

1 **Draft**

2 Prescribing Information as of April 2000

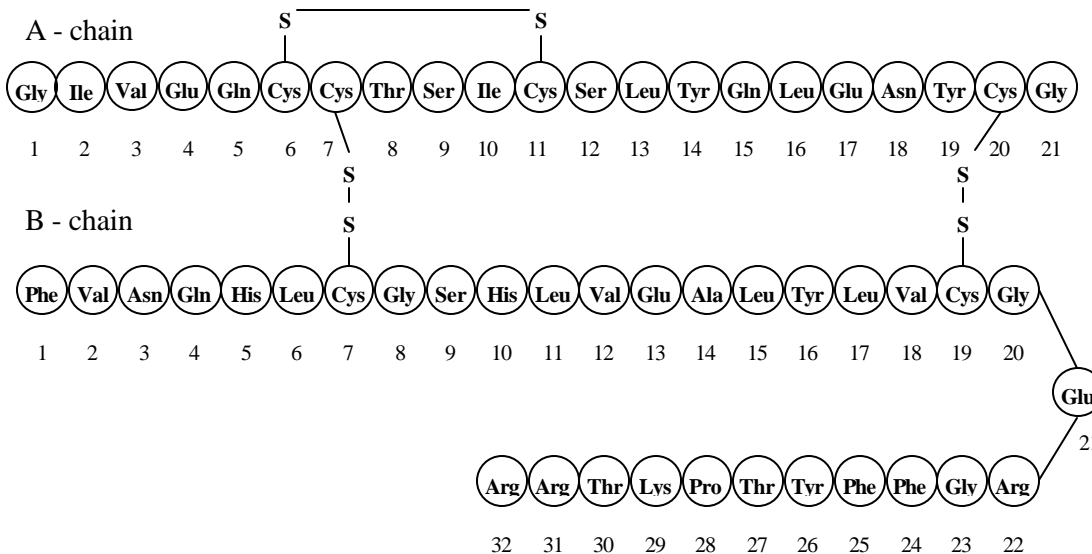
3 **LANTUS®**

4 (insulin glargine [rDNA origin] injection)

5 **LANTUS® must not be diluted or mixed with any other insulin or solution.**

6 **DESCRIPTION**

7 LANTUS® (insulin glargine [rDNA origin] injection) is a sterile solution of insulin glargine for use
 8 as an injection. Insulin glargine is a recombinant human insulin analog that is a long-acting (up to 24-
 9 hour duration of action), parenteral blood-glucose-lowering agent (see CLINICAL
 10 PHARMACOLOGY). LANTUS is produced by recombinant DNA technology utilizing a non-
 11 pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin glargine
 12 differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine
 13 and two arginines are added to the C-terminus of the B-chain. Chemically, it is 21^A-Gly-30^Ba-L-
 14 Arg-30^Bb-L-Arg-human insulin and has the empirical formula C₂₆₇H₄₀₄N₇₂O₇₈S₆ and a molecular
 15 weight of 6063. It has the following structural formula:



16

17 LANTUS consists of insulin glargine dissolved in a clear aqueous fluid. Each milliliter of LANTUS
 18 (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-
 19 cresol, 20 mg glycerol 85%, and water for injection. The pH is adjusted by addition of aqueous
 20 solutions of hydrochloric acid and sodium hydroxide. LANTUS has a pH of approximately 4.

