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**INFORMATION FOR THE PATIENT
3 ML PREFILLED INSULIN DELIVERY DEVICE**

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**HUMULIN[®] N Pen
NPH
HUMAN INSULIN
(rDNA ORIGIN) ISOPHANE SUSPENSION
100 UNITS PER ML (U-100)**

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WARNINGS

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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.

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ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

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

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TO OBTAIN AN ACCURATE DOSE, CAREFULLY READ AND FOLLOW THE INSULIN DELIVERY DEVICE USER MANUAL AND THIS "INFORMATION FOR THE PATIENT" INSERT BEFORE USING THIS PRODUCT.

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THE PEN MUST BE PRIMED TO A STREAM OF INSULIN (NOT JUST A FEW DROPS) BEFORE EACH INJECTION TO MAKE SURE THE PEN IS READY TO DOSE. YOU MAY NEED TO PRIME A NEW PEN UP TO SIX TIMES BEFORE A STREAM OF INSULIN APPEARS.

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PRIMING THE PEN IS IMPORTANT TO CONFIRM THAT INSULIN COMES OUT WHEN YOU PUSH THE INJECTION BUTTON AND TO REMOVE AIR THAT MAY COLLECT IN THE INSULIN CARTRIDGE DURING NORMAL USE. IF YOU DO NOT PRIME, YOU MAY RECEIVE TOO MUCH OR TOO LITTLE INSULIN (*see also* INSTRUCTIONS FOR INSULIN PEN USE section).

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DIABETES

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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.

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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%, you should talk to 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 by your doctor.

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

52 NPH HUMAN INSULIN

53 Description

54 Humulin is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli*
 55 bacteria that has been genetically altered to produce human insulin. Humulin N [Human insulin
 56 (rDNA origin) isophane suspension] is a crystalline suspension of human insulin with protamine
 57 and zinc providing an intermediate-acting insulin with a slower onset of action and a longer
 58 duration of activity (up to 24 hours) than that of Regular human insulin. The time course of
 59 action of any insulin may vary considerably in different individuals or at different times in the
 60 same individual. As with all insulin preparations, the duration of action of Humulin N is
 61 dependent on dose, site of injection, blood supply, temperature, and physical activity. Humulin N
 62 is a sterile suspension and is for subcutaneous injection only. It should not be used intravenously
 63 or intramuscularly. The concentration of Humulin N is 100 units/mL (U-100).

64 Identification

65 Human insulin from Eli Lilly and Company has the trademark Humulin. Your doctor has
 66 prescribed the type of insulin that he/she believes is best for you.

67 **DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND**
 68 **DIRECTION.**

69 **The Humulin N Pen is available in boxes of 5 prefilled insulin delivery devices ("insulin**
 70 **Pens"). The Humulin N Pen is not designed to allow any other insulin to be mixed in its**
 71 **cartridge, or for the cartridge to be removed.**

72 Always check the carton and the Pen label for the name and letter designation of the insulin
 73 you receive from your pharmacy to make sure it is the same as prescribed by your doctor.

74 Always check the appearance of Humulin N suspension in your insulin Pen before using. A
 75 cartridge of Humulin N contains a small glass bead to assist in mixing. Roll the Pen back and
 76 forth between the palms 10 times (*see* Figure 1). Gently turn the Pen up and down 10 times until
 77 the insulin is evenly mixed (*see* Figure 2). If not evenly mixed, repeat the above steps until
 78 contents are mixed. Pens containing Humulin N suspension should be examined frequently.

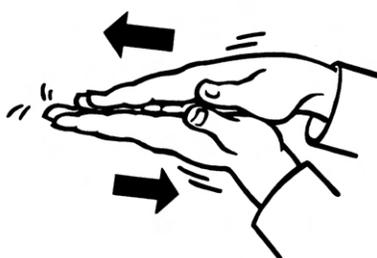


Figure 1.

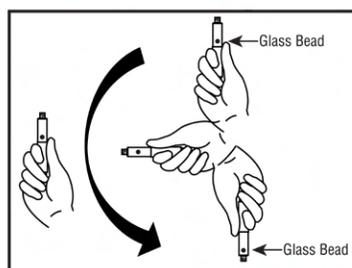


Figure 2.

79 Do not use Humulin N:

- 80 • if the insulin substance (the white material) remains visibly separated from the liquid after
- 81 mixing or
- 82 • if there are clumps in the insulin after mixing, or
- 83 • if solid white particles stick to the walls of the cartridge, giving a frosted appearance.

84 If you see anything unusual in the appearance of the Humulin N suspension in your Pen or
 85 notice your insulin requirements changing, talk to your doctor.

86 Never attempt to remove the cartridge from the Humulin N Pen. Inspect the cartridge through
 87 the clear cartridge holder.

88 **Storage**

89 **Not in-use (unopened):** Humulin N Pens not in-use should be stored in a refrigerator, but not
90 in the freezer.

91 **In-use (opened):** Humulin N Pens in-use should **NOT** be refrigerated but should be kept at
92 room temperature [below 86°F (30°C)] away from direct heat and light. The Humulin N Pen you
93 are currently using must be discarded **2 weeks** after the first use, even if it still contains Humulin
94 N.

95 **Do not use Humulin N after the expiration date stamped on the label or if it has been**
96 **frozen.**

97 **INSTRUCTIONS FOR INSULIN PEN USE**

98 **It is important to read, understand, and follow the instructions in the Insulin Delivery**
99 **Device User Manual before using. Failure to follow instructions may result in getting too**
100 **much or too little insulin. The needle must be changed and the Pen must be primed to a**
101 **stream of insulin (not just a few drops) before each injection to make sure the Pen is ready**
102 **to dose. You may need to prime a new Pen up to six times before a stream of insulin**
103 **appears. Performing these steps before each injection is important to confirm that insulin**
104 **comes out when you push the injection button, and to remove air that may collect in the**
105 **insulin cartridge during normal use.**

106 **Every time you inject:**

- 107 • **Use a new needle.**
- 108 • **Prime to a stream of insulin (not just a few drops) to make sure the Pen is ready to dose.**
- 109 • **Make sure you got your full dose.**

110 **NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES.**

111 **PREPARING FOR INJECTION**

- 112 1. Wash your hands.
- 113 2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the
114 previous injection site. The usual sites of injection are abdomen, thighs, and arms.
- 115 3. Follow the instructions in your Insulin Delivery Device User Manual to prepare for
116 injection.
- 117 4. After injecting the dose, pull the needle out and apply gentle pressure over the injection
118 site for several seconds. **Do not rub the area.**
- 119 5. After the injection, remove the needle from the Humulin N Pen. **Do not reuse needles.**
- 120 6. Place the used needle in a puncture-resistant disposable container and properly dispose of
121 the puncture-resistant container as directed by your Health Care Professional.

122 **DOSAGE**

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

125 Your usual dose of Humulin N may be affected by changes in your diet, activity, or work
126 schedule. Carefully follow your doctor's instructions to allow for these changes. Other things
127 that may affect your Humulin N dose are:

128 **Illness**

129 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
130 Even if you are not eating, you will still require insulin. You and your doctor should establish a
131 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
132 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

133 **Pregnancy**

134 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may
135 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or
136 are nursing a baby, talk to your doctor.

137 **Medication**

138 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
 139 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
 140 requirements may be reduced in the presence of drugs that lower blood glucose or affect how
 141 your body responds to insulin, such as oral antidiabetic agents, salicylates (for example, aspirin),
 142 sulfa antibiotics, alcohol, certain antidepressants and some kidney and blood pressure medicines.
 143 Your Health Care Professional may be aware of other medications that may affect your diabetes
 144 control. Therefore, always discuss any medications you are taking with your doctor.

145 **Exercise**

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

151 **Travel**

152 When traveling across more than 2 time zones, you should talk to your doctor concerning
 153 adjustments in your insulin schedule.

154 **COMMON PROBLEMS OF DIABETES**

155 **Hypoglycemia (Low Blood Sugar)**

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

- 158 1. **Missing or delaying meals.**
- 159 2. Taking too much insulin.
- 160 3. Exercising or working more than usual.
- 161 4. An infection or illness associated with diarrhea or vomiting.
- 162 5. A change in the body's need for insulin.
- 163 6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver
 164 disease.
- 165 7. Interactions with certain drugs, such as oral antidiabetic agents, salicylates (for example,
 166 aspirin), sulfa antibiotics, certain antidepressants and some kidney and blood pressure
 167 medicines.
- 168 8. Consumption of alcoholic beverages.

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

- | | |
|----------------------------------------------------|-----------------------|
| 170 • sweating | • drowsiness |
| 171 • dizziness | • sleep disturbances |
| 172 • palpitation | • anxiety |
| 173 • tremor | • blurred vision |
| 174 • hunger | • slurred speech |
| 175 • restlessness | • depressed mood |
| 176 • tingling in the hands, feet, lips, or tongue | • irritability |
| 177 • lightheadedness | • abnormal behavior |
| 178 • inability to concentrate | • unsteady movement |
| 179 • headache | • personality changes |

180 Signs of severe hypoglycemia can include:

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|-----------------------|------------|
| 181 • disorientation | • seizures |
| 182 • unconsciousness | • death |

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

184 Early warning symptoms of hypoglycemia may be different or less pronounced under certain
 185 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as

186 beta-blockers, changing insulin preparations, or intensified control (3 or more insulin injections
187 per day) of diabetes.

188 **A few patients who have experienced hypoglycemic reactions after transfer from animal-**
189 **source insulin to human insulin have reported that the early warning symptoms of**
190 **hypoglycemia were less pronounced or different from those experienced with their**
191 **previous insulin.**

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

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

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

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

209 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

210 Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.
211 Hyperglycemia can be brought about by any of the following:

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

215 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in
216 DKA (a life-threatening emergency). The first symptoms of DKA usually come on gradually,
217 over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite,
218 and fruity odor on the breath. With DKA, blood and urine tests show large amounts of glucose
219 and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected,
220 prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach pain, dehydration, loss
221 of consciousness, or death. Therefore, it is important that you obtain medical assistance
222 immediately.

223 **Lipodystrophy**

224 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
225 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
226 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
227 the problem.

228 **Allergy**

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

233 *Systemic Allergy* — Less common, but potentially more serious, is generalized allergy to
234 insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in
235 blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life

236 threatening. If you think you are having a generalized allergic reaction to insulin, call your
237 doctor immediately.

238 **ADDITIONAL INFORMATION**

239 Information about diabetes may be obtained from your diabetes educator.

240 Additional information about diabetes and Humulin can be obtained by calling The Lilly
241 Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

242 Patient Information revised Month dd, yyyy

243 **Pens manufactured by**
244 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
245 **Lilly France, F-67640 Fegersheim, France**

246
247 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**

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251 **PRINTED IN USA**

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**HUMULIN[®] 70/30 Pen
70% HUMAN INSULIN
ISOPHANE SUSPENSION
AND
30% HUMAN INSULIN INJECTION
(rDNA ORIGIN)
100 UNITS PER ML (U-100)**

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THE PEN MUST BE PRIMED TO A STREAM OF INSULIN (NOT JUST A FEW DROPS) BEFORE EACH INJECTION TO MAKE SURE THE PEN IS READY TO DOSE. YOU MAY NEED TO PRIME A NEW PEN UP TO SIX TIMES BEFORE A STREAM OF INSULIN APPEARS.

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PRIMING THE PEN IS IMPORTANT TO CONFIRM THAT INSULIN COMES OUT WHEN YOU PUSH THE INJECTION BUTTON AND TO REMOVE AIR THAT MAY COLLECT IN THE INSULIN CARTRIDGE DURING NORMAL USE. IF YOU DO NOT PRIME, YOU MAY RECEIVE TOO MUCH OR TOO LITTLE INSULIN (*see also INSTRUCTIONS FOR INSULIN PEN USE section*).

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48 your doctor know. Proper control of your diabetes requires close and constant cooperation with
 49 your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet,
 50 exercise regularly, and take your insulin injections as prescribed by your doctor.

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

70/30 HUMAN INSULIN

Description

56 Humulin is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli*
 57 bacteria that has been genetically altered to produce human insulin. Humulin 70/30 is a mixture
 58 of 70% Human Insulin Isophane Suspension and 30% Human Insulin Injection, (rDNA origin).
 59 It is an intermediate-acting insulin combined with the more rapid onset of action of Regular
 60 human insulin. The duration of activity may last up to 24 hours following injection. The time
 61 course of action of any insulin may vary considerably in different individuals or at different
 62 times in the same individual. As with all insulin preparations, the duration of action of Humulin
 63 70/30 is dependent on dose, site of injection, blood supply, temperature, and physical activity.
 64 Humulin 70/30 is a sterile suspension and is for subcutaneous injection only. It should not be
 65 used intravenously or intramuscularly. The concentration of Humulin 70/30 is 100 units/mL
 66 (U-100).

Identification

68 Human insulin from Eli Lilly and Company has the trademark Humulin.

69 Your doctor has prescribed the type of insulin that he/she believes is best for you.

70 **DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND**
 71 **DIRECTION.**

72 **The Humulin 70/30 Pen is available in boxes of 5 prefilled insulin delivery devices**
 73 **("insulin Pens"). The Humulin 70/30 Pen is not designed to allow any other insulin to be**
 74 **mixed in its cartridge, or for the cartridge to be removed.**

75 Always check the carton and the Pen label for the name and letter designation of the insulin
 76 you receive from your pharmacy to make sure it is the same as prescribed by your doctor.

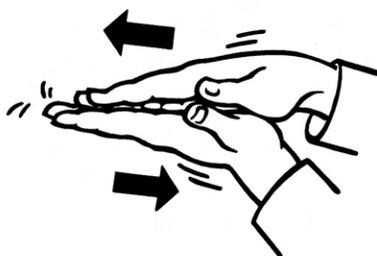


Figure 1.

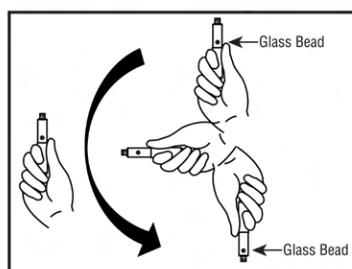


Figure 2.

77 Always check the appearance of Humulin 70/30 suspension in your insulin Pen before using. A
 78 cartridge of Humulin 70/30 contains a small glass bead to assist in mixing. Roll the Pen back and
 79 forth between the palms 10 times (*see* Figure 1). Gently turn the Pen up and down 10 times until
 80 the insulin is evenly mixed (*see* Figure 2). If not evenly mixed, repeat the above steps until
 81 contents are mixed. Pens containing Humulin 70/30 suspension should be examined frequently.

82 Do not use Humulin 70/30:

- 83 • if the insulin substance (the white material) remains visibly separated from the liquid after
- 84 mixing or
- 85 • if there are clumps in the insulin after mixing, or
- 86 • if solid white particles stick to the walls of the cartridge, giving a frosted appearance.

87 If you see anything unusual in the appearance of the Humulin 70/30 suspension in your Pen or
88 notice your insulin requirements changing, talk to your doctor.

89 Never attempt to remove the cartridge from the Humulin 70/30 Pen. Inspect the cartridge
90 through the clear cartridge holder.

91 **Storage**

92 **Not in-use (unopened):** Humulin 70/30 Pens not in-use should be stored in a refrigerator, but
93 not in the freezer.

94 **In-use (opened):** Humulin 70/30 Pens in-use should **NOT** be refrigerated but should be kept at
95 room temperature [below 86°F (30°C)] away from direct heat and light. The Humulin 70/30 Pen
96 you are currently using must be discarded **10 days** after the first use, even if it still contains
97 Humulin 70/30.

