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164**INFORMATION FOR THE PATIENT**165
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170**HUMULIN[®] R
REGULAR
U-500 (CONCENTRATED)
INSULIN HUMAN INJECTION, USP
(rDNA ORIGIN)**171
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175**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 PURITY, STRENGTH, BRAND (MANUFACTURER), TYPE (REGULAR, NPH, E.G., LENTE), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN), AND/OR METHOD OF MANUFACTURE (rDNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

SOME PATIENTS TAKING HUMULIN[®] (HUMAN INSULIN, rDNA ORIGIN, LILLY) MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH ANIMAL-SOURCE INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.

This insulin preparation contains 500 units of insulin in each milliliter. Extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in irreversible insulin shock. Serious consequences may result if it is used other than under constant medical supervision.

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DIABETES

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs.

To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near-normal level. You have been instructed to test your blood and/or your urine regularly for glucose. Studies have shown that some chronic complications of diabetes such as eye disease, kidney disease, and nerve disease can be significantly reduced if the blood sugar is maintained as close to normal as possible. The American Diabetes Association recommends that if your pre-meal glucose levels are consistently above 130 mg/dL or your hemoglobin A_{1c} (HbA_{1c}) is more than 7%, consult your doctor. A change in your diabetes therapy may be needed. If your blood tests consistently show below-normal glucose levels you should also let your doctor know. Proper control of your diabetes requires close and constant cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly, and take your insulin injections as prescribed.

Always keep an extra supply of insulin as well as a spare syringe and needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

208

REGULAR HUMAN INSULIN

209

210 Description

211 Humulin is synthesized in a special non-disease-producing laboratory strain of *Escherichia*
 212 *coli* bacteria that has been genetically altered by the addition of the gene for human insulin
 213 production. Humulin R (U-500) consists of zinc-insulin crystals dissolved in a clear fluid.
 214 Humulin R (U-500) has had nothing added to change the speed or length of its action. It takes
 215 effect rapidly but has a relatively long duration of activity (up to 24 hours) as compared with
 216 other Regular insulins. The time course of action of any insulin may vary considerably in
 217 different individuals or at different times in the same individual. As with all insulin preparations,
 218 the duration of action of Humulin R (U-500) is dependent on dose, site of injection, blood
 219 supply, temperature, and physical activity. Humulin R (U-500), is a sterile solution and is for
 220 subcutaneous injection only. It should not be used intravenously or intramuscularly. The
 221 concentration of Humulin R (U-500) is 500 units/mL.

222 Identification

223 Human insulin by Eli Lilly and Company has the trademark Humulin and is available in
 224 6 formulations — Regular (**R**), NPH (**N**), Lente (**L**), Ultralente[®] (**U**), 50% Human Insulin
 225 Isophane Suspension [NPH]/50% Human Insulin Injection [regular] (**50/50**), and 70% Human
 226 Insulin Isophane Suspension [NPH]/30% Human Insulin Injection [regular] (**70/30**). Humulin R
 227 (U-500) is the only human insulin by Eli Lilly and Company that has a concentration of
 228 500 units/mL. Your doctor has prescribed the type of insulin that he/she believes is best for you.

229 **DO NOT USE ANY OTHER INSULIN EXCEPT ON HIS/HER ADVICE AND** 230 **DIRECTION.**

231 Always check the carton and the bottle label for the name and letter designation of the insulin
 232 you receive from your pharmacy to make sure it is the same as that your doctor has prescribed.

233 Always examine the appearance of your bottle of insulin before withdrawing each dose.
 234 Humulin R (U-500) is a clear and colorless liquid with a water-like appearance and consistency.
 235 Do not use if it appears cloudy, thickened, or slightly colored or if solid particles are visible.
 236 Always check the appearance of your bottle of insulin before using, and if you note anything
 237 unusual in the appearance of your insulin or notice your insulin requirements changing
 238 markedly, consult your doctor.

239 Storage

240 Insulin should be stored in a refrigerator but not in the freezer. If refrigeration is not possible,
 241 the bottle of insulin that you are currently using can be kept unrefrigerated as long as it is kept as
 242 cool as possible (below 30°C [86°F]) and away from heat and light. Do not use insulin if it has
 243 been frozen. Do not use a bottle of Humulin R (U-500) after the expiration date stamped on the
 244 label.

245

INJECTION PROCEDURES

246 Correct Syringe Type

247 Doses of insulin are measured in **units**. U-500 insulin contains 500 units/mL (1 mL=1 cc).
 248 With Humulin R (U-500), it is important to use a tuberculin (or similar) syringe as instructed by
 249 your doctor. Failure to use the proper syringe type can lead to a mistake in dosage, causing
 250 serious problems for you, such as a blood glucose level that is too low or too high.