21 **CLINICAL PHARMACOLOGY**

22 **Mechanism of Action**

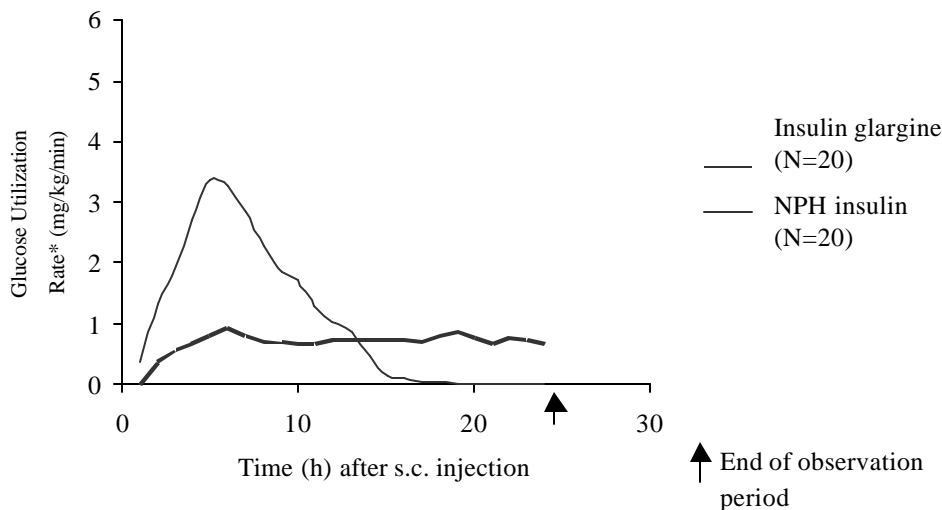
23 The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism.
24 Insulin and its analogs lower blood glucose levels by stimulating peripheral glucose uptake,
25 especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits
26 lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

27 **Pharmacodynamics**

28 Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at
29 neutral pH. At pH 4, as in the LANTUS injection solution, it is completely soluble. After injection
30 into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of
31 microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a
32 relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile
33 allows once-daily dosing as a patient's basal insulin.

34 In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of
35 intravenous insulin glargine is approximately the same as human insulin. In euglycemic clamp
36 studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous
37 insulin glargine was slower than NPH human insulin. The effect profile of insulin glargine was
38 relatively constant with no pronounced peak and the duration of its effect was prolonged compared to
39 NPH human insulin. *Figure 1* shows results from a study in patients with type 1 diabetes conducted
40 for a maximum of 24 hours after the injection. The median time between injection and the end of
41 pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH human insulin, and 24
42 hours (range: 10.8 to >24.0 hours) (24 hours was the end of the observation period) for insulin
43 glargine.

Figure 1. Activity Profile in Patients with Type 1 Diabetes[†]



44

45 *Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean
46 values); indicative of insulin activity.

47 [†]Between-patient variability (CV, coefficient of variation); insulin glargine, 84% and NPH, 78%.

48 The longer duration of action (up to 24 hours) of LANTUS is directly related to its slower rate of
49 absorption and supports once-daily subcutaneous administration. The time course of action of
50 insulins, including LANTUS, may vary between individuals and/or within the same individual.

51 **Pharmacokinetics**

52 **Absorption and Bioavailability.** After subcutaneous injection of insulin glargine in healthy subjects
53 and in patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged
54 absorption and a relatively constant concentration/time profile over 24 hours with no pronounced
55 peak in comparison to NPH human insulin. Serum insulin concentrations were thus consistent with
56 the time profile of the pharmacodynamic activity of insulin glargine.

57 After subcutaneous injection of 0.3 IU/kg insulin glargine in patients with type 1 diabetes, a relatively
58 constant concentration/time profile has been demonstrated. The duration of action after abdominal,
59 deltoid, or thigh subcutaneous administration was similar.

60 **Metabolism.** A metabolism study in humans indicates that insulin glargine is partly metabolized at
61 the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in
62 vitro activity similar to that of insulin, M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des-30^B-Thr-insulin).
63 Unchanged drug and these degradation products are also present in the circulation.

64 **Special populations**

65 ***Age, Race, and Gender.*** Information on the effect of age, race, and gender on the pharmacokinetics
66 of LANTUS is not available. However, in controlled clinical trials in adults (n=3890) and a
67 controlled clinical trial in pediatric patients (n=349), subgroup analyses based on age, race, and
68 gender did not show differences in safety and efficacy between insulin glargine and NPH human
69 insulin.

70 ***Smoking.*** The effect of smoking on the pharmacokinetics/pharmacodynamics of LANTUS has not
71 been studied.

72 ***Pregnancy.*** The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LANTUS
73 has not been studied (see PRECAUTIONS, Pregnancy).