98 **Do not use Humulin 70/30 after the expiration date stamped on the label or if it has been**
99 **frozen.**

100 **INSTRUCTIONS FOR INSULIN PEN USE**

101 **It is important to read, understand, and follow the instructions in the Insulin Delivery**
102 **Device User Manual before using. Failure to follow instructions may result in getting too**
103 **much or too little insulin. The needle must be changed and the Pen must be primed to a**
104 **stream of insulin (not just a few drops) before each injection to make sure the Pen is ready**
105 **to dose. You may need to prime a new Pen up to six times before a stream of insulin**
106 **appears. Performing these steps before each injection is important to confirm that insulin**
107 **comes out when you push the injection button, and to remove air that may collect in the**
108 **insulin cartridge during normal use.**

109 **Every time you inject:**

- 110 • **Use a new needle.**
- 111 • **Prime to a stream of insulin (not just a few drops) to make sure the Pen is ready to dose.**
- 112 • **Make sure you got your full dose.**

113 **NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES.**

114 **PREPARING FOR INJECTION**

- 115 1. Wash your hands.
- 116 2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the
117 previous injection site. The usual sites of injection are abdomen, thighs, and arms.
- 118 3. Follow the instructions in your Insulin Delivery Device User Manual to prepare for
119 injection.
- 120 4. After injecting the dose, pull the needle out and apply gentle pressure over the injection
121 site for several seconds. **Do not rub the area.**
- 122 5. After the injection, remove the needle from the Humulin 70/30 Pen. **Do not reuse**
123 **needles.**
- 124 6. Place the used needle in a puncture-resistant disposable container and properly dispose of
125 the puncture-resistant container as directed by your Health Care Professional.

126 **DOSAGE**

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

129 Your usual dose of Humulin 70/30 may be affected by changes in your diet, activity, or work
130 schedule. Carefully follow your doctor's instructions to allow for these changes. Other things
131 that may affect your Humulin 70/30 dose are:

132 **Illness**

133 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
134 Even if you are not eating, you will still require insulin. You and your doctor should establish a
135 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
136 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

137 **Pregnancy**

138 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may
139 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or
140 are nursing a baby, talk to your doctor.

141 **Medication**

142 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
143 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
144 requirements may be reduced in the presence of drugs that lower blood glucose or affect how
145 your body responds to insulin, such as oral antidiabetic agents, salicylates (for example, aspirin),
146 sulfa antibiotics, alcohol, certain antidepressants and some kidney and blood pressure medicines.
147 Your Health Care Professional may be aware of other medications that may affect your diabetes
148 control. Therefore, always discuss any medications you are taking with your doctor.

149 **Exercise**

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

155 **Travel**

156 When traveling across more than 2 time zones, you should talk to your doctor concerning
157 adjustments in your insulin schedule.

158 **COMMON PROBLEMS OF DIABETES**

159 **Hypoglycemia (Low Blood Sugar)**

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

- 162 1. **Missing or delaying meals.**
- 163 2. Taking too much insulin.
- 164 3. Exercising or working more than usual.
- 165 4. An infection or illness associated with diarrhea or vomiting.
- 166 5. A change in the body's need for insulin.
- 167 6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver
168 disease.
- 169 7. Interactions with certain drugs, such as oral antidiabetic agents, salicylates (for example,
170 aspirin), sulfa antibiotics, certain antidepressants and some kidney and blood pressure
171 medicines.
- 172 8. Consumption of alcoholic beverages.

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

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| 174 • sweating | • drowsiness |
| 175 • dizziness | • sleep disturbances |
| 176 • palpitation | • anxiety |
| 177 • tremor | • blurred vision |
| 178 • hunger | • slurred speech |
| 179 • restlessness | • depressed mood |
| 180 • tingling in the hands, feet, lips, or tongue | • irritability |
| 181 • lightheadedness | • abnormal behavior |
| 182 • inability to concentrate | • unsteady movement |
| 183 • headache | • personality changes |

184 Signs of severe hypoglycemia can include:

- | | |
|-----------------------|------------|
| 185 • disorientation | • seizures |
| 186 • unconsciousness | • death |

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

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

192 **A few patients who have experienced hypoglycemic reactions after transfer from animal-**
193 **source insulin to human insulin have reported that the early warning symptoms of**
194 **hypoglycemia were less pronounced or different from those experienced with their**
195 **previous insulin.**

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

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

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

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

213 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

214 Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.
215 Hyperglycemia can be brought about by any of the following:

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

219 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in
220 DKA (a life-threatening emergency). The first symptoms of DKA usually come on gradually,
221 over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite,
222 and fruity odor on the breath. With DKA, blood and urine tests show large amounts of glucose
223 and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected,
224 prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach pain, dehydration, loss
225 of consciousness, or death. Therefore, it is important that you obtain medical assistance
226 immediately.

227 **Lipodystrophy**

228 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
229 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
230 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
231 the problem.

232 **Allergy**

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

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

242 **ADDITIONAL INFORMATION**

243 Information about diabetes may be obtained from your diabetes educator.

244 Additional information about diabetes and Humulin can be obtained by calling The Lilly
245 Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

246 Patient Information revised Month dd, yyyy

247 **Pens manufactured by**

248 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
249 **Lilly France, F-67640 Fegersheim, France**

250 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**

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HUMALOG[®]

INSULIN LISPRO INJECTION, USP (rDNA ORIGIN)

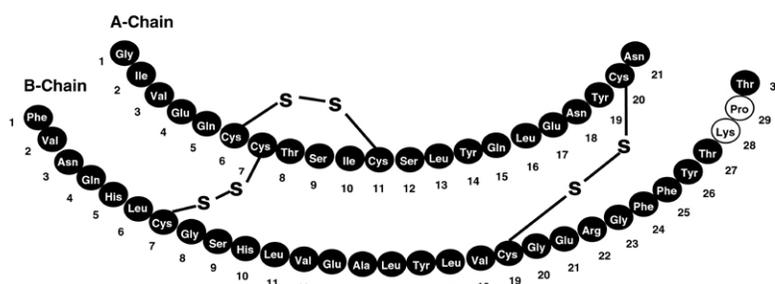
100 UNITS PER ML (U-100)

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DESCRIPTION

Humalog[®] [insulin lispro injection, USP (rDNA origin)] is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. Chemically, it is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Humalog is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce insulin lispro.

Humalog has the following primary structure:



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Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

The vials, cartridges, and Pens contain a sterile solution of Humalog for use as an injection. Humalog injection consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid.

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Each milliliter of Humalog injection contains insulin lispro 100 units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg Metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and Water for Injection. Insulin lispro has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

22

CLINICAL PHARMACOLOGY

23

Antidiabetic Activity

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The primary activity of insulin, including Humalog, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

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Humalog has been shown to be equipotent to human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of shorter duration. The glucose-lowering activity of Humalog and Regular human insulin is comparable when administered to nondiabetic subjects by the intravenous route.

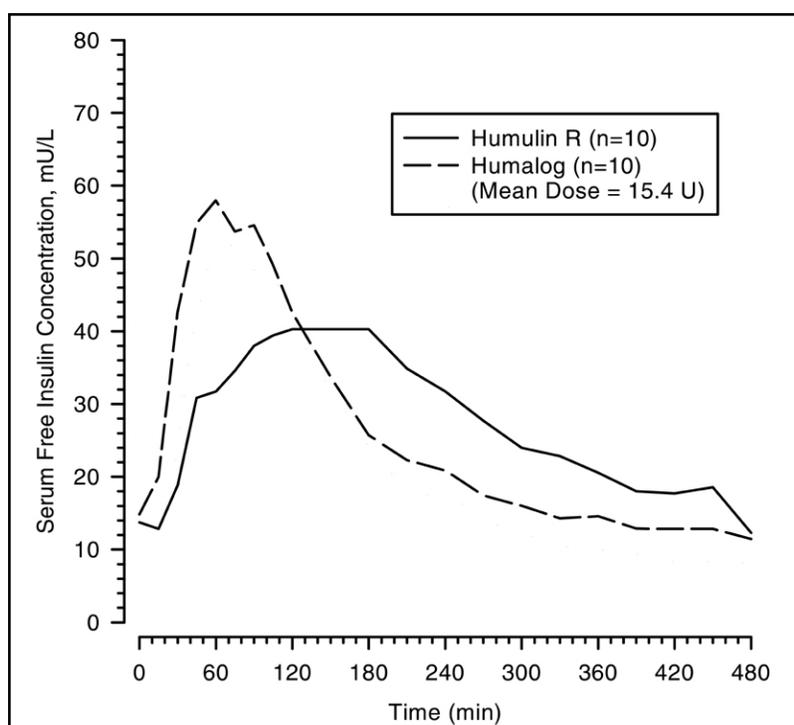
35

Pharmacokinetics

36
37

Absorption and Bioavailability — Humalog is as bioavailable as Regular human insulin, with absolute bioavailability ranging between 55% to 77% with doses between 0.1 to 0.2 U/kg,

38 inclusive. Studies in nondiabetic subjects and patients with type 1 (insulin-dependent) diabetes
 39 demonstrated that Humalog is absorbed faster than Regular human insulin (U-100) (*see* Figure
 40 1). In nondiabetic subjects given subcutaneous doses of Humalog ranging from 0.1 to 0.4 U/kg,
 41 peak serum concentrations were observed 30 to 90 minutes after dosing. When nondiabetic
 42 subjects received equivalent doses of Regular human insulin, peak insulin concentrations
 43 occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type
 44 1 diabetes. The pharmacokinetic profiles of Humalog and Regular human insulin are comparable
 45 to one another when administered to nondiabetic subjects by the intravenous route. Humalog was
 46 absorbed at a consistently faster rate than Regular human insulin in healthy male volunteers
 47 given 0.2 U/kg Regular human insulin or Humalog at abdominal, deltoid, or femoral
 48 subcutaneous sites, the three sites often used by patients with diabetes. After abdominal
 49 administration of Humalog, serum drug levels are higher and the duration of action is slightly
 50 shorter than after deltoid or thigh administration (*see* DOSAGE AND ADMINISTRATION).
 51 Humalog has less intra- and inter-patient variability compared with Regular human insulin.



52 **Figure 1: Serum Humalog and Insulin Levels After Subcutaneous Injection of Regular**
 53 **Human Insulin or Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in**
 54 **10 Patients with Type 1 Diabetes. ***

55 * Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.
 56

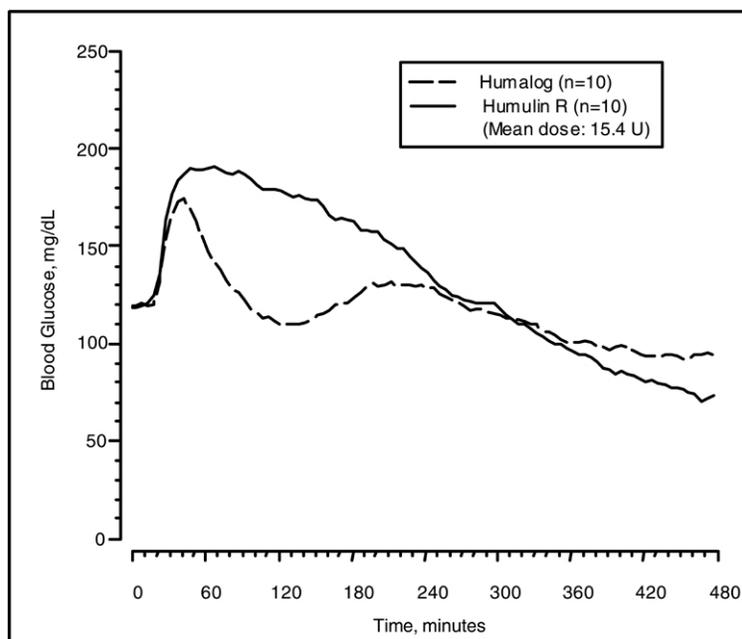
57 *Distribution* — The volume of distribution following injection of Humalog is identical to that
 58 of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

59 *Metabolism* — Human metabolism studies have not been conducted. However, animal studies
 60 indicate that the metabolism of Humalog is identical to that of Regular human insulin.

61 *Elimination* — When Humalog is given subcutaneously, its $t_{1/2}$ is shorter than that of Regular
 62 human insulin (1 versus 1.5 hours, respectively). When given intravenously, Humalog and
 63 Regular human insulin show identical dose-dependent elimination, with a $t_{1/2}$ of 26 and 52
 64 minutes at 0.1 U/kg and 0.2 U/kg, respectively.

65 Pharmacodynamics

66 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
 67 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
 68 duration of glucose-lowering activity than Regular human insulin (*see* Figure 2). The earlier
 69 onset of activity of Humalog is directly related to its more rapid rate of absorption. The time
 70 course of action of insulin and insulin analogs, such as Humalog, may vary considerably in
 71 different individuals or within the same individual. The parameters of Humalog activity (time of
 72 onset, peak time, and duration) as presented in Figure 2 should be considered only as general
 73 guidelines. The rate of insulin absorption and consequently the onset of activity is known to be
 74 affected by the site of injection, exercise, and other variables (*see* General *under*
 75 PRECAUTIONS).



76 **Figure 2: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or**
 77 **Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with**
 78 **Type 1 Diabetes. ***

79 * Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

80 Special Populations

81 *Age and Gender* — Information on the effect of age and gender on the pharmacokinetics of
 82 Humalog is unavailable. However, in large clinical trials, sub-group analysis based on age and
 83 gender did not indicate any difference in postprandial glucose parameters between Humalog and
 84 Regular human insulin.

85 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of
 86 Humalog has not been studied.

87 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of
 88 Humalog has not been studied.

89 *Obesity* — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics
 90 and pharmacodynamics of Humalog has not been studied. In large clinical trials, which included
 91 patients with Body Mass Index up to and including 35 kg/m², no consistent differences were
 92 observed between Humalog and Humulin[®] R with respect to postprandial glucose parameters.

93 *Renal Impairment* — Some studies with human insulin have shown increased circulating levels
 94 of insulin in patients with renal failure. In a study of 25 patients with type 2 diabetes and a wide
 95 range of renal function, the pharmacokinetic differences between Humalog and Regular human

96 insulin were generally maintained. However, the sensitivity of the patients to insulin did change,
 97 with an increased response to insulin as the renal function declined. Careful glucose monitoring
 98 and dose reductions of insulin, including Humalog, may be necessary in patients with renal
 99 dysfunction.

100 *Hepatic Impairment* — Some studies with human insulin have shown increased circulating
 101 levels of insulin in patients with hepatic failure. In a study of 22 patients with type 2 diabetes,
 102 impaired hepatic function did not affect the subcutaneous absorption or general disposition of
 103 Humalog when compared with patients with no history of hepatic dysfunction. In that study,
 104 Humalog maintained its more rapid absorption and elimination when compared with Regular
 105 human insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog,
 106 may be necessary in patients with hepatic dysfunction.

107 CLINICAL STUDIES

108 In open-label, cross-over studies of 1008 patients with type 1 diabetes and 722 patients with
 109 type 2 (non-insulin-dependent) diabetes, Humalog reduced postprandial glucose compared with
 110 Regular human insulin (*see* Table 1). The clinical significance of improvement in postprandial
 111 hyperglycemia has not been established.

