential adverse effects on the breastfed child from HUMULIN R or from the underlying maternal condition.

#### 8.4 Pediatric Use

HUMULIN R is indicated to improve glycemic control in pediatric patients with diabetes mellitus.

The dosage of HUMULIN R must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose to reduce the risk of hypoglycemia [see Dosage and Administration (2.3), Warnings and Precautions (5.3)].

#### 8.5 Geriatric Use

The effect of age on the pharmacokinetics and pharmacodynamics of HUMULIN R has not been studied. Elderly patients using HUMULIN R may be at increased risk of hypoglycemia due to co-morbid disease [see Warnings and Precautions (5.3)].

#### 8.6 Renal Impairment
The effect of renal impairment on the pharmacokinetics and pharmacodynamics of HUMULIN R has not been studied. Patients with renal impairment are at increased risk of hypoglycemia and may require more frequent HUMULIN R dose adjustment and more frequent blood glucose monitoring. See Warnings and Precautions (5.3).

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of HUMULIN R has not been studied. Patients with hepatic impairment are at increased risk of hypoglycemia and may require more frequent HUMULIN R dose adjustment and more frequent blood glucose monitoring. See Warnings and Precautions (5.3).

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular or subcutaneous glucagon or intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately. See Warnings and Precautions (5.3, 5.6).

11 DESCRIPTION

HUMULIN R (insulin human injection) is a short-acting human insulin for subcutaneous or intravenous use. HUMULIN R is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. HUMULIN R is regular human insulin and has the empirical formula \( \text{C}_{257}\text{H}_{383}\text{N}_{65}\text{O}_{77}\text{S}_{6} \) with a molecular weight of 5808.

HUMULIN R is a sterile, aqueous, clear, and colorless solution. HUMULIN R contains 100 units of insulin in each milliliter. Each milliliter of HUMULIN R also contains glycerin 16 mg, metacresol 2.5 mg, endogenous zinc (approximately 0.015 mg/100 units,) and Water for Injection. Sodium hydroxide and hydrochloric acid may be added during manufacture to adjust the pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin, including HUMULIN R, is the regulation of glucose metabolism. Insulin lowers blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

12.2 Pharmacodynamics

The time course of insulin action (i.e., glucose lowering) may vary considerably in different individuals or within the same individual. With subcutaneous use, the pharmacologic effect of HUMULIN R begins approximately 30 minutes (range: 10 to 75 minutes) after administration of doses in the 0.05 to 0.4 units/kg range (Figure 1). The effect is maximal at approximately 3 hours (range: 20 minutes to 7 hours) and terminates after approximately 8 hours (range: 3 to 14 hours). In a study that administered 50 and 100 units doses subcutaneously to obese subjects, mean time of termination of effect was prolonged to approximately 18 hours (range approximately 12-24 hours).

![Figure 1: Mean Insulin Activity Versus Time Profile After Subcutaneous Injection of HUMULIN R (0.3 unit/kg) in Healthy Subjects.](image)
With intravenous use, the pharmacologic effect of HUMULIN R begins at approximately 10 to 15 minutes and terminates at a median time of approximately 4 hours (range: 2 to 6 hours) after administration of doses in the range of 0.1 to 0.2 units/kg.

The intravenous administration of HUMULIN R was tested in 21 people with type 1 diabetes. During the 6-hour assessment phase patients received intravenous HUMULIN R at an initial dose of 0.5 units/hour, 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 therapy are summarized below in Table 2. All patients achieved near normoglycemia during the 6-hour assessment phase. The average time (± SE) required to attain near normoglycemia was 161 ± 14 minutes for HUMULIN R.