74 ***Obesity.*** In controlled clinical trials, which included patients with Body Mass Index (BMI) up to and
75 including 49.6 kg/m², subgroup analyses based on BMI did not show any differences in safety and
76 efficacy between insulin glargine and NPH human insulin.

77 ***Renal impairment.*** The effect of renal impairment on the pharmacokinetics of LANTUS has not
78 been studied. However, some studies with human insulin have shown increased circulating levels of
79 insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin,
80 including LANTUS, may be necessary in patients with renal dysfunction (see PRECAUTIONS,
81 Renal Impairment).

82 ***Hepatic impairment.*** The effect of hepatic impairment on the pharmacokinetics of LANTUS has not
83 been studied. However, some studies with human insulin have shown increased circulating levels of
84 insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin,
85 including LANTUS, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS,
86 Hepatic Impairment).

87 **CLINICAL STUDIES**

88 The safety and effectiveness of insulin glargine given once-daily at bedtime was compared to that of
89 once-daily and twice-daily NPH human insulin in open-label, randomized, active-control, parallel
90 studies of 2327 adult patients and 349 pediatric patients with type 1 diabetes mellitus and 1563 adult
91 patients with type 2 diabetes mellitus (see Tables 1-3). In general, LANTUS achieved a level of
92 glycemic control similar to NPH human insulin as measured by glycated hemoglobin (GHb). The
93 overall rate of hypoglycemia did not differ between patients with diabetes treated with LANTUS
94 compared with NPH human insulin.

95 **Type 1 diabetes - adult (see Table 1).** In two large, randomized, controlled clinical studies (Studies
96 A and B), patients with type 1 diabetes (Study A; n=585, Study B; n=534) were randomized to basal-
97 bolus treatment with LANTUS once daily or to NPH human insulin once or twice daily and treated
98 for 28 weeks. Regular human insulin was administered before each meal. LANTUS was
99 administered at bedtime. NPH human insulin was administered once daily at bedtime or in the
100 morning and at bedtime when used twice daily. In one large, randomized, controlled clinical study
101 (Study C), patients with type 1 diabetes (n=619) were treated for 16 weeks with a basal-bolus insulin
102 regimen where insulin lispro was used before each meal. LANTUS was administered once daily at

103 bedtime and NPH human insulin was administered once or twice daily. In these studies, LANTUS
 104 and NPH human insulin had a similar effect on glycohemoglobin with a similar overall rate of
 105 hypoglycemia.

106 **Table 1: Type 1 diabetes mellitus — Adult**

Treatment duration Treatment in combination with	Study A 28 weeks		Study B 28 weeks		Study C 16 weeks	
	Regular insulin		Regular insulin		Insulin lispro	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Number of subjects treated	292	293	264	270	310	309
Ghb						
Endstudy mean	8.13	8.07	7.55	7.49	7.53	7.60
Adj. mean change from baseline	+0.21	+0.10	-0.16	-0.21	-0.07	-0.08
LANTUS – NPH	+0.11		+0.05		+0.01	
95% CI for Treatment difference	(-0.03; +0.24)		(-0.08; +0.19)		(-0.11; +0.13)	
Basal insulin dose						
Endstudy mean	19.2	22.8	24.8	31.3	23.9	29.2
Mean change from baseline	-1.7	-0.3	-4.1	+1.8	-4.5	+0.9
Total insulin dose						
Endstudy mean	46.7	51.7	50.3	54.8	47.4	50.7
Mean change from baseline	-1.1	-0.1	+0.3	+3.7	-2.9	+0.3
Fasting blood glucose (mg/dL)						
Endstudy mean	146.3	150.8	147.8	154.4	144.4	161.3
Adj. mean change from baseline	-21.1	-16.0	-20.2	-16.9	-29.3	-11.9

107 **Type 1 diabetes – pediatric (see Table 2).** In a randomized, controlled clinical study (Study D),
 108 pediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks
 109 with a basal-bolus insulin regimen where regular human insulin was used before each meal.
 110 LANTUS was administered once daily at bedtime and NPH human insulin was administered once or
 111 twice daily. Similar effects on glycohemoglobin and the incidence of hypoglycemia were observed in
 112 both treatment groups.