112 **Table 1: Comparison of Means of Glycemic Parameters at the End of Combined**
 113 **Treatment Periods. All Randomized Patients in Cross-Over Studies (3 Months for Each**
 114 **Treatment)**
 115

Type 1, N=1008		
Glycemic Parameter, (mg/dL)	Humalog ^a	Humulin R ^{a*}
Fasting Blood Glucose	209.5 ± 91.6	204.1 ± 89.3
1-Hour Postprandial	232.4 ± 97.7	250.0 ± 96.7
2-Hour Postprandial	200.9 ± 95.4	231.7 ± 103.9
HbA _{1c} (%)	8.2 ± 1.5	8.2 ± 1.5
Type 2, N=722		
Glycemic Parameter, (mg/dL)	Humalog ^a	Humulin R ^a
Fasting Blood Glucose	192.1 ± 67.9	183.1 ± 66.1
1-Hour Postprandial	238.1 ± 79.7	250.0 ± 75.2
2-Hour Postprandial	217.4 ± 83.2	236.5 ± 80.6
HbA _{1c} (%)	8.2 ± 1.3	8.2 ± 1.4

116 ^a Mean ± Standard Deviation.

117 * REGULAR insulin human injection, USP (rDNA origin).

118
 119 In 12-month parallel studies in patients with type 1 and type 2 diabetes, HbA_{1c} did not differ
 120 between patients treated with Regular human insulin and those treated with Humalog.

121 *Hypoglycemia* — While the overall rate of hypoglycemia did not differ between patients with
 122 type 1 and type 2 diabetes treated with Humalog compared with Regular human insulin, patients
 123 with type 1 diabetes treated with Humalog had fewer hypoglycemic episodes between midnight
 124 and 6 a.m. The lower rate of hypoglycemia in the Humalog-treated group may have been related
 125 to higher nocturnal blood glucose levels, as reflected by a small increase in mean fasting blood
 126 glucose levels.

127 *Humalog in Combination with Sulfonylurea Agents* — In a two-month study in patients with
 128 fasting hyperglycemia despite maximal dosing with sulfonylureas (SU), patients were
 129 randomized to one of three treatment regimens; Humulin[®] NPH at bedtime plus SU, Humalog
 130 three times a day before meals plus SU, or Humalog three times a day before meals and Humulin
 131 NPH at bedtime. The combination of Humalog and SU resulted in an improvement in HbA_{1c}
 132 accompanied by a weight gain (*see* Table 2).

133
134
135**Table 2: Results of a Two-Month Study in Which Humalog Was Added to Sulfonylurea Therapy in Patients Not Adequately Controlled on Sulfonylurea Alone**

	Humulin N h.s. + SU ^a	Humalog a.c. + SU	Humalog a.c. + Humulin N h.s.
Randomized (n)	135	139	149
HbA _{1c} (%) at baseline	9.9	10.0	10.0
HbA _{1c} (%) at 2-months	8.7	8.4	8.5
HbA _{1c} (%) change from baseline	-1.2	-1.6	-1.4
Weight gain at 2-months (kg)	0.6	1.2	1.5
Hypoglycemia* (events/mo)	0.11	0.03	0.09
Number of injections	1	3	4
Total insulin dose (U/kg) at 2-months	0.23	0.33	0.52

136
137
138^a a.c.-three times a day before meals. h.s.-at bedtime. SU-oral sulfonylurea agent.

* blood glucose ≤36 mg/dL or needing assistance from third party.

139 *Humalog in External Insulin Pumps* — To evaluate the administration of Humalog via external
140 insulin pumps, two open-label cross-over design studies were performed in patients with type 1
141 diabetes. One study involved 39 patients treated for 24 weeks with Humalog or Regular human
142 insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.8% to 7.2% in the
143 Humalog-treated patients and from 7.8% to 7.5% in the Regular human insulin-treated patients.
144 Another study involved 60 patients treated for 24 weeks with either Humalog or Regular human
145 insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.7% to 7.4% in the
146 Humalog-treated patients and remained unchanged from 7.7% in the Regular human insulin-
147 treated patients. Rates of hypoglycemia were comparable between treatment groups in both
148 studies. Humalog administration in insulin pumps has not been studied in patients with type 2
149 diabetes.

150

INDICATIONS AND USAGE

151 Humalog is an insulin analog that is indicated in the treatment of patients with diabetes
152 mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration
153 of action than Regular human insulin. Therefore, in patients with type 1 diabetes, Humalog
154 should be used in regimens that include a longer-acting insulin. However, in patients with type 2
155 diabetes, Humalog may be used without a longer-acting insulin when used in combination
156 therapy with sulfonylurea agents.

157 Humalog may be used in an external insulin pump, but should not be diluted or mixed with any
158 other insulin when used in the pump.

159

CONTRAINDICATIONS

160 Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to
161 Humalog or any of its excipients.

162

WARNINGS

163 **This human insulin analog differs from Regular human insulin by its rapid onset of**
164 **action as well as a shorter duration of activity. When used as a meal-time insulin, the dose**
165 **of Humalog should be given within 15 minutes before or immediately after the meal.**
166 **Because of the short duration of action of Humalog, patients with type 1 diabetes also**
167 **require a longer-acting insulin to maintain glucose control (except when using an external**
168 **insulin pump). Glucose monitoring is recommended for all patients with diabetes and is**
169 **particularly important for patients using an external insulin pump.**

170 **Hypoglycemia is the most common adverse effect associated with insulins, including**
171 **Humalog. As with all insulins, the timing of hypoglycemia may differ among various**
172 **insulin formulations. Glucose monitoring is recommended for all patients with diabetes.**

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

176 **External Insulin Pumps: When used in an external insulin pump, Humalog should not be**
177 **diluted or mixed with any other insulin. Patients should carefully read and follow the**
178 **external insulin pump manufacturer's instructions and the Patient Information leaflet**
179 **before using Humalog.**

180 Physicians should carefully evaluate information on external insulin pump use in this Humalog
181 physician package insert and in the external insulin pump manufacturer's instructions. If
182 unexplained hyperglycemia or ketosis occurs during external insulin pump use, prompt
183 identification and correction of the cause is necessary. The patient may require interim therapy
184 with subcutaneous insulin injections (*see PRECAUTIONS, For Patients Using External Insulin*
185 *Pumps, and DOSAGE AND ADMINISTRATION*).

186

PRECAUTIONS

187 **General**

188 Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated
189 with the use of all insulins. Because of differences in the action of Humalog and other insulins,
190 care should be taken in patients in whom such potential side effects might be clinically relevant
191 (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering
192 drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and
193 hypersensitivity are among other potential clinical adverse effects associated with the use of all
194 insulins.

195 As with all insulin preparations, the time course of Humalog action may vary in different
196 individuals or at different times in the same individual and is dependent on site of injection,
197 blood supply, temperature, and physical activity.

198 Adjustment of dosage of any insulin may be necessary if patients change their physical activity
199 or their usual meal plan. Insulin requirements may be altered during illness, emotional
200 disturbances, or other stress.

201 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated
202 with the administration of Humalog. Rapid changes in serum glucose concentrations may induce
203 symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early
204 warning symptoms of hypoglycemia may be different or less pronounced under certain
205 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as
206 beta-blockers, or intensified diabetes control.

207 **Renal Impairment** — The requirements for insulin may be reduced in patients with renal
208 impairment.

209 **Hepatic Impairment** — Although impaired hepatic function does not affect the absorption or
210 disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including
211 Humalog, may be necessary.

212 **Allergy** — Local Allergy — As with any insulin therapy, patients may experience redness,
213 swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to
214 a few weeks. In some instances, these reactions may be related to factors other than insulin, such
215 as irritants in the skin cleansing agent or poor injection technique.

216 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to
217 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,
218 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized

219 allergy, including anaphylactic reaction, may be life threatening. In controlled clinical trials,
 220 pruritus (with or without rash) was seen in 17 patients receiving Humulin R (N=2969) and 30
 221 patients receiving Humalog (N=2944) (p=0.053). Localized reactions and generalized myalgias
 222 have been reported with the use of cresol as an injectable excipient.

223 **Antibody Production** — In large clinical trials, antibodies that cross-react with human insulin
 224 and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As
 225 expected, the largest increase in the antibody levels during the 12-month clinical trials was
 226 observed with patients new to insulin therapy.

227 **Use in External Insulin Pumps** — **The infusion set (reservoir syringe, tubing, and**
 228 **catheter), Disetronic® D-TRON®^{2,3} or D-TRON®^{2,3} plus cartridge adapter, and Humalog**
 229 **in the external insulin pump reservoir should be replaced and a new infusion site selected**
 230 **every 48 hours or less. Humalog in the external insulin pump should not be exposed to**
 231 **temperatures above 37°C (98.6°F).**

232 In the D-TRON®^{2,3} or D-TRON®^{2,3} plus pump, Humalog 3 mL cartridges may be used for up
 233 to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and
 234 a new infusion site should be selected every 48 hours or less.

235 When used in an external insulin pump, Humalog should not be diluted or mixed with any
 236 other insulin (*see* INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, *For Patients*
 237 *Using External Insulin Pumps, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and*
 238 *Storage*).

239 **Information for Patients**

240 Patients should be informed of the potential risks and advantages of Humalog and alternative
 241 therapies. Patients should also be informed about the importance of proper insulin storage,
 242 injection technique, timing of dosage, adherence to meal planning, regular physical activity,
 243 regular blood glucose monitoring, periodic hemoglobin A_{1c} testing, recognition and management
 244 of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

245 Patients should be advised to inform their physician if they are pregnant or intend to become
 246 pregnant.

247 Refer patients to the Patient Information leaflet for timing of Humalog dosing (≤15 minutes
 248 before or immediately after a meal), storing insulin, and common adverse effects.

249 *For Patients Using Insulin Pen Delivery Devices:* Before starting therapy, patients should read
 250 the Patient Information leaflet that accompanies the drug product and the User Manual that
 251 accompanies the delivery device and re-read them each time the prescription is renewed. Patients
 252 should be instructed on how to properly use the delivery device, prime the Pen to a stream of
 253 insulin, and properly dispose of needles. Patients should be advised not to share their Pens with
 254 others.

255 *For Patients Using External Insulin Pumps:* Patients using an external infusion pump should
 256 be trained in intensive insulin therapy and in the function of their external insulin pump and
 257 pump accessories. Humalog was tested in the MiniMed®¹ Models 506, 507, and 508 insulin
 258 pumps using MiniMed®¹ Polyfin®¹ infusion sets. Humalog was also tested in Disetronic®² H-
 259 TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), and the Disetronic D-
 260 TRON®^{2,3} and D-TRON®^{2,3} plus insulin pumps (with Humalog 3 mL cartridges) using
 261 Disetronic Rapid®² infusion sets.

262 **The infusion set (reservoir syringe, tubing, catheter), D-TRON®^{2,3} or D-TRON®^{2,3} plus**
 263 **cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced,**
 264 **and a new infusion site selected every 48 hours or less. Humalog in the external pump**
 265 **should not be exposed to temperatures above 37°C (98.6°F).** A Humalog 3 mL cartridge used
 266 in the D-TRON®^{2,3} or D-TRON®^{2,3} plus pump should be discarded after 7 days, even if it still

267 contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported
268 to medical personnel, and a new site selected.

269 **Humalog should not be diluted or mixed with any other insulin when used in an external**
270 **insulin pump.**

271 **Laboratory Tests**

272 As with all insulins, the therapeutic response to Humalog should be monitored by periodic
273 blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the
274 monitoring of long-term glycemic control.

275 **Drug Interactions**

276 Insulin requirements may be increased by medications with hyperglycemic activity such as
277 corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral
278 contraceptives, phenothiazines, and thyroid replacement therapy (*see* CLINICAL
279 PHARMACOLOGY).

280 Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity
281 or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics,
282 certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme
283 inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of
284 pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the
285 symptoms of hypoglycemia in some patients.

286 **Mixing of Insulins** — Care should be taken when mixing all insulins as a change in peak
287 action may occur. The American Diabetes Association warns in its Position Statement on Insulin
288 Administration, “On mixing, physiochemical changes in the mixture may occur (either
289 immediately or over time). As a result, the physiological response to the insulin mixture may
290 differ from that of the injection of the insulins separately.” Mixing Humalog with Humulin N or
291 Humulin[®] U does not decrease the absorption rate or the total bioavailability of Humalog. Given
292 alone or mixed with Humulin N, Humalog results in a more rapid absorption and
293 glucose-lowering effect compared with Regular human insulin.

294 The effects of mixing Humalog with insulins of animal source or insulin preparations produced
295 by other manufacturers have not been studied (*see* WARNINGS).

296 If Humalog is mixed with a longer-acting insulin, such as Humulin N or Humulin U, Humalog
297 should be drawn into the syringe first to prevent clouding of the Humalog by the longer-acting
298 insulin. Injection should be made immediately after mixing. Mixtures should not be administered
299 intravenously.

300 The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the
301 cartridge, for the Humalog in the cartridge to be diluted or for the cartridge to be refilled with
302 insulin. Humalog should not be diluted or mixed with any other insulin when used in an external
303 insulin pump.

304 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

305 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
306 Humalog, Humalog Mix75/25, or Humalog Mix50/50. Insulin lispro was not mutagenic in a
307 battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA
308 synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test).
309 There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

310 **Pregnancy**

311 **Teratogenic Effects** — **Pregnancy Category B** — Reproduction studies have been performed in
312 pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average
313 human dose (40 units/day) based on body surface area. The results have revealed no evidence of
314 impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and

315 well-controlled studies with Humalog, Humalog Mix75/25, or Humalog Mix50/50 in pregnant
 316 women. Because animal reproduction studies are not always predictive of human response, this
 317 drug should be used during pregnancy only if clearly needed.

318 Although there are limited clinical studies of the use of Humalog in pregnancy, published
 319 studies with human insulins suggest that optimizing overall glycemic control, including
 320 postprandial control, before conception and during pregnancy improves fetal outcome. Although
 321 the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also
 322 has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first
 323 trimester and increase during the second and third trimesters. Careful monitoring of the patient is
 324 required throughout pregnancy. During the perinatal period, careful monitoring of infants born to
 325 mothers with diabetes is warranted.

326 **Nursing Mothers**

327 It is unknown whether Humalog is excreted in significant amounts in human milk. Many
 328 drugs, including human insulin, are excreted in human milk. For this reason, caution should be
 329 exercised when Humalog is administered to a nursing woman. Patients with diabetes who are
 330 lactating may require adjustments in Humalog dose, meal plan, or both.

331 **Pediatric Use**

332 In a 9-month, cross-over study of pre-pubescent children (n=60), aged 3 to 11 years,
 333 comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group:
 334 Regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%,
 335 and Humalog immediately after meals 8.5%. In an 8-month, cross-over study of adolescents
 336 (n=463), aged 9 to 19 years, comparable glycemic control as measured by HbA_{1c} was achieved
 337 regardless of treatment group: Regular human insulin 30 to 45 minutes before meals 8.7% and
 338 Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all
 339 three treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in
 340 dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the
 341 Humalog vial, the shelf-life may be reduced (*see* DOSAGE AND ADMINISTRATION).

342 **Geriatric Use**

343 Of the total number of subjects (n=2834) in eight clinical studies of Humalog, twelve percent
 344 (n=338) were 65 years of age or over. The majority of these were patients with type 2 diabetes.
 345 HbA_{1c} values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic
 346 studies to assess the effect of age on the onset of Humalog action have not been performed.

347 **ADVERSE REACTIONS**

348 Clinical studies comparing Humalog with Regular human insulin did not demonstrate a
 349 difference in frequency of adverse events between the two treatments.

350 Adverse events commonly associated with human insulin therapy include the following:

351 **Body as a Whole** — allergic reactions (*see* PRECAUTIONS).

352 **Skin and Appendages** — injection site reaction, lipodystrophy, pruritus, rash.

353 **Other** — hypoglycemia (*see* WARNINGS and PRECAUTIONS).