251 Syringe Use

252 To help avoid contamination and possible infection, follow these instructions exactly.

253 Disposable plastic syringes and needles should be used only once and then discarded in a
 254 responsible manner. **NEEDLES AND SYRINGES MUST NOT BE SHARED.**

255 Reusable glass syringes and needles must be sterilized before each injection. **Follow the**
 256 **package directions supplied with your syringe.** Described below are 2 methods of sterilizing.

257 Boiling

258 1. Put syringe, plunger, and needle in strainer, place in saucepan, and cover with water. Boil
 259 for 5 minutes.

- 260 2. Remove articles from water. When they have cooled, insert plunger into barrel, and fasten
 261 needle to syringe with a slight twist.
 262 3. Push plunger in and out several times until water is completely removed.

263 **Isopropyl Alcohol**

264 If the syringe, plunger, and needle cannot be boiled, as when you are traveling, they may be
 265 sterilized by immersion for at least 5 minutes in Isopropyl Alcohol, 91%. Do not use bathing,
 266 rubbing, or medicated alcohol for this sterilization. If the syringe is sterilized with alcohol, it
 267 must be absolutely dry before use.

268 **Preparing the Dose**

- 269 1. Wash your hands.
 270 2. Inspect the insulin. Humulin R (U-500) should look clear and colorless. Do not use
 271 Humulin R (U-500) if it appears cloudy, thickened, or slightly colored or if solid particles
 272 are visible.
 273 3. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper.
 274 When using a new bottle, wipe the top of the bottle with an alcohol swab.
 275 4. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top
 276 of the insulin bottle and inject the air into the bottle.
 277 5. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.
 278 6. Making sure the tip of the needle is in the insulin, withdraw the correct dose of insulin
 279 into the syringe.
 280 7. Before removing the needle from the bottle, check your syringe for air bubbles which
 281 reduce the amount of insulin in it. If bubbles are present, hold the syringe straight up and
 282 tap its side until the bubbles float to the top. Push them out with the plunger and withdraw
 283 the correct dose.
 284 8. Remove the needle from the bottle and lay the syringe down so that the needle does not
 285 touch anything.

286 **Injection**

287 Once you have chosen an injection site, cleanse the skin with alcohol where the injection is to
 288 be made. Stabilize the skin by spreading it or pinching up a large area. Insert the needle as
 289 instructed by your doctor. Push the plunger in as far as it will go. Pull the needle out and apply
 290 gentle pressure over the injection site for several seconds. **Do not rub the area.** To avoid tissue
 291 damage, give the next injection at a site at least 1/2 inch from the previous site.

292 **DOSAGE**

293 Your doctor has told you which insulin to use, how much, and when and how often to inject it.
 294 Because each patient's case of diabetes is different, this schedule has been individualized for
 295 you.

296 Your usual insulin dose may be affected by changes in your food, activity, or work schedule.
 297 Carefully follow your doctor's instructions to allow for these changes. Other things that may
 298 affect your insulin dose are:

299 **Illness**

300 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
 301 Even if you are not eating, you will still require insulin. You and your doctor should establish a
 302 sick day plan for you to use in case of illness. When you are sick, test your blood glucose/urine
 303 glucose and ketones frequently and call your doctor as instructed.

304 **Pregnancy**

305 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may
 306 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or
 307 are nursing a baby, consult your doctor.

308 **Medication**

309 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
 310 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin

311 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
 312 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol,
 313 certain antidepressants and some kidney and blood pressure medicines. Your Health Care
 314 Professional may be aware of other medications that may affect your diabetes control. Therefore,
 315 always discuss any medications you are taking with your doctor.

316 **Exercise**

317 Exercise may lower your body's need for insulin during and for some time after the activity.
 318 Exercise may also speed up the effect of an insulin dose, especially if the exercise involves the
 319 area of injection site (for example, the leg should not be used for injection just prior to running).
 320 Discuss with your doctor how you should adjust your regimen to accommodate exercise.

321 **Travel**

322 Persons traveling across more than 2 time zones should consult their doctor concerning
 323 adjustments in their insulin schedule.

324 **COMMON PROBLEMS OF DIABETES**

325 **Hypoglycemia (Low Blood Sugar)**

326 Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events
 327 experienced by insulin users. It can be brought about by:

- 328 1. Missing or delaying meals.
- 329 2. Taking too much insulin.
- 330 3. Exercising or working more than usual.
- 331 4. An infection or illness (especially with diarrhea or vomiting).
- 332 5. A change in the body's need for insulin.
- 333 6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver
 334 disease.
- 335 7. **Interactions with other drugs that lower blood glucose**, such as oral antidiabetic agents,
 336 salicylates (for example, aspirin), sulfa antibiotics, certain antidepressants and **some**
 337 **kidney and blood pressure medicines.**
- 338 8. Consumption of alcoholic beverages.