### Table 2: Mean Blood Glucose Concentrations (mg/dL) during Intravenous Infusions of HUMULIN R

<table>
<thead>
<tr>
<th>Time from Start of Infusion (minutes)</th>
<th>Mean Blood Glucose (mg/dL) Intravenous&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>220 ± 11</td>
</tr>
<tr>
<td>30</td>
<td>204 ± 17</td>
</tr>
<tr>
<td>60</td>
<td>193 ± 18</td>
</tr>
<tr>
<td>120</td>
<td>172 ± 28</td>
</tr>
<tr>
<td>180</td>
<td>153 ± 30</td>
</tr>
<tr>
<td>240</td>
<td>139 ± 24</td>
</tr>
<tr>
<td>300</td>
<td>131 ± 22</td>
</tr>
<tr>
<td>360</td>
<td>128 ± 18</td>
</tr>
</tbody>
</table>

<sup>a</sup>Results shown as mean ± Standard Deviation.

12.3 Pharmacokinetics

**Absorption** — In healthy subjects given subcutaneous doses of HUMULIN R ranging from 0.05 to 0.4 unit/kg, mean peak serum levels occurred between 36 to 150 minutes after dosing. After subcutaneous administration of a single 12 unit dose (approximately 0.15 units/kg) to patients with type 1 diabetes, the median peak serum level occurred at approximately 2 hours (range: 20 minutes-6 hours). In a study that administered 50 units (0.4-0.6 unit/kg) and 100 units (0.8-1.3 unit/kg) doses subcutaneously to healthy obese subjects, median peak serum levels were prolonged to approximately 3 hours (range 1 to 8 hours). The absolute bioavailability after a single subcutaneous injection of HUMULIN R ranges from 48% to 89% in the 0.1 to 0.3 unit/kg dose range.

**Distribution** — When HUMULIN R is administered intravenously at doses of 0.1 or 0.2 unit/kg, the mean volume of distribution ranges between 0.32 to 0.67 L/kg.

**Metabolism** — The uptake and degradation of insulin occurs predominantly in liver, kidney, muscle, and adipocytes, with the liver being the major organ involved in the clearance of insulin.

**Excretion** — After subcutaneous administration of HUMULIN R doses in the 0.05-0.4 unit/kg dose range, the median apparent half-life is approximately 1.5 hours (range: 40 minutes-7 hours). Mean apparent half-life of HUMULIN R after subcutaneous administration of higher doses (50 and 100 units) to healthy obese subjects was approximately 3.6 hours (range= 1.6-8.6 hours).

When administered intravenously, HUMULIN R had a mean half-life of approximately 20 minutes at a 0.1 unit/kg dose and 1 hour at a 0.2 unit/kg dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and fertility studies were not performed in animals.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HUMULIN R injection is 100 units per mL (U-100), a clear and colorless solution available as:

- 10 mL vials NDC 0002-8215-01
- 3 mL vials NDC 0002-8215-17

Patients using HUMULIN R vials must never share needles or syringes with another person.

16.2 Storage and Handling

Protect from heat and light. Do not freeze. Do not use HUMULIN R after the expiration date printed on the label or if it has been frozen.
Table 3. Storage Conditions and Expiration Dates for HUMULIN R

<table>
<thead>
<tr>
<th></th>
<th>Not In-Use (Unopened)</th>
<th>Not In-Use (Unopened)</th>
<th>In-Use (Opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Refrigerated</td>
<td>Room Temperature</td>
<td>Refrigerated or</td>
</tr>
<tr>
<td></td>
<td>(36° to 46°F [2° to 8°C])</td>
<td>(below 86°F [30°C])</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>10 mL vial</td>
<td>Until expiration date</td>
<td>31 days</td>
<td>31 days</td>
</tr>
<tr>
<td>3 mL vial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16.3 Admixture for Intravenous Administration

Intravenous infusion bags prepared with HUMULIN R are stable when stored in a refrigerator (36° to 46°F [2° to 8°C]) for 48 hours and then may be used at room temperature for up to an additional 48 hours [see Dosage and Administration (2.2)].

17 PATIENT COUNSELING INFORMATION

Advising the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Never Share Needles or Syringes between Patients

Advise patients using HUMULIN R vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of HUMULIN R therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia [see Warnings and Precautions (5.3)].

Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products [see Warnings and Precautions (5.4)].

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with HUMULIN R. Inform patients on the symptoms of hypersensitivity reactions and to seek medical attention if they occur [see Warnings and Precautions (5.5)].

Literature Revised: May 2018

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