354 **OVERDOSAGE**

355 Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy
 356 expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose.
 357 Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes
 358 with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous
 359 glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation
 360 may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

361
362 Humalog is intended for subcutaneous administration, including use in select external insulin
363 pumps (*see* DOSAGE AND ADMINISTRATION, *External Insulin Pumps*). Dosage regimens of
364 Humalog will vary among patients and should be determined by the healthcare provider familiar
365 with the patient's metabolic needs, eating habits, and other lifestyle variables. Pharmacokinetic
366 and pharmacodynamic studies showed Humalog to be equipotent to Regular human insulin (i.e.,
367 one unit of Humalog has the same glucose-lowering effect as one unit of Regular human insulin),
368 but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the
369 more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal
370 insulin may be needed when a patient changes from other insulins to Humalog, particularly to
371 prevent pre-meal hyperglycemia.

372 When used as a meal-time insulin, Humalog should be given within 15 minutes before or
373 immediately after a meal. Regular human insulin is best given 30 to 60 minutes before a meal.
374 To achieve optimal glucose control, the amount of longer-acting insulin being given may need to
375 be adjusted when using Humalog.

376 The rate of insulin absorption and consequently the onset of activity are known to be affected
377 by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently
378 faster rate than Regular human insulin in healthy male volunteers given 0.2 U/kg Regular human
379 insulin or Humalog at abdominal, deltoid, or femoral sites, the three sites often used by patients
380 with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its
381 rapid onset of action and has less variability in its onset of action among injection sites compared
382 with Regular human insulin (*see* PRECAUTIONS). After abdominal administration, Humalog
383 concentrations are higher than those following deltoid or thigh injections. Also, the duration of
384 action of Humalog is slightly shorter following abdominal injection, compared with deltoid and
385 femoral injections. As with all insulin preparations, the time course of action of Humalog may
386 vary considerably in different individuals or within the same individual. Patients must be
387 educated to use proper injection techniques.

388 Humalog in a vial may be diluted with STERILE DILUENT for Humalog[®], Humulin[®] N,
389 Humulin[®] R, Humulin[®] 70/30, and Humulin[®] R U-500 to a concentration of 1:10 (equivalent to
390 U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when
391 stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog
392 contained in a cartridge or Humalog used in an external insulin pump.

393 Parenteral drug products should be inspected visually before use whenever the solution and the
394 container permit. If the solution is cloudy, contains particulate matter, is thickened, or is
395 discolored, the contents must not be injected. Humalog should not be used after its expiration
396 date.

397 The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the
398 cartridge or for the cartridge to be refilled with insulin.

399 *External Insulin Pumps* — Humalog was tested in MiniMed^{®1} Models 506, 507, and 508
400 insulin pumps using MiniMed^{®1} Polyfin^{®1} infusion sets. Humalog was also tested in the
401 Disetronic^{®2} H-TRONplus[®] V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the
402 Disetronic D-TRON^{®2,3} and D-TRON^{®2,3}plus pumps (with Humalog 3 mL cartridges) using
403 Disetronic Rapid^{®2} infusion sets.

404 Humalog should not be diluted or mixed with any other insulin when used in an external
405 insulin pump.

HOW SUPPLIED

406 Humalog [insulin lispro injection, USP (rDNA origin)] is available in the following package
407 sizes: each presentation containing 100 units insulin lispro per mL (U-100).
408
409

10 mL vials	NDC 0002-7510-01 (VL-7510)
5 x 3 mL cartridges ³	NDC 0002-7516-59 (VL-7516)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8725-59 (HP-8725)
5 x 3 mL prefilled insulin delivery devices (KwikPen™)	NDC 0002-8799-59 (HP-8799)

410

411

412

413 1 MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

414 2 Disetronic®, H-TRONplus®, D-TRON®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.

415 3 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD
416 insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3 mL insulin delivery device and Disetronic D-

417 TRON® and D-TRON®plus pumps. Autopen® is a registered trademark of Owen Mumford, Ltd. HumaPen®,

418 HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD are trademarks of Eli Lilly and Company.

419 Other product and company names may be the trademarks of their respective owners.

420

421 *Storage* — Unopened Humalog should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but

422 not in the freezer. Do not use Humalog if it has been frozen. Unrefrigerated [below 30°C (86°F)]

423 vials, cartridges, Pens, and KwikPens must be used within 28 days or be discarded, even if they

424 still contain Humalog. Protect from direct heat and light. See table below:

425

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Cartridge	28 days	Until expiration date	28 days, Do not refrigerate.
3 mL Pen and KwikPen (prefilled)	28 days	Until expiration date	28 days, Do not refrigerate.

426

427 *Use in an External Insulin Pump* — A Humalog 3 mL cartridge used in the D-TRON®^{2,3} or D-428 TRON®^{2,3}plus should be discarded after 7 days, even if it still contains Humalog. Infusion sets,429 D-TRON®^{2,3} and D-TRON®^{2,3}plus cartridge adapters, and Humalog in the external insulin

430 pump reservoir should be discarded every 48 hours or less.

431 Literature revised Month dd, yyyy

432 KwikPens manufactured by
433 Eli Lilly and Company, Indianapolis, IN 46285, USA
434 Pens manufactured by
435 Eli Lilly and Company, Indianapolis, IN 46285, USA or
436 Lilly France, F-67640 Fegersheim, France
437 Vials manufactured by
438 Eli Lilly and Company, Indianapolis, IN 46285, USA or
439 Hospira, Inc., Lake Forest, IL 60045, USA or
440 Lilly France, F-67640 Fegersheim, France
441 Cartridges manufactured by
442 Lilly France, F-67640 Fegersheim, France
443
444 for Eli Lilly and Company, Indianapolis, IN 46285, USA
445

446 www.humalog.com

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HUMALOG[®] Mix75/25[™]

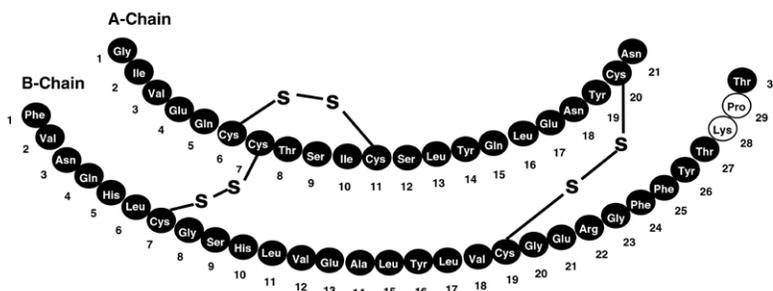
75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN) 100 UNITS PER ML (U-100)

7
8

DESCRIPTION

9 Humalog[®] Mix75/25[™] [75% insulin lispro protamine suspension and 25% insulin lispro
10 injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-
11 lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-
12 lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created
13 when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is
14 synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has
15 been genetically altered to produce insulin lispro. Insulin lispro protamine suspension (NPL
16 component) is a suspension of crystals produced from combining insulin lispro and protamine
17 sulfate under appropriate conditions for crystal formation.

18 Insulin lispro has the following primary structure:



19 Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808,
20 both identical to that of human insulin.

21 Humalog Mix75/25 vials and Pens contain a sterile suspension of insulin lispro protamine
22 suspension mixed with soluble insulin lispro for use as an injection.

23 Each milliliter of Humalog Mix75/25 injection contains insulin lispro 100 units, 0.28 mg
24 protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg Metacresol, zinc
25 oxide content adjusted to provide 0.025 mg zinc ion, 0.715 mg phenol, and Water for Injection.
26 Humalog Mix75/25 has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10%
27 may have been added to adjust pH.

28

CLINICAL PHARMACOLOGY

29

Antidiabetic Activity

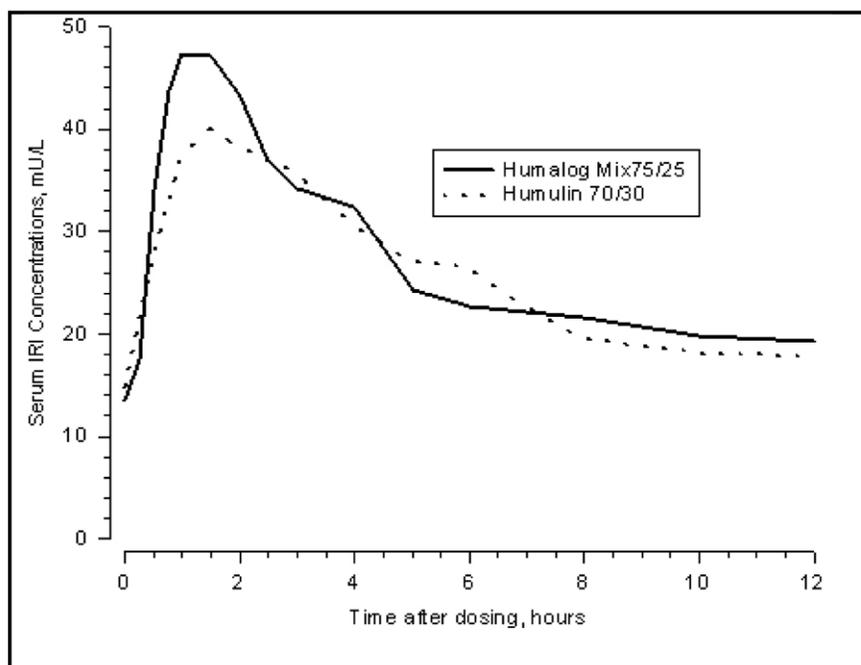
30 The primary activity of insulin, including Humalog Mix75/25, is the regulation of glucose
31 metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many
32 tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport
33 of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism.
34 In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits
35 gluconeogenesis, and promotes the conversion of excess glucose into fat.

36 Insulin lispro, the rapid-acting component of Humalog Mix75/25, has been shown to be
37 equipotent to Regular human insulin on a molar basis. One unit of Humalog[®] has the same

38 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
 39 shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared with
 40 Humulin® 70/30 on a unit for unit basis.

41 **Pharmacokinetics**

42 *Absorption* — Studies in nondiabetic subjects and patients with type 1 (insulin-dependent)
 43 diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix75/25, is
 44 absorbed faster than Regular human insulin (U-100). In nondiabetic subjects given subcutaneous
 45 doses of Humalog ranging from 0.1 to 0.4 U/kg, peak serum concentrations were observed 30 to
 46 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human
 47 insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar
 48 results were seen in patients with type 1 diabetes.



49 **Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous**
 50 **Injection of Humalog Mix75/25 or Humulin 70/30 in Healthy Nondiabetic Subjects.**

51 Humalog Mix75/25 has two phases of absorption. The early phase represents insulin lispro and
 52 its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin
 53 lispro protamine suspension. In 30 healthy nondiabetic subjects given subcutaneous doses
 54 (0.3 U/kg) of Humalog Mix75/25, peak serum concentrations were observed 30 to 240 minutes
 55 (median, 60 minutes) after dosing (*see* Figure 1). Identical results were found in patients with
 56 type 1 diabetes. The rapid absorption characteristics of Humalog are maintained with Humalog
 57 Mix75/25 (*see* Figure 1).

58 Figure 1 represents serum insulin concentration versus time curves of Humalog Mix75/25 and
 59 Humulin 70/30. Humalog Mix75/25 has a more rapid absorption than Humulin 70/30, which has
 60 been confirmed in patients with type 1 diabetes.

61 *Distribution* — Radiolabeled distribution studies of Humalog Mix75/25 have not been
 62 conducted. However, the volume of distribution following injection of Humalog is identical to
 63 that of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

64 *Metabolism* — Human metabolism studies of Humalog Mix75/25 have not been conducted.
 65 Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of
 66 Humalog Mix75/25, is identical to that of Regular human insulin.

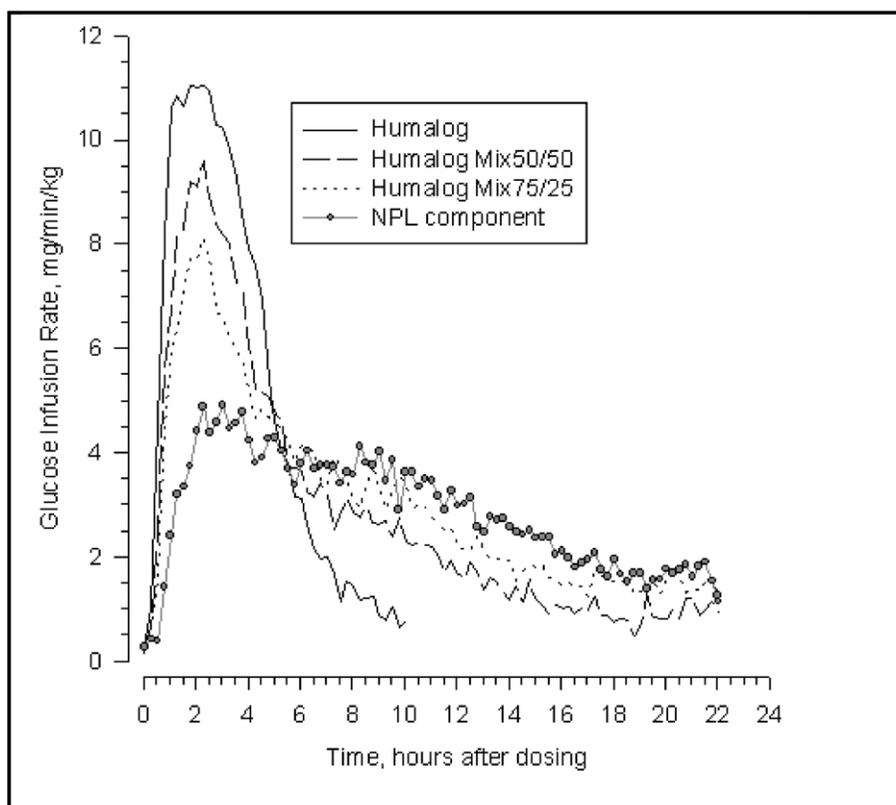
67 *Elimination* — Humalog Mix75/25 has two absorption phases, a rapid and a prolonged phase,
68 representative of the insulin lispro and insulin lispro protamine suspension components of the
69 mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot
70 be calculated after administration of Humalog Mix75/25 because of the prolonged insulin lispro
71 protamine suspension absorption.

72 **Pharmacodynamics**

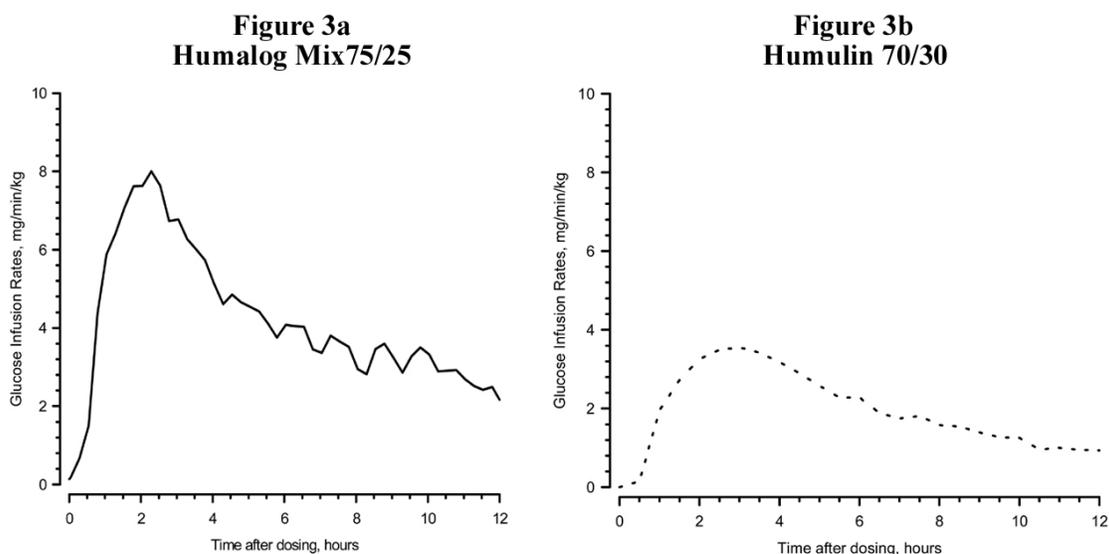
73 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
74 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
75 duration of glucose-lowering activity than Regular human insulin. The early onset of activity of
76 Humalog Mix75/25 is directly related to the rapid absorption of Humalog. The time course of
77 action of insulin and insulin analogs, such as Humalog (and hence Humalog Mix75/25), may
78 vary considerably in different individuals or within the same individual. The parameters of
79 Humalog Mix75/25 activity (time of onset, peak time, and duration) as presented in Figures 2
80 and 3 should be considered only as general guidelines. The rate of insulin absorption and
81 consequently the onset of activity is known to be affected by the site of injection, exercise, and
82 other variables (*see General under PRECAUTIONS*).

