Novolin® R

Regular,
Human Insulin Injection
(recombinant DNA origin) USP

100 units/mL

DESCRIPTION

Novolin® R Regular, Human Insulin Injection (rDNA origin) USP is a polypeptide hormone structurally identical to natural human insulin and is produced by rDNA technology, utilizing *Saccharomyces cerevisiae* (bakers' yeast) as the production organism. Human insulin has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808 Da.

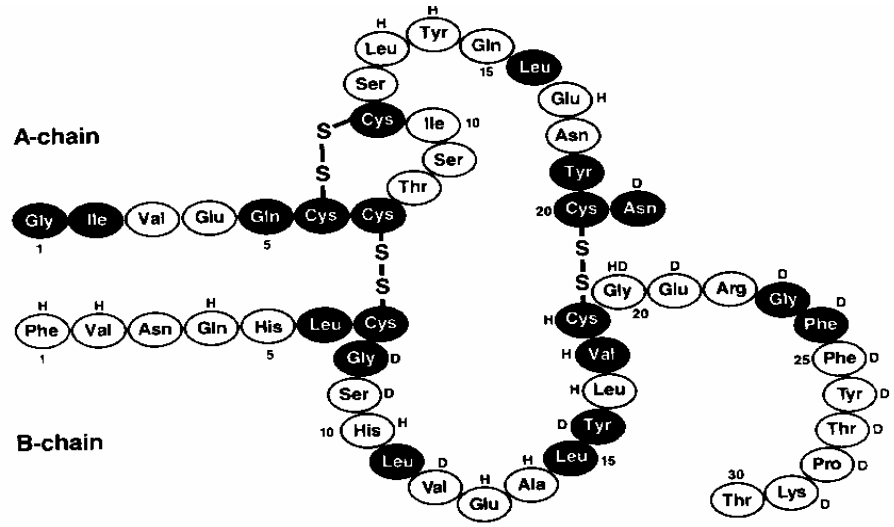

Figure 1. Structural formula of human insulin

Novolin R is a sterile, clear, aqueous, and colorless solution, that contains human insulin (rDNA origin) 100 units/mL, glycerin 16 mg/ml, metacresol 3 mg/mL and zinc chloride approximately 7 µg/mL. The pH is adjusted to 7.4. Hydrochloric acid 2N and/or sodium hydroxide 2N may be added to adjust pH.

CLINICAL PHARMACOLOGY

Insulin is a polypeptide hormone that controls the storage and metabolism of carbohydrates, proteins, and fats. This activity occurs primarily in the liver, in muscle, and in adipose tissues after binding of the insulin molecules to receptor sites on cellular plasma membranes.

Insulin promotes uptake of carbohydrates, proteins, and fats in most tissues. Also, insulin influences carbohydrate, protein, and fat metabolism by stimulating protein and free fatty acid synthesis, and by inhibiting release of free fatty acid from adipose cells. Insulin increases active glucose transport through muscle and adipose cellular membranes, and promotes conversion of intracellular glucose and free fatty acid to the appropriate storage forms (glycogen and triglyceride, respectively). Although the liver does not require active glucose transport, insulin increases hepatic glucose conversion to glycogen and suppresses hepatic glucose output. Even though the actions of exogenous insulin are identical to those of endogenous insulin, the ability to negatively affect hepatic glucose output differs on a unit per unit basis because a smaller quantity of an exogenous insulin dose reaches the portal vein.

Administered insulin, including Novolin R, substitutes for inadequate endogenous insulin secretion and partially corrects the disordered metabolism and inappropriate hyperglycemia of diabetes mellitus, which are caused by either a deficiency or a reduction in the biologic effectiveness of insulin. When administered in appropriate doses at prescribed intervals to patients with diabetes mellitus, Novolin R temporarily restores their ability to metabolize carbohydrates, proteins and fats.