339 Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- | | |
|--|-----------------------|
| 340 • sweating | • drowsiness |
| 341 • dizziness | • sleep disturbances |
| 342 • palpitation | • anxiety |
| 343 • tremor | • blurred vision |
| 344 • hunger | • slurred speech |
| 345 • restlessness | • depressive mood |
| 346 • tingling in the hands, feet, lips, or tongue | • irritability |
| 347 • lightheadedness | • abnormal behavior |
| 348 • inability to concentrate | • unsteady movement |
| 349 • headache | • personality changes |

350 Signs of severe hypoglycemia can include:

- | | |
|-----------------------|------------|
| 351 • disorientation | • seizures |
| 352 • unconsciousness | • death |

353 Therefore, it is important that assistance be obtained immediately.

354 Early warning symptoms of hypoglycemia may be different or less pronounced under certain
 355 conditions, such as long duration of diabetes, diabetic nerve disease, medications such as
 356 beta-blockers, change in insulin preparations, or intensified control (3 or more insulin injections
 357 per day) of diabetes.

358 **A few patients who have experienced hypoglycemic reactions after transfer from**
 359 **animal-source insulin to human insulin have reported that the early warning symptoms of**

360 **hypoglycemia were less pronounced or different from those experienced with their**
 361 **previous insulin.**

362 Without recognition of early warning symptoms, you may not be able to take steps to avoid
 363 more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate
 364 hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should
 365 monitor their blood glucose frequently, especially prior to activities such as driving. If the blood
 366 glucose is below your normal fasting glucose, you should consider eating or drinking
 367 sugar-containing foods to treat your hypoglycemia.

368 Mild to moderate hypoglycemia may be treated by eating foods or taking drinks that contain
 369 sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose
 370 tablets. More severe hypoglycemia may require the assistance of another person. Patients who
 371 are unable to take sugar orally or who are unconscious require an injection of glucagon or should
 372 be treated with intravenous administration of glucose at a medical facility.

373 Hypoglycemia when using Humulin R (U-500) can be prolonged and severe. All
 374 hypoglycemic episodes should be reported to your doctor.

375 You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain
 376 about these symptoms, you should monitor your blood glucose frequently to help you learn to
 377 recognize the symptoms that you experience with hypoglycemia.

378 If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the
 379 symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans,
 380 and/or exercise programs to help you avoid hypoglycemia.

381 **Hyperglycemia and Diabetic Ketoacidosis (DKA)**

382 Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.
 383 Hyperglycemia can be brought about by:

- 384 1. Omitting your insulin or taking less than the doctor has prescribed.
- 385 2. Eating significantly more than your meal plan suggests.
- 386 3. Developing a fever, infection, or other significant stressful situation.

387 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in
 388 DKA. The first symptoms of DKA usually come on gradually, over a period of hours or days,
 389 and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath.
 390 With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid
 391 pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or DKA can lead to
 392 nausea, vomiting, dehydration, loss of consciousness or death. Therefore, it is important that you
 393 obtain medical assistance immediately.

394 **Lipodystrophy**

395 Rarely, administration of insulin subcutaneously can result in lipodystrophy (depression in the
 396 skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these
 397 conditions, consult your doctor. A change in your injection technique may help alleviate the
 398 problem.

399 **Allergy to Insulin**

400 *Local Allergy* — Patients occasionally experience redness, swelling, and itching at the site of
 401 injection of insulin. This condition, called local allergy, usually clears up in a few days to a few
 402 weeks. In some instances, this condition may be related to factors other than insulin, such as
 403 irritants in the skin cleansing agent or poor injection technique. If you have local reactions,
 404 contact your doctor.

405 *Systemic Allergy* — Less common, but potentially more serious, is generalized allergy to
 406 insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in
 407 blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life
 408 threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor
 409 immediately.

410

ADDITIONAL INFORMATION

411 Additional information about diabetes may be obtained from your diabetes educator.
412 **DIABETES FORECAST** is a magazine designed especially for people with diabetes and their
413 families. It is available by subscription from the American Diabetes Association (ADA), P.O.
414 Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383).

415 Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research
416 Foundation International (JDRFI), 120 Wall Street 19th Floor, New York, NY 10005,
417 1-800-533-CURE (1-800-533-2873).

418 Additional information about Humulin can be obtained by calling The Lilly Answers Center at
419 1-800-LillyRx (1-800-545-5979).

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