83 In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and glucose-
84 lowering activity of Humalog, Humalog[®] Mix50/50[™], Humalog Mix75/25, and insulin lispro
85 protamine suspension (NPL component) were compared (*see* Figure 2). Graphs of mean glucose
86 infusion rate versus time showed a distinct insulin activity profile for each formulation. The
87 rapid onset of glucose-lowering activity characteristic of Humalog was maintained in Humalog
88 Mix75/25.

89 In separate glucose clamp studies performed in nondiabetic subjects, pharmacodynamics of
90 Humalog Mix75/25 and Humulin 70/30 were assessed and are presented in Figure 3. Humalog
91 Mix75/25 has a duration of activity similar to that of Humulin 70/30.



92 **Figure 2: Insulin Activity After Injection of Humalog, Humalog Mix50/50, Humalog**
 93 **Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic**
 94 **Subjects.**
 95



96 **Figure 3: Insulin Activity After Injection of Humalog Mix75/25 and Humulin 70/30 in**
 97 **Nondiabetic Subjects.**

98 Figures 2 and 3 represent insulin activity profiles as measured by glucose clamp studies in
 99 healthy nondiabetic subjects.

100 Figure 2 shows the time activity profiles of Humalog, Humalog Mix50/50, Humalog
 101 Mix75/25, and insulin lispro protamine suspension (NPL component).

102 Figure 3 is a comparison of the time activity profiles of Humalog Mix75/25 (*see* Figure 3a) and
 103 of Humulin 70/30 (*see* Figure 3b) from two different studies.

104 Special Populations

105 *Age and Gender* — Information on the effect of age on the pharmacokinetics of Humalog
 106 Mix75/25 is unavailable. Pharmacokinetic and pharmacodynamic comparisons between men and
 107 women administered Humalog Mix75/25 showed no gender differences. In large Humalog
 108 clinical trials, sub-group analysis based on age and gender demonstrated that differences between
 109 Humalog and Regular human insulin in postprandial glucose parameters are maintained across
 110 sub-groups.

111 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of
 112 Humalog Mix75/25 has not been studied.

113 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of
 114 Humalog Mix75/25 has not been studied.

115 *Obesity* — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics
 116 and pharmacodynamics of Humalog Mix75/25 has not been studied. In large clinical trials,
 117 which included patients with Body Mass Index up to and including 35 kg/m², no consistent
 118 differences were observed between Humalog and Humulin[®] R with respect to postprandial
 119 glucose parameters.

120 *Renal Impairment* — The effect of renal impairment on the pharmacokinetics and
 121 pharmacodynamics of Humalog Mix75/25 has not been studied. In a study of 25 patients with
 122 type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between
 123 Humalog and Regular human insulin were generally maintained. However, the sensitivity of the

124 patients to insulin did change, with an increased response to insulin as the renal function
125 declined. Careful glucose monitoring and dose reductions of insulin, including Humalog
126 Mix75/25, may be necessary in patients with renal dysfunction.

127 *Hepatic Impairment* — Some studies with human insulin have shown increased circulating
128 levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the
129 pharmacokinetics and pharmacodynamics of Humalog Mix75/25 has not been studied. However,
130 in a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the
131 subcutaneous absorption or general disposition of Humalog when compared with patients with
132 no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption
133 and elimination when compared with Regular human insulin. Careful glucose monitoring and
134 dose adjustments of insulin, including Humalog Mix75/25, may be necessary in patients with
135 hepatic dysfunction.

136 **INDICATIONS AND USAGE**

137 Humalog Mix75/25, a mixture of 75% insulin lispro protamine suspension and 25% insulin
138 lispro injection, (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for
139 the control of hyperglycemia. Humalog Mix75/25 has a more rapid onset of glucose-lowering
140 activity compared with Humulin 70/30 while having a similar duration of action. This profile is
141 achieved by combining the rapid onset of Humalog with the intermediate action of insulin lispro
142 protamine suspension.

143 **CONTRAINDICATIONS**

144 Humalog Mix75/25 is contraindicated during episodes of hypoglycemia and in patients
145 sensitive to insulin lispro or any of the excipients contained in the formulation.

146 **WARNINGS**

147 **Humalog differs from Regular human insulin by its rapid onset of action as well as a**
148 **shorter duration of activity. Therefore, the dose of Humalog Mix75/25 should be given**
149 **within 15 minutes before a meal.**

150 **Hypoglycemia is the most common adverse effect associated with the use of insulins,**
151 **including Humalog Mix75/25. As with all insulins, the timing of hypoglycemia may differ**
152 **among various insulin formulations. Glucose monitoring is recommended for all patients**
153 **with diabetes.**

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

157 **PRECAUTIONS**

158 **General**

159 Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated
160 with the use of all insulins. Because of differences in the action of Humalog Mix75/25 and other
161 insulins, care should be taken in patients in whom such potential side effects might be clinically
162 relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-
163 lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and
164 hypersensitivity are among other potential clinical adverse effects associated with the use of all
165 insulins.

166 As with all insulin preparations, the time course of Humalog Mix75/25 action may vary in
167 different individuals or at different times in the same individual and is dependent on site of
168 injection, blood supply, temperature, and physical activity.

169 Adjustment of dosage of any insulin may be necessary if patients change their physical activity
170 or their usual meal plan. Insulin requirements may be altered during illness, emotional
171 disturbances, or other stress.

172 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated
173 with the administration of Humalog Mix75/25. Rapid changes in serum glucose concentrations
174 may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value.
175 Early warning symptoms of hypoglycemia may be different or less pronounced under certain
176 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as
177 beta-blockers, or intensified diabetes control.

178 **Renal Impairment** — As with other insulins, the requirements for Humalog Mix75/25 may be
179 reduced in patients with renal impairment.

180 **Hepatic Impairment** — Although impaired hepatic function does not affect the absorption or
181 disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including
182 Humalog Mix75/25, may be necessary.

183 **Allergy** — Local Allergy — As with any insulin therapy, patients may experience redness,
184 swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to
185 a few weeks. In some instances, these reactions may be related to factors other than insulin, such
186 as irritants in the skin cleansing agent or poor injection technique.

187 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to
188 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,
189 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized
190 allergy, including anaphylactic reaction, may be life threatening. Localized reactions and
191 generalized myalgias have been reported with the use of cresol as an injectable excipient.

192 Antibody Production — In clinical trials, antibodies that cross-react with human insulin and
193 insulin lispro were observed in both human insulin mixtures and insulin lispro mixtures
194 treatment groups.

195 **Information for Patients**

196 Patients should be informed of the potential risks and advantages of Humalog Mix75/25 and
197 alternative therapies. Patients should not mix Humalog Mix75/25 with any other insulin. They
198 should also be informed about the importance of proper insulin storage, injection technique,
199 timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose
200 monitoring, periodic hemoglobin A_{1c} testing, recognition and management of hypo- and
201 hyperglycemia, and periodic assessment for diabetes complications.

202 Patients should be advised to inform their physician if they are pregnant or intend to become
203 pregnant.

204 Refer patients to the Patient Information leaflet for information on normal appearance, timing
205 of dosing (within 15 minutes before a meal), storing, and common adverse effects.

206 *For Patients Using Insulin Pen Delivery Devices:* Before starting therapy, patients should read
207 the Patient Information leaflet that accompanies the drug product and the User Manual that
208 accompanies the delivery device and re-read them each time the prescription is renewed. Patients
209 should be instructed on how to properly use the delivery device, prime the Pen to a stream of
210 insulin, and properly dispose of needles. Patients should be advised not to share their Pens with
211 others.

212 **Laboratory Tests**

213 As with all insulins, the therapeutic response to Humalog Mix75/25 should be monitored by
214 periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the
215 monitoring of long-term glycemic control.

216 **Drug Interactions**

217 Insulin requirements may be increased by medications with hyperglycemic activity such as
218 corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral
219 contraceptives, phenothiazines, and thyroid replacement therapy.

220 Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity
 221 or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics,
 222 certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme
 223 inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of
 224 pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the
 225 symptoms of hypoglycemia in some patients.

226 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

227 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
 228 Humalog, Humalog Mix75/25, or Humalog Mix50/50. Insulin lispro was not mutagenic in a
 229 battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA
 230 synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test).
 231 There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

232 **Pregnancy**

233 *Teratogenic Effects — Pregnancy Category B* — Reproduction studies with insulin lispro have
 234 been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times,
 235 respectively, the average human dose (40 units/day) based on body surface area. The results have
 236 revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are,
 237 however, no adequate and well-controlled studies with Humalog, Humalog Mix75/25, or
 238 Humalog Mix50/50 in pregnant women. Because animal reproduction studies are not always
 239 predictive of human response, this drug should be used during pregnancy only if clearly needed.

240 **Nursing Mothers**

241 It is unknown whether insulin lispro is excreted in significant amounts in human milk. Many
 242 drugs, including human insulin, are excreted in human milk. For this reason, caution should be
 243 exercised when Humalog Mix75/25 is administered to a nursing woman. Patients with diabetes
 244 who are lactating may require adjustments in Humalog Mix75/25 dose, meal plan, or both.

245 **Pediatric Use**

246 Safety and effectiveness of Humalog Mix75/25 in patients less than 18 years of age have not
 247 been established.

248 **Geriatric Use**

249 Clinical studies of Humalog Mix75/25 did not include sufficient numbers of patients aged 65
 250 and over to determine whether they respond differently than younger patients. In general, dose
 251 selection for an elderly patient should take into consideration the greater frequency of decreased
 252 hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this
 253 population.

254 **ADVERSE REACTIONS**

255 Clinical studies comparing Humalog Mix75/25 with human insulin mixtures did not
 256 demonstrate a difference in frequency of adverse events between the two treatments.

257 Adverse events commonly associated with human insulin therapy include the following:

258 **Body as a Whole** — allergic reactions (*see* PRECAUTIONS).

259 **Skin and Appendages** — injection site reaction, lipodystrophy, pruritus, rash.

260 **Other** — hypoglycemia (*see* WARNINGS and PRECAUTIONS).

261 **OVERDOSAGE**

262 Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy
 263 expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose.
 264 Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes
 265 with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous

266 glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation
267 may be necessary because hypoglycemia may recur after apparent clinical recovery.

268 **DOSAGE AND ADMINISTRATION**

269 **Table 1*: Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-**
270 **Study Comparison)**

Insulin Products	Dose, U/kg	Time of Peak Activity, Hours After Dosing	Percent of Total Activity Occurring in the First 4 Hours
Humalog	0.3	2.4 (0.8 - 4.3)	70% (49 - 89%)
Humulin R	0.32 (0.26 - 0.37)	4.4 (4.0 - 5.5)	54% (38 - 65%)
Humalog Mix75/25	0.3	2.6 (1.0 - 6.5)	35% (21 - 56%)
Humulin 70/30	0.3	4.4 (1.5 - 16)	32% (14 - 60%)
Humalog Mix50/50	0.3	2.3 (0.8 - 4.8)	45% (27 - 69%)
Humulin 50/50	0.3	3.3 (2.0 - 5.5)	44% (21 - 60%)
NPH	0.32 (0.27 - 0.40)	5.5 (3.5 - 9.5)	14% (3.0 - 48%)
NPL component	0.3	5.8 (1.3 - 18.3)	22% (6.3 - 40%)

272 * The information supplied in Table 1 indicates when peak insulin activity can be expected and the percent of the
273 total insulin activity occurring during the first 4 hours. The information was derived from 3 separate glucose clamp
274 studies in nondiabetic subjects. Values represent means, with ranges provided in parentheses.
275

276 Humalog Mix75/25 is intended only for subcutaneous administration. Humalog Mix75/25
277 should not be administered intravenously. Dosage regimens of Humalog Mix75/25 will vary
278 among patients and should be determined by the healthcare provider familiar with the patient's
279 metabolic needs, eating habits, and other lifestyle variables. Humalog has been shown to be
280 equipotent to Regular human insulin on a molar basis. One unit of Humalog has the same
281 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
282 shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared with
283 Humulin 70/30 on a unit for unit basis. The quicker glucose-lowering effect of Humalog is
284 related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

285 Humalog Mix75/25 starts lowering blood glucose more quickly than Regular human insulin,
286 allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast,
287 mixtures containing Regular human insulin should be given 30 to 60 minutes before a meal.

288 The rate of insulin absorption and consequently the onset of activity are known to be affected
289 by the site of injection, exercise, and other variables. As with all insulin preparations, the time
290 course of action of Humalog Mix75/25 may vary considerably in different individuals or within
291 the same individual. Patients must be educated to use proper injection techniques.

292 Humalog Mix75/25 should be inspected visually before use. Humalog Mix75/25 should be
293 used only if it appears uniformly cloudy after mixing. Humalog Mix75/25 should not be used
294 after its expiration date.

HOW SUPPLIED

295
 296 Humalog Mix75/25 [75% insulin lispro protamine suspension and 25% insulin lispro injection,
 297 (rDNA origin)] is available in the following package sizes: each presentation containing 100
 298 units insulin lispro per mL (U-100).
 299

10 mL vials	NDC 0002-7511-01 (VL-7511)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8794-59 (HP-8794)
5 x 3 mL prefilled insulin delivery devices (KwikPen™)	NDC 0002-8797-59 (HP-8797)

300
 301 *Storage* — Humalog Mix75/25 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but
 302 not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated [below
 303 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain
 304 Humalog Mix75/25. Unrefrigerated [below 30°C (86°F)] Pens, and KwikPens must be used
 305 within 10 days or be discarded, even if they still contain Humalog Mix75/25. Protect from direct
 306 heat and light. See table below:
 307

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen and KwikPen (prefilled)	10 days	Until expiration date	10 days. Do not refrigerate.