Novolin R is a sterile, aqueous, and colorless solution of human insulin with a short duration of action. The pharmacologic effect of Novolin R begins approximately one-half (½) hour after subcutaneous administration. The effect is maximal between 2½ and 5 hours and terminates after approximately 8 hours. The onset of action of intravenous insulin is more rapid.

INDICATIONS AND USAGE

Novolin R is indicated for subcutaneous administration for the treatment of patients with diabetes mellitus, for the control of hyperglycemia. Treatment with Novolin R is as an adjunct to diet and exercise for lowering blood glucose in patients with Type 1 diabetes or in patients with Type 2 diabetes for whom oral antidiabetic therapy is inadequate.

Novolin R may be administered intravenously under proper medical supervision in a clinical setting for glycemic control. (See DOSAGE AND ADMINISTRATION and RECOMMENDED STORAGE.)

CONTRAINDICATIONS

Insulin is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Novolin R or one of its excipients.

WARNING

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog, etc.), species

(animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Special care should be taken when the transfer is from a standard beef or mixed species insulin to a purified pork or human insulin. If a dosage adjustment is needed, it will usually become apparent either in the first few days or over a period of several weeks. Any change in treatment should be carefully monitored.

PRECAUTIONS

General

Hypoglycemia, hypokalemia, lipodystrophy and hypersensitivity are among the potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of Novolin R 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.

Novolin R should only be used if it is clear and colorless. Due to the risk of precipitation in some pump catheters, Novolin R is not recommended for use in insulin pumps.

Hypoglycemia and hypokalemia - As with all insulin preparations, hypoglycemic and hypokalemic reactions may be associated with the administration of Novolin R, particularly via the IV route. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia. Severe hypoglycemia can result in temporary or permanent impairment of brain function and 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 hypoglycemia and hypokalemia is necessary. Therefore, glucose and potassium levels must be monitored closely when NovoLog or any other insulin is administered intravenously.

In certain cases, the nature and intensity of the warning symptoms of hypoglycemia may change. A few patients have reported that after being transferred to human insulin, the early warning symptoms for hypoglycemia had been less pronounced than they were with animal-source insulin.

Hyperglycemia and ketosis – Hyperglycemia, diabetic ketoacidosis, or diabetic coma may develop if the patient takes less Novolin R than needed to control blood glucose levels. This could be due to insulin demand during illness or infection, neglect of diet, omission or improper administration of prescribed insulin doses. A developing ketoacidosis will be revealed by urine tests which show large amounts of sugar and acetone. The symptoms of polydipsia, polyurea,

loss of appetite, fatigue, dry skin and deep and rapid breathing come on gradually, usually over a period of some hours or days. Severe sustained hyperglycemia may result in diabetic coma or death.

Renal Impairment - As with other insulins, the dose requirements for Novolin R may be reduced in patients with renal impairment.

Hepatic Impairment - As with other insulins, the dose requirements for Novolin R may be reduced in patients with hepatic impairment.

Allergy - Local Allergy - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of Novolin R. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.
Systemic Allergy - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.
Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Usage in Pregnancy
It is particularly important for patients to maintain good control of diabetes during pregnancy and special attention must be paid to diet, exercise and insulin regimens. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant.

Information for Patients
Patients should be informed about potential risks and advantages of Novolin R therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction in the use of injection devices, and proper storage of insulin. Patients should be informed that frequent, patient performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant.

Laboratory Tests
As with all insulin therapy, the therapeutic response to Novolin R should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control. Urine ketones should be monitored frequently.
When Novolin R is administered intravenously, glucose and potassium levels must be closely monitored to avoid potentially fatal hypoglycemia and hypokalemia.