308
 309 Literature revised Month dd, yyyy

310 **KwikPens manufactured by**
 311 **Eli Lilly and Company, Indianapolis, IN 46285, USA**
 312 **Pens manufactured by**
 313 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 314 **Lilly France, F-67640 Fegersheim, France**
 315 **Vials manufactured by**
 316 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 317 **Lilly France, F-67640 Fegersheim, France**
 318
 319 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**
 320

321 **www.humalog.com**

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HUMALOG[®] Mix50/50[™]

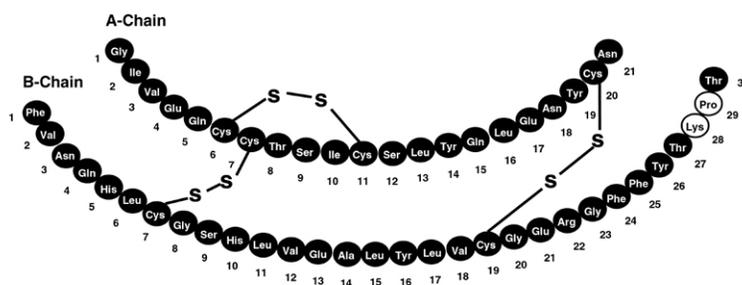
50% INSULIN LISPRO PROTAMINE SUSPENSION AND 50% INSULIN LISPRO INJECTION (rDNA ORIGIN) 100 UNITS PER ML (U-100)

7
8

DESCRIPTION

9 Humalog[®] Mix50/50[™] [50% insulin lispro protamine suspension and 50% insulin lispro
10 injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-
11 lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-
12 lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created
13 when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is
14 synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has
15 been genetically altered to produce insulin lispro. Insulin lispro protamine suspension (NPL
16 component) is a suspension of crystals produced from combining insulin lispro and protamine
17 sulfate under appropriate conditions for crystal formation.

18 Insulin lispro has the following primary structure:



19 Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808,
20 both identical to that of human insulin.

21 Humalog Mix50/50 vials and Pens contain a sterile suspension of insulin lispro protamine
22 suspension mixed with soluble insulin lispro for use as an injection.

23 Each milliliter of Humalog Mix50/50 injection contains insulin lispro 100 units, 0.19 mg
24 protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 2.20 mg Metacresol, zinc
25 oxide content adjusted to provide 0.0305 mg zinc ion, 0.89 mg phenol, and Water for Injection.
26 Humalog Mix50/50 has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10%
27 may have been added to adjust pH.

28

CLINICAL PHARMACOLOGY

29

Antidiabetic Activity

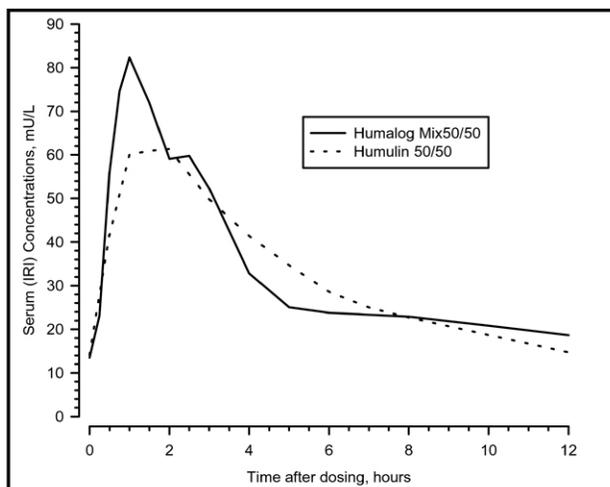
30 The primary activity of insulin, including Humalog Mix50/50, is the regulation of glucose
31 metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many
32 tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport
33 of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism.
34 In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits
35 gluconeogenesis, and promotes the conversion of excess glucose into fat.

36 Insulin lispro, the rapid-acting component of Humalog Mix50/50, has been shown to be
37 equipotent to Regular human insulin on a molar basis. One unit of Humalog[®] has the same

38 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
39 shorter duration.

40 **Pharmacokinetics**

41 *Absorption* — Studies in nondiabetic subjects and patients with type 1 (insulin-dependent)
42 diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix50/50, is
43 absorbed faster than Regular human insulin (U-100). In nondiabetic subjects given subcutaneous
44 doses of Humalog ranging from 0.1 to 0.4 U/kg, peak serum concentrations were observed 30 to
45 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human
46 insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar
47 results were seen in patients with type 1 diabetes.



48 **Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous**
49 **Injection of Humalog Mix50/50 or Humulin 50/50 in Healthy Nondiabetic Subjects.**

50 Humalog Mix50/50 has two phases of absorption. The early phase represents insulin lispro and
51 its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin
52 lispro protamine suspension. In 30 healthy nondiabetic subjects given subcutaneous doses
53 (0.3 U/kg) of Humalog Mix50/50, peak serum concentrations were observed 45 minutes to 13.5
54 hours (median, 60 minutes) after dosing (*see* Figure 1). In patients with type 1 diabetes, peak
55 serum concentrations were observed 45 minutes to 120 minutes (median, 60 minutes) after
56 dosing. The rapid absorption characteristics of Humalog are maintained with Humalog Mix50/50
57 (*see* Figure 1).

58 Direct comparison of Humalog Mix50/50 and Humulin 50/50 was not performed. However, a
59 cross-study comparison shown in Figure 1 suggests that Humalog Mix50/50 has a more rapid
60 absorption than Humulin 50/50.

61 *Distribution* — Radiolabeled distribution studies of Humalog Mix50/50 have not been
62 conducted. However, the volume of distribution following injection of Humalog is identical to
63 that of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

64 *Metabolism* — Human metabolism studies of Humalog Mix50/50 have not been conducted.
65 Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of
66 Humalog Mix50/50, is identical to that of Regular human insulin.

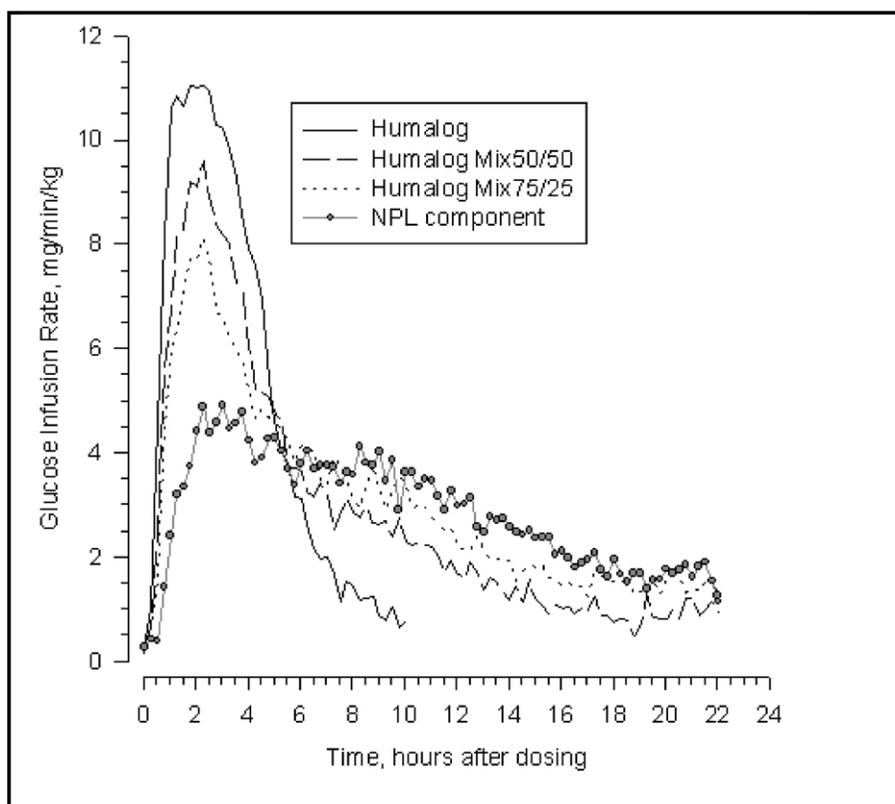
67 *Elimination* — Humalog Mix50/50 has two absorption phases, a rapid and a prolonged phase,
68 representative of the insulin lispro and insulin lispro protamine suspension components of the
69 mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot
70 be calculated after administration of Humalog Mix50/50 because of the prolonged insulin lispro
71 protamine suspension absorption.

72 Pharmacodynamics

73 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
 74 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
 75 duration of glucose-lowering activity than Regular human insulin. The early onset of activity of
 76 Humalog Mix50/50 is directly related to the rapid absorption of Humalog. The time course of
 77 action of insulin and insulin analogs, such as Humalog (and hence Humalog Mix50/50), may
 78 vary considerably in different individuals or within the same individual. The parameters of
 79 Humalog Mix50/50 activity (time of onset, peak time, and duration) as presented in Figures 2
 80 and 3 should be considered only as general guidelines. The rate of insulin absorption and
 81 consequently the onset of activity is known to be affected by the site of injection, exercise, and
 82 other variables (*see General under PRECAUTIONS*).

83 In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and glucose-
 84 lowering activity of Humalog, Humalog Mix50/50, Humalog[®] Mix75/25[™], and insulin lispro
 85 protamine suspension (NPL component) were compared (*see Figure 2*). Graphs of mean glucose
 86 infusion rate versus time showed a distinct insulin activity profile for each formulation. The
 87 rapid onset of glucose-lowering activity characteristic of Humalog was maintained in Humalog
 88 Mix50/50.

89 Direct comparison between Humalog Mix50/50 and Humulin 50/50 was not performed.
 90 However, a cross-study comparison shown on Figure 3 suggests that Humalog Mix50/50 has a
 91 duration of activity that is similar to Humulin 50/50.



92 **Figure 2: Glucose Infusion Rates (A Measure of Insulin Activity) After Injection of**
 93 **Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension**
 94 **(NPL Component) in 30 Nondiabetic Subjects.**
 95
 96
 97

98
99

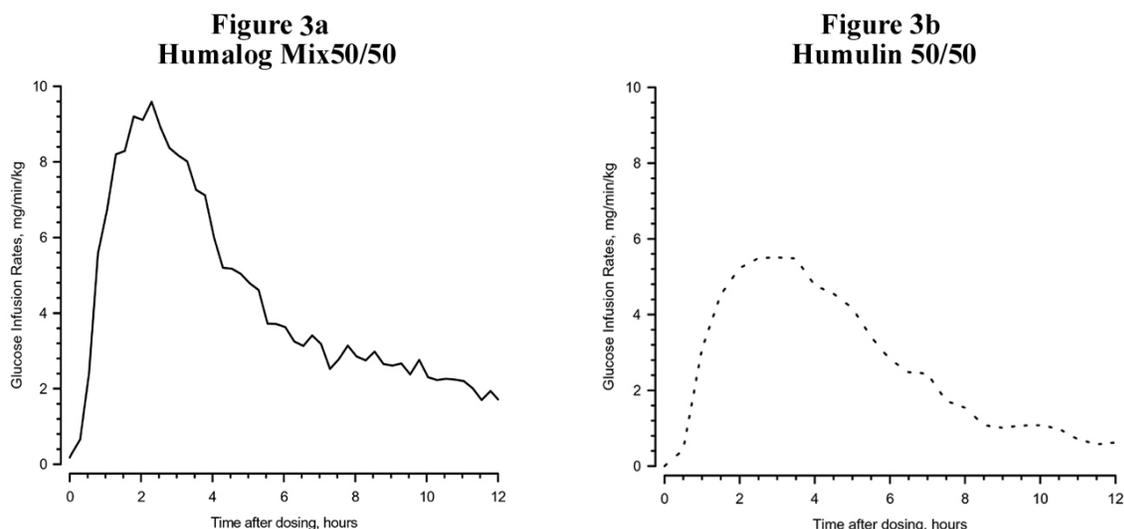


Figure 3: Insulin Activity After Subcutaneous Injection of Humalog Mix50/50 and Humulin 50/50 in Nondiabetic Subjects.

100
101
102 Figures 2 and 3 represent insulin activity profiles as measured by glucose clamp studies in
103 healthy nondiabetic subjects.

104 Figure 2 shows the time activity profiles of Humalog, Humalog Mix75/25, Humalog
105 Mix50/50, and insulin lispro protamine suspension (NPL component).

106 Figure 3 is a comparison of the time activity profiles of Humalog Mix50/50 (*see* Figure 3a) and
107 of Humulin 50/50 (*see* Figure 3b) from two different studies.

108 Special Populations

109 *Age and Gender* — Information on the effect of age on the pharmacokinetics of Humalog
110 Mix50/50 is unavailable. Pharmacokinetic and pharmacodynamic comparisons between men and
111 women administered Humalog Mix50/50 showed no gender differences. In large Humalog
112 clinical trials, sub-group analysis based on age and gender demonstrated that differences between
113 Humalog and Regular human insulin in postprandial glucose parameters are maintained across
114 sub-groups.

115 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of
116 Humalog Mix50/50 has not been studied.

117 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of
118 Humalog Mix50/50 has not been studied.

119 *Obesity* — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics
120 and pharmacodynamics of Humalog Mix50/50 has not been studied. In large clinical trials,
121 which included patients with Body Mass Index up to and including 35 kg/m², no consistent
122 differences were observed between Humalog and Humulin[®] R with respect to postprandial
123 glucose parameters.

124 *Renal Impairment* — The effect of renal impairment on the pharmacokinetics and
125 pharmacodynamics of Humalog Mix50/50 has not been studied. In a study of 25 patients with
126 type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between
127 Humalog and Regular human insulin were generally maintained. However, the sensitivity of the
128 patients to insulin did change, with an increased response to insulin as the renal function
129 declined. Careful glucose monitoring and dose reductions of insulin, including Humalog
130 Mix50/50, may be necessary in patients with renal dysfunction.

131 *Hepatic Impairment* — Some studies with human insulin have shown increased circulating
132 levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the
133 pharmacokinetics and pharmacodynamics of Humalog Mix50/50 has not been studied. However,
134 in a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the
135 subcutaneous absorption or general disposition of Humalog when compared with patients with
136 no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption
137 and elimination when compared with Regular human insulin. Careful glucose monitoring and
138 dose adjustments of insulin, including Humalog Mix50/50, may be necessary in patients with
139 hepatic dysfunction.

140 **INDICATIONS AND USAGE**

141 Humalog Mix50/50, a mixture of 50% insulin lispro protamine suspension and 50% insulin
142 lispro injection, (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for
143 the control of hyperglycemia. Based on cross-study comparisons of the pharmacodynamics of
144 Humalog Mix50/50 and Humulin 50/50, it is likely that Humalog Mix50/50 has a more rapid
145 onset of glucose-lowering activity compared with Humulin 50/50 while having a similar duration
146 of action. This profile is achieved by combining the rapid onset of Humalog with the
147 intermediate action of insulin lispro protamine suspension.

148 **CONTRAINDICATIONS**

149 Humalog Mix50/50 is contraindicated during episodes of hypoglycemia and in patients
150 sensitive to insulin lispro or any of the excipients contained in the formulation.

151 **WARNINGS**

152 **Humalog differs from Regular human insulin by its rapid onset of action as well as a**
153 **shorter duration of activity. Therefore, the dose of Humalog Mix50/50 should be given**
154 **within 15 minutes before a meal.**

155 **Hypoglycemia is the most common adverse effect associated with the use of insulins,**
156 **including Humalog Mix50/50. As with all insulins, the timing of hypoglycemia may differ**
157 **among various insulin formulations. Glucose monitoring is recommended for all patients**
158 **with diabetes.**

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

162 **PRECAUTIONS**

163 **General**

164 Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated
165 with the use of all insulins. Because of differences in the action of Humalog Mix50/50 and other
166 insulins, care should be taken in patients in whom such potential side effects might be clinically
167 relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using
168 potassium-lowering drugs or patients taking drugs sensitive to serum potassium level).
169 Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated
170 with the use of all insulins.

171 As with all insulin preparations, the time course of Humalog Mix50/50 action may vary in
172 different individuals or at different times in the same individual and is dependent on site of
173 injection, blood supply, temperature, and physical activity.

174 Adjustment of dosage of any insulin may be necessary if patients change their physical activity
175 or their usual meal plan. Insulin requirements may be altered during illness, emotional
176 disturbances, or other stress.

177 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated
178 with the administration of Humalog Mix50/50. Rapid changes in serum glucose concentrations

179 may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value.
180 Early warning symptoms of hypoglycemia may be different or less pronounced under certain
181 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as
182 beta-blockers, or intensified diabetes control.

183 **Renal Impairment** — As with other insulins, the requirements for Humalog Mix50/50 may be
184 reduced in patients with renal impairment.

185 **Hepatic Impairment** — Although impaired hepatic function does not affect the absorption or
186 disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including
187 Humalog Mix50/50, may be necessary.

188 **Allergy** — Local Allergy — As with any insulin therapy, patients may experience redness,
189 swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to
190 a few weeks. In some instances, these reactions may be related to factors other than insulin, such
191 as irritants in the skin cleansing agent or poor injection technique.

192 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to
193 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,
194 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized
195 allergy, including anaphylactic reaction, may be life threatening. Localized reactions and
196 generalized myalgias have been reported with the use of cresol as an injectable excipient.

197 Antibody Production — In clinical trials, antibodies that cross-react with human insulin and
198 insulin lispro were observed in both human insulin mixtures and insulin lispro mixtures
199 treatment groups.

200 **Information for Patients**

201 Patients should be informed of the potential risks and advantages of Humalog Mix50/50 and
202 alternative therapies. Patients should not mix Humalog Mix50/50 with any other insulin. They
203 should also be informed about the importance of proper insulin storage, injection technique,
204 timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose
205 monitoring, periodic hemoglobin A_{1c} testing, recognition and management of hypo- and
206 hyperglycemia, and periodic assessment for diabetes complications.

207 Patients should be advised to inform their physician if they are pregnant or intend to become
208 pregnant.

209 Refer patients to the Patient Information leaflet for information on normal appearance, timing
210 of dosing (within 15 minutes before a meal), storing, and common adverse effects.

211 *For Patients Using Insulin Pen Delivery Devices:* Before starting therapy, patients should read
212 the Patient Information leaflet that accompanies the drug product and the User Manual that
213 accompanies the delivery device and re-read them each time the prescription is renewed. Patients
214 should be instructed on how to properly use the delivery device, prime the Pen to a stream of
215 insulin, and properly dispose of needles. Patients should be advised not to share their Pens with
216 others.

217 **Laboratory Tests**

218 As with all insulins, the therapeutic response to Humalog Mix50/50 should be monitored by
219 periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the
220 monitoring of long-term glycemic control.

221 **Drug Interactions**

222 Insulin requirements may be increased by medications with hyperglycemic activity such as
223 corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral
224 contraceptives, phenothiazines, and thyroid replacement therapy.

225 Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity
226 or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics,

227 certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme
 228 inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of
 229 pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the
 230 symptoms of hypoglycemia in some patients.

231 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

232 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
 233 Humalog, Humalog Mix75/25, or Humalog Mix50/50. Insulin lispro was not mutagenic in a
 234 battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA
 235 synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test).
 236 There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

237 **Pregnancy**

238 *Teratogenic Effects — Pregnancy Category B* — Reproduction studies with insulin lispro have
 239 been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times,
 240 respectively, the average human dose (40 units/day) based on body surface area. The results have
 241 revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are,
 242 however, no adequate and well-controlled studies with Humalog, Humalog Mix75/25, or
 243 Humalog Mix50/50 in pregnant women. Because animal reproduction studies are not always
 244 predictive of human response, this drug should be used during pregnancy only if clearly needed.

245 **Nursing Mothers**

246 It is unknown whether insulin lispro is excreted in significant amounts in human milk. Many
 247 drugs, including human insulin, are excreted in human milk. For this reason, caution should be
 248 exercised when Humalog Mix50/50 is administered to a nursing woman. Patients with diabetes
 249 who are lactating may require adjustments in Humalog Mix50/50 dose, meal plan, or both.

250 **Pediatric Use**

251 Safety and effectiveness of Humalog Mix50/50 in patients less than 18 years of age have not
 252 been established.

253 **Geriatric Use**

254 Clinical studies of Humalog Mix50/50 did not include sufficient numbers of patients aged 65
 255 and over to determine whether they respond differently than younger patients. In general, dose
 256 selection for an elderly patient should take into consideration the greater frequency of decreased
 257 hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this
 258 population.

259 **ADVERSE REACTIONS**

260 Clinical studies comparing Humalog Mix50/50 with human insulin mixtures did not
 261 demonstrate a difference in frequency of adverse events between the two treatments.

262 Adverse events commonly associated with human insulin therapy include the following:

263 **Body as a Whole** — allergic reactions (*see* PRECAUTIONS).

264 **Skin and Appendages** — injection site reaction, lipodystrophy, pruritus, rash.

265 **Other** — hypoglycemia (*see* WARNINGS and PRECAUTIONS).

266 **OVERDOSAGE**

267 Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy
 268 expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose.
 269 Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes
 270 with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous
 271 glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation
 272 may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

Table 1*: Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-Study Comparison)

Insulin Products	Dose, U/kg	Time of Peak Activity, Hours After Dosing	Percent of Total Activity Occurring in the First 4 Hours
Humalog	0.3	2.4 (0.8 - 4.3)	70% (49 - 89%)
Humulin R	0.32 (0.26 - 0.37)	4.4 (4.0 - 5.5)	54% (38 - 65%)
Humalog Mix75/25	0.3	2.6 (1.0 - 6.5)	35% (21 - 56%)
Humulin 70/30	0.3	4.4 (1.5 - 16)	32% (14 - 60%)
Humalog Mix50/50	0.3	2.3 (0.8 - 4.8)	45% (27 - 69%)
Humulin 50/50	0.3	3.3 (2.0 - 5.5)	44% (21 - 60%)
NPH	0.32 (0.27 - 0.40)	5.5 (3.5 - 9.5)	14% (3.0 - 48%)
NPL component	0.3	5.8 (1.3 - 18.3)	22% (6.3 - 40%)

* The information supplied in Table 1 indicates when peak insulin activity can be expected and the percent of the total insulin activity occurring during the first 4 hours. The information was derived from 3 separate glucose clamp studies in nondiabetic subjects. Values represent means, with ranges provided in parentheses.

Humalog Mix50/50 is intended only for subcutaneous administration. Humalog Mix50/50 should not be administered intravenously. Dosage regimens of Humalog Mix50/50 will vary among patients and should be determined by the healthcare provider familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Humalog has been shown to be equipotent to Regular human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of shorter duration. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

Direct comparison between Humalog Mix50/50 and Humulin 50/50 was not performed. However, a cross-study comparison shown in Figure 3 suggests that Humalog Mix50/50 has a duration of activity that is similar to Humulin 50/50.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. As with all insulin preparations, the time course of action of Humalog Mix50/50 may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog Mix50/50 should be inspected visually before use. Humalog Mix50/50 should be used only if it appears uniformly cloudy after mixing. Humalog Mix50/50 should not be used after its expiration date.

HOW SUPPLIED

Humalog Mix50/50 [50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)] is available in the following package sizes: each presentation containing 100 units insulin lispro per mL (U-100).

303

10 mL vials	NDC 0002-7512-01 (VL-7512)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8793-59 (HP-8793)
5 x 3 mL prefilled insulin delivery devices (KwikPen™)	NDC 0002-8798-59 (HP-8798)

304

305 *Storage* — Humalog Mix50/50 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but
 306 not in the freezer. Do not use Humalog Mix50/50 if it has been frozen. Unrefrigerated [below
 307 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain
 308 Humalog Mix50/50. Unrefrigerated [below 30°C (86°F)] Pens, and KwikPens must be used
 309 within 10 days or be discarded, even if they still contain Humalog Mix50/50. Protect from direct
 310 heat and light. See table below:

311

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen and KwikPen (prefilled)	10 days	Until expiration date	10 days. Do not refrigerate.

312 Literature revised Month dd, yyyy

313

314 **KwikPens manufactured by**
Eli Lilly and Company, Indianapolis, IN 46285, USA

315

316 **Pens manufactured by**
Eli Lilly and Company, Indianapolis, IN 46285, USA

317

318 **Vials manufactured by**
Eli Lilly and Company, Indianapolis, IN 46285, USA or

319

Lilly France, F-67640 Fegersheim, France

320

321 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**

322

www.humalog.com

323

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324

325

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Lilly

Prefilled Insulin Delivery Device
User Manual

Instructions for Use

Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.

Every time you inject:

- Use a new needle
- Prime to make sure the Pen is ready to dose
- Make sure you got your full dose (see page 18)



Also, read the “Patient Information” enclosed in your Pen box.

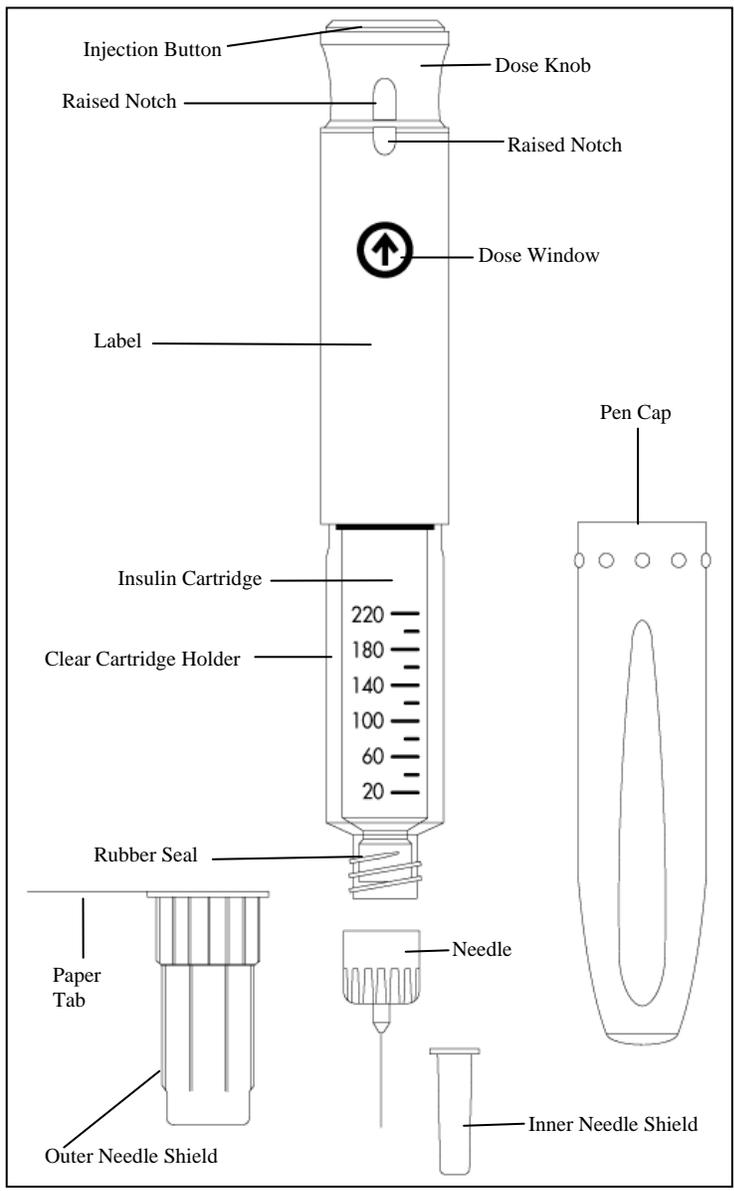
Pen Features

- A multiple dose, prefilled insulin delivery device (“insulin Pen”) containing 3 mL (300 units) of U-100 insulin
 - Delivers up to 60 units per dose
 - Doses can be dialed by single units
-

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Pen Parts



Important Notes

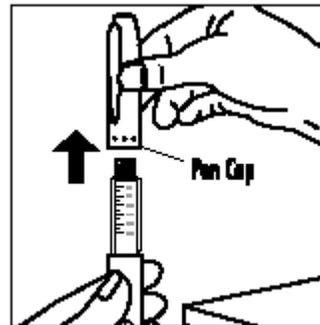
- **Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.**
- **Use a new needle for each injection.**
 - **Be sure a needle is completely attached to the Pen before priming, setting the dose and injecting your insulin.**
- **Prime every time.**
 - **The Pen must be primed before each injection to make sure the Pen is ready to dose.** Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use. **See Section III. “Priming the Pen”, pages 10-13.**
 - **If you do not prime, you may get too much or too little insulin.**
- **Make sure you get your full dose.**
 - To make sure you get your full dose, you must push the injection button all the way down until you see a diamond (◆) or an arrow (→) in the center of the dose window. See “Following an Injection”, page 18.
- The numbers on the clear cartridge holder give an estimate of the amount of insulin remaining in the cartridge. Do not use these numbers for measuring an insulin dose.
- Do not share your Pen or needles.
- Keep your Pen and needles out of the reach of children.
- Pens that have not been used should be stored in a refrigerator but not in a freezer. Do not use a Pen if it has been frozen. Refer to the “Patient Information” for complete storage instructions.

Important Notes (Continued)

- After a Pen is used for the first time, it should **NOT** be refrigerated but should be kept at room temperature [below 86°F (30°C)] and away from direct heat and light.
- An unrefrigerated Pen should be discarded according to the time specified in the “Patient Information”, even if it still contains insulin.
- Never use a Pen after the expiration date stamped on the label.
- Do not store your Pen with the needle attached. Doing so may allow insulin to leak from the Pen and air bubbles to form in the cartridge. Additionally, with suspension (cloudy) insulins, crystals may clog the needle.
- Always carry an extra Pen in case yours is lost or damaged.
- Follow your Health Care Professional’s instruction for safe handling of needles and disposal of empty pens.
- This Pen is not recommended for use by blind or visually impaired persons without the assistance of a person trained in the proper use of the product.
- The directions regarding needle handling are not intended to replace local, Health Care Professional, or institutional policies.
- **Any changes in insulin should be made cautiously and only under medical supervision.**

I. Preparing the Pen

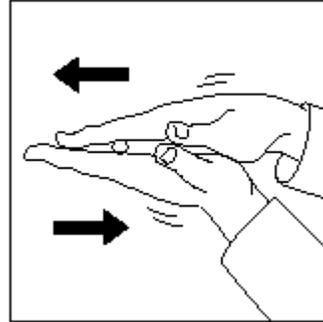
1. Before proceeding, refer to the “Patient Information” for instructions on checking the appearance of your insulin.
2. Check the label on the Pen to be sure the Pen contains the type of insulin that has been prescribed for you.
3. Always wash your hands before preparing your Pen for use.
4. Pull the Pen cap to remove.



I. Preparing the Pen (Continued)

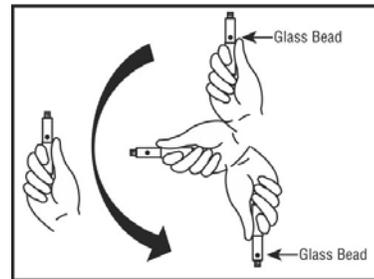
5. If your insulin is a suspension (cloudy):

- a. Roll the Pen back and forth 10 times then perform step b.

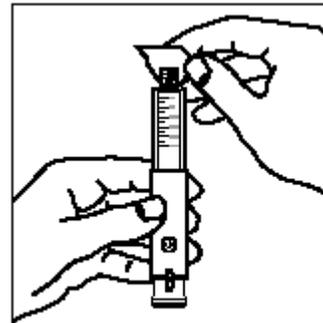


- b. Gently turn the Pen up and down 10 times until the insulin is evenly mixed.

Note: Suspension (cloudy) insulin cartridges contain a small glass bead to assist in mixing.