Drug Interactions
A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

- The following are examples of substances that may reduce insulin requirement: oral hypoglycemic agents (OHA), octreotide, monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, sulphonamide antibiotics, anabolic steroids, quinine, quinidine and alpha-adrenergic blocking agents.
- The following are examples of substances that may increase insulin requirement: oral contraceptives, thiazides, glucocorticoids, thryroid hormones and sympathomimetics, growth hormone, diazoxide, asparaginase and nicotinic acid.
- Beta-blocking agents may mask the symptoms of hypoglycemia and delay recovery from hypoglycemia.
- Alcohol may intensify and prolong the hypoglycemic effect of insulin.

Mixing of Insulins

- Novolin R should only be mixed as directed by the physician.
- Novolin R is a short-acting insulin 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 a longer-acting insulin (e.g. NPH insulin isophane suspensions) is mixed with short-acting soluble insulin (e.g., regular), the short-acting insulin should be drawn into the syringe first.

ADVERSE REACTIONS
Adverse events commonly associated with human insulin therapy include the following:
Body as Whole - *Allergic reactions* (see PRECAUTIONS, Allergy).
Skin and Appendages - *Injection site reaction, lipodystrophy, pruritus, rash* (see PRECAUTIONS, Allergy).
Other – *Hypoglycemia, Hyperglycemia and ketosis* (see PRECAUTIONS).

OVERDOSAGE
Excess insulin may cause hypoglycemia and hypokalemia, particularly after IV administration. Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. 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/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSAGE AND ADMINISTRATION
Novolin R, when used alone subcutaneously, is usually given three or more times daily before meals. The dosage and timing of Novolin R should be individualized and determined, base on

the physician's advice, in accordance with the needs of the patient. Novolin R may also be used in combination with oral antidiabetic agents or longer-acting insulin products to suit the needs of the individual patients. The injection of Novolin R 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 lies between 0.5 and 1.0 IU/kg. However, in pre-pubertal children it usually varies from 0.7 to 1.0 IU/kg, but can be much lower during the period of partial remission. In severe insulin resistance, e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher. Initial dosages for Type 2 diabetes patients are often lower, e.g. 0.2 to 0.4 IU/kg/day.

Novolin R should 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 insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

Intramuscular and intravenous administrations of Novolin R are possible under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia.
For intravenous use, Novolin R should be used at concentrations from 0.05 U/mL to 1.0 U/mL in infusion systems with the infusion fluids 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use Novolin R if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. **Novolin R should not be used after the printed expiration date.**

RECOMMENDED STORAGE
Novolin R vials, Novolin® R PenFill® cartridges, and Novolin® R InnoLet® prefilled insulin syringes should be stored in a cold (36° - 46°F [2° - 8°C]) place, preferably in a refrigerator, but not in the freezer. **Do not freeze.** Keep Novolin R vials, Novolin R PenFill cartridges and Novolin R InnoLet in their cartons so that they will stay clean and protected from light. They should not be exposed to heat or sunlight. A Novolin R vial in use can be kept unrefrigerated as long as it is kept as cool as possible and away from heat or sunlight. A Novolin R PenFill cartridge and Novolin R InnoLet in use should not be refrigerated but should be kept as cool as possible (below 86°F [30°C]) and away from direct heat and light. Unrefrigerated Novolin R PenFill cartridges and Novolin R InnoLet must be discarded 28 days after the first use, even if they still contain Novolin R insulin.

Infusion bags prepared as indicated under DOSAGE AND ADMINISTRATION are stable at room temperature for 24 hours. A certain amount of insulin will be initially adsorbed to the material of the infusion bag.

Never use insulin after the expiration date which is printed on the label and carton.

HOW SUPPLIED

Novolin R, Regular, Human Insulin Injection (rDNA origin) USP, 100 units/mL, is supplied as follows:

10 mL vial	NDC 0169-1833-11
3 mL PenFill cartridges*	NDC 0169-3473-18
3 mL Novolin R InnoLet	NDC 0169-2313-21

*Novolin R PenFill 3 mL cartridges are designed for use with Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices, the NovoPen® 3 PenMate® and with NovoFine® disposable needles.

Date of issue:
8-XXXX-XX-XXX-X

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