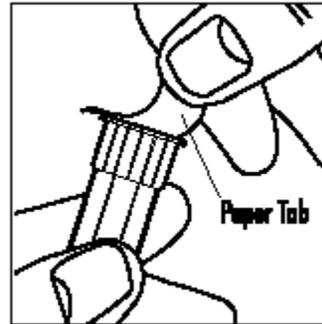
6. Use an alcohol swab to wipe the rubber seal on the end of the Pen.



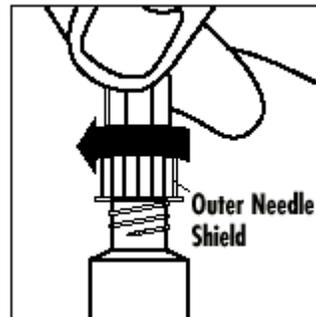
II. Attaching the Needle

This device is suitable for use with Becton Dickinson and Company's insulin pen needles.

1. Always use a new needle for each injection. Do not push injection button without a needle attached. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.
2. Remove the paper tab from the outer needle shield.

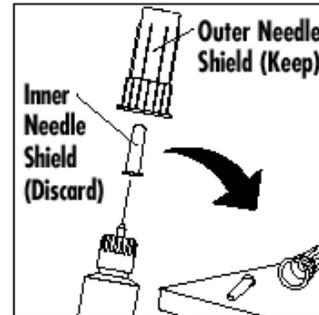


3. Attach the capped needle onto the end of the Pen by turning it clockwise until tight.



II. Attaching the Needle (Continued)

4. Hold the Pen with the needle pointing up and remove the **outer needle shield**. **Keep it to use during needle removal.**

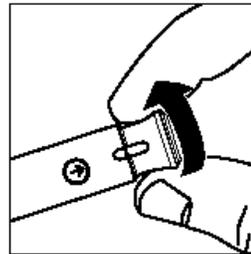


5. Remove the inner needle shield and discard.

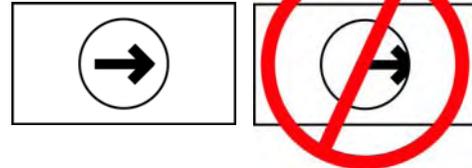
III. Priming the Pen

- **Prime every time.** The Pen must be primed to a stream of insulin (not just a few drops) before each injection to make sure the Pen is ready to dose.
- You may need to prime a new Pen up to six times before a stream of insulin appears.
- **If you do not prime, you may get too much or too little insulin.**
- **Always use a new needle for each injection.**

1. Make sure the arrow (→) is in the center of the dose window as shown.



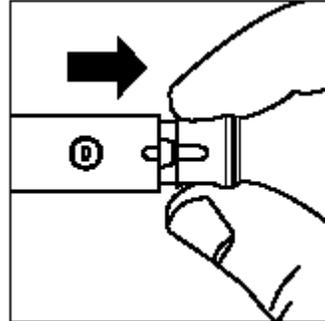
2. If you do not see the arrow in the center of the dose window, push in the injection button fully and turn the dose knob until the arrow is seen in the center of the dose window.



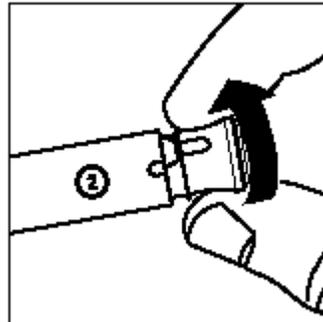
Correct

III. Priming the Pen (Continued)

3. With the arrow in the center of the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window.



4. Turn the dose knob clockwise until the number "2" is seen in the dose window. If the number you have dialed is too high, simply turn the dose knob backward until the number "2" is seen in the dose window.

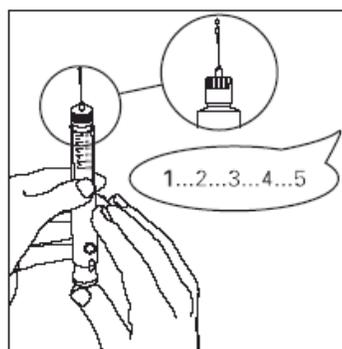


III. Priming the Pen (Continued)

5. Hold your Pen with the needle pointing straight up. Tap the clear cartridge holder gently with your finger so any air bubbles collect near the top.

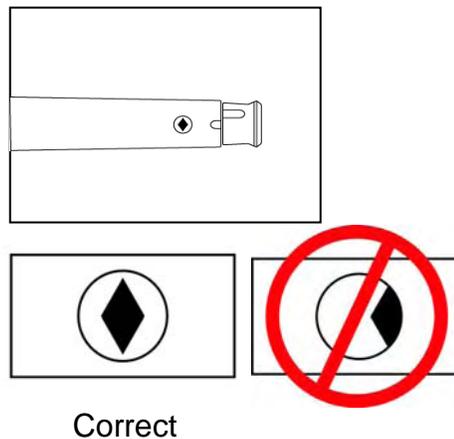
Using your thumb, if possible, push in the injection button completely. Keep pressing and continue to hold the injection button **firmly** while counting **slowly** to 5. You should see a stream of insulin come out of the tip of the needle.

If a stream of insulin does not come out of the tip of the needle, repeat steps 1 through 5. If after six attempts a stream of insulin does not come out of the tip of the needle, change the needle. Repeat steps 1 through 5 up to two more times. If you are still unable to get insulin flowing out of the needle, **do NOT use** the Pen. Contact your Health Care Professional or Lilly.



III. Priming the Pen (Continued)

6. At the completion of the priming step, a diamond (◆) must be seen in the center of the dose window. If a diamond (◆) is not seen in the center of the dose window, continue pushing on the injection button until you see a diamond (◆) in the center of the dose window.



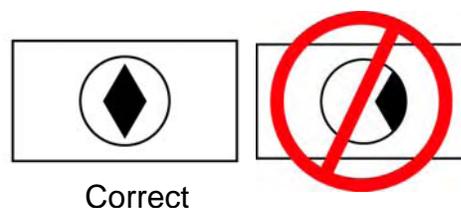
Note: A small air bubble may remain in the cartridge after the completion of the priming step. If you have properly primed the Pen, this small air bubble will not affect your insulin dose.

7. Now you are ready to set your dose. See next page.

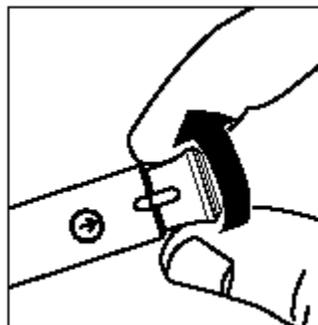
IV. Setting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**
 - **Caution: Do not push in the injection button while setting your dose. Failure to follow these instructions carefully may result in getting too much or too little insulin. If you accidentally push the injection button while setting your dose, you must prime the Pen again before injecting your dose. See Section III. “Priming the Pen”, pages 10-13.**
1. A diamond must be seen in the center of the dose window before setting your dose.

If you do not see a diamond in the center of the dose window, the Pen has not been primed correctly and you are not ready to set your dose. Before continuing, repeat the priming steps.

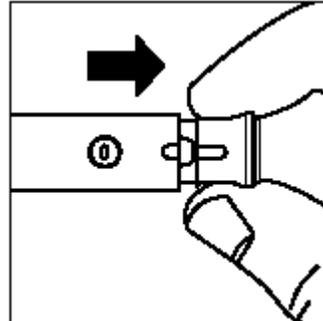


2. Turn the dose knob clockwise until the arrow (→) is seen in the center of the dose window and the notches on the Pen and dose knob are in line.

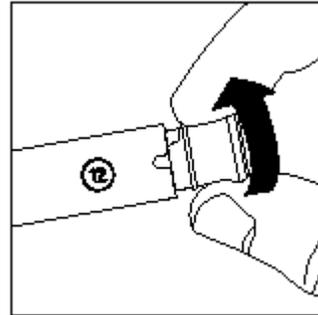


IV. Setting a Dose (Continued)

3. With the arrow (→) in the center of the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window. A dose cannot be dialed until the dose knob is pulled out.



4. Turn the dose knob clockwise until your dose is seen in the dose window. If the dose you have dialed is too high, simply turn the dose knob backward until the correct dose is seen in the dose window.



5. If you cannot dial your full dose, see the "Questions and Answers" section, Question 5, at the end of this manual.

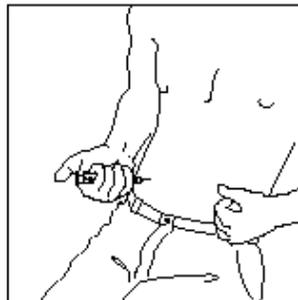
V. Injecting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**
- **Caution: Do not attempt to change the dose after you begin to push in the injection button. Failure to follow these instructions carefully may result in getting too much or too little insulin.**
- **The effort needed to push in the injection button may increase while you are injecting your insulin dose. If you cannot completely push in the injection button, refer to the “Questions and Answers” section, Question 7, at the end of this manual.**
- Do not inject a dose unless the Pen is primed, just before injection, or you may get too much or too little insulin.
- If you have set a dose and pushed in the injection button without a needle attached or if no insulin comes out of the needle, see the “Questions and Answers” section, Questions 1 and 2.

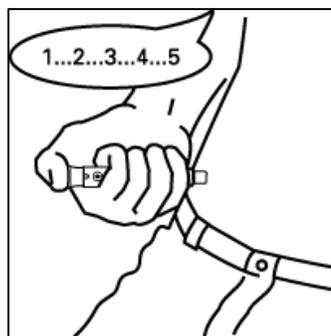
V. Injecting a Dose (Continued)

1. Wash hands. Prepare the skin and use the injection technique recommended by your Health Care Professional.

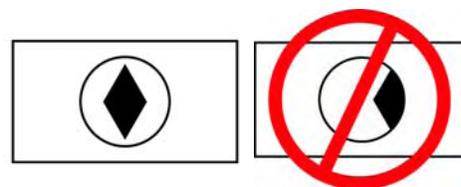
2. Insert the needle into your skin. Inject the insulin by using your thumb, if possible, to push in the injection button completely.



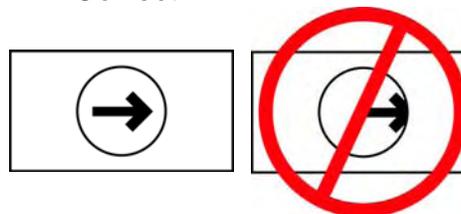
3. Keep pressing and continue to hold the injection button **firmly** while counting **slowly** to 5.



4. When the injection is done, a diamond (◆) or an arrow (➔) must be seen in the center of the dose window. This means your full dose has been delivered. **If you do not see a diamond or an arrow in the center of the dose window, you did not get your full dose. Contact your Health Care Professional for additional instructions.**



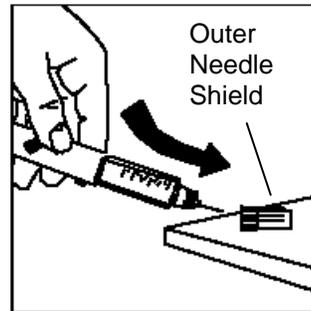
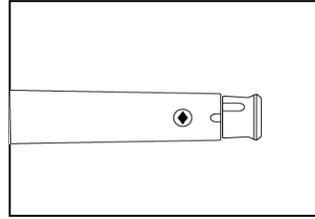
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Correct

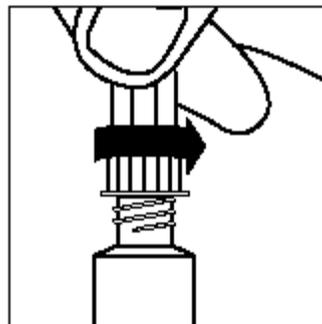
VI. Following an Injection

1. Make sure you got your full dose by checking that the injection button has been completely pushed in and you can see a diamond (◆) or an arrow (➔) in the center of the dose window. If you do not see a diamond (◆) or an arrow (➔) in the center of the dose window, you have not received your full dose. Contact your Health Care Professional for additional instructions.
2. Carefully replace the **outer needle shield** as instructed by your Health Care Professional.

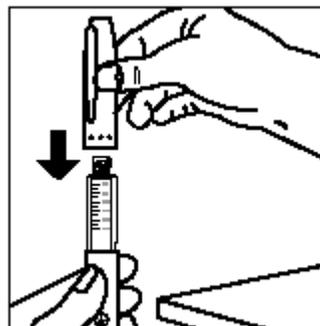


VI. Following an Injection (Continued)

3. Remove the capped needle by turning it counterclockwise. Place the used needle in a puncture-resistant disposable container and properly throw it away as directed by your Health Care Professional.



4. Replace the cap on the Pen.



5. The Pen that you are using should **NOT** be refrigerated but should be kept at room temperature [below 86°F (30°C)] and away from direct heat and light. It should be discarded according to the time specified in the “Patient Information”, even if it still contains insulin.

Do not store or dispose of the Pen with a needle attached. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.

Questions and Answers

Problem	Action
<p>1. Dose dialed and injection button pushed in without a needle attached.</p>	<p>To obtain an accurate dose you must:</p> <ol style="list-style-type: none"> 1) Attach a new needle. 2) Push in the injection button completely (even if a “0” is seen in the window) until a diamond (◆) or an arrow (→) is seen in the center of the dose window. 3) Prime the Pen.
<p>2. Insulin does not come out of the needle.</p> <p>Note: You may need to prime a new pen up to six times before a stream of insulin appears.</p>	<p>To obtain an accurate dose you must:</p> <ol style="list-style-type: none"> 1) Attach a new needle. 2) Push in the injection button completely (even if a “0” is seen in the window) until a diamond (◆) or an arrow (→) is seen in the center of the dose window. 3) Prime the Pen. See Section III. “Priming the Pen”, pages 10-13.

**Questions and Answers
(Continued)**

Problem	Action
3. Why do I need to prime a new pen up to six times?	The first time you use a new pen, priming up to six times may be needed to see a stream of insulin come out of the tip of the needle. If you do not prime until you see a stream of insulin, you may get too much or too little insulin.
4. Wrong dose (too high or too low) dialed.	If you have not pushed in the injection button, simply turn the dose knob backward or forward to correct the dose.
5. Not sure how much insulin remains in the cartridge.	Hold the Pen with the needle end pointing down. The scale (20 units between marks) on the clear cartridge holder shows an estimate of the number of units remaining. These numbers should not be used for measuring an insulin dose.

Questions and Answers (Continued)

Problem	Action
6. Full dose cannot be dialed.	The Pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the Pen, you will not be able to dial past 25. Do not attempt to dial past this point. (The insulin that remains is unusable and not part of the 300 units.) If a partial dose remains in the Pen you may either: 1) Give the partial dose and then give the remaining dose using a new Pen, or 2) Give the full dose with a new Pen.
7. A small amount of insulin remains in the cartridge but a dose cannot be dialed.	The Pen design prevents the cartridge from being completely emptied. The Pen has delivered 300 units of usable insulin.

Questions and Answers (Continued)

Problem	Action
8. Cannot completely push in the injection button when priming the Pen or injecting a dose.	<ol style="list-style-type: none">1) Needle is not attached or is clogged.<ol style="list-style-type: none">a. Attach a new needle.b. Push in the injection button completely (even if a "0" is seen in the window) until a diamond (◆) or an arrow (→) is seen in the center of the dose window.c. Prime the Pen.2) If you are sure insulin is coming out of the needle, push in the injection button more slowly to reduce the effort needed and maintain a constant pressure until the injection button is completely pushed in.

**For additional information call,
1-800-LILLY-RX (1-800-545-5979),
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