113 **Table 2: Type 1 diabetes mellitus — Pediatric**

Treatment duration Treatment in combination with	Study D 28 weeks	
	Regular insulin	
	LANTUS	NPH
Number of subjects treated	174	175
Ghb		
Endstudy mean	8.91	9.18
Adj. mean change from baseline	+0.28	+0.27
LANTUS – NPH	+0.01	
95% CI for Treatment difference	(-0.24; +0.26)	
Basal insulin dose		
Endstudy mean	18.2	21.1
Mean change from baseline	-1.3	+2.4
Total insulin dose		
Endstudy mean	45.0	46.0
Mean change from baseline	+1.9	+3.4
Fasting blood glucose (mg/dL)		
Endstudy mean	171.9	182.7
Adj. mean change from baseline	-23.2	-12.2

114 **Type 2 diabetes - adult (see Table 3).** In a large, randomized, controlled clinical study (Study E)
 115 (n=570), LANTUS was evaluated for 52 weeks as part of a regimen of combination therapy with
 116 insulin and oral antidiabetic agents (a sulfonylurea, metformin, acarbose, or combinations of these
 117 drugs). LANTUS administered once daily at bedtime was as effective as NPH human insulin
 118 administered once daily at bedtime in reducing glycohemoglobin and fasting glucose. There was a
 119 low rate of hypoglycemia that was similar in LANTUS and NPH human insulin treated patients. In a
 120 large, randomized, controlled clinical study (Study F), in patients with type 2 diabetes not using oral
 121 antidiabetic agents (n=518), a basal-bolus regimen of LANTUS once daily at bedtime or NPH human
 122 insulin administered once or twice daily was evaluated for 28 weeks. Regular human insulin was
 123 used before meals as needed. LANTUS had similar effectiveness as either once- or twice-daily NPH
 124 human insulin in reducing glycohemoglobin and fasting glucose with a similar incidence of
 125 hypoglycemia.

126 **Table 3: Type 2 diabetes mellitus — Adult**

Treatment duration Treatment in combination with	Study E 52 weeks		Study F 28 weeks	
	LANTUS	NPH	LANTUS	NPH
Number of subjects treated	289	281	259	259
GHb				
Endstudy mean	8.51	8.47	8.14	7.96
Adj. mean change from baseline	-0.46	-0.38	-0.41	-0.59
LANTUS – NPH		-0.08		+0.17
95% CI for Treatment difference		(-0.28; +0.12)		(-0.00; +0.35)
Basal insulin dose				
Endstudy mean	25.9	23.6	42.9	52.5
Mean change from baseline	+11.5	+9.0	-1.2	+7.0
Total insulin dose				
Endstudy mean	25.9	23.6	74.3	80.0
Mean change from baseline	+11.5	+9.0	+10.0	+13.1
Fasting blood glucose (mg/dL)				
Endstudy mean	126.9	129.4	141.5	144.5
Adj. mean change from baseline	-49.0	-46.3	-23.8	-21.6

127 **INDICATIONS AND USAGE**

128 LANTUS is indicated for once-daily subcutaneous administration at bedtime in the treatment of adult
 129 and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who
 130 require basal (long-acting) insulin for the control of hyperglycemia.

131 **CONTRAINDICATIONS**

132 LANTUS is contraindicated in patients hypersensitive to insulin glargine or the excipients.

133 **WARNINGS**

134 **Hypoglycemia is the most common adverse effect of insulin, including LANTUS. As with all**
135 **insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose**
136 **monitoring is recommended for all patients with diabetes.**

137 **Any change of insulin should be made cautiously and only under medical supervision. Changes**
138 **in insulin strength, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal,**
139 **human), or method of manufacture (recombinant DNA versus animal-source insulin) may**
140 **result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to**
141 **be adjusted.**

142 **PRECAUTIONS**

143 **General**

144 LANTUS is not intended for intravenous administration. The prolonged duration of activity of
145 insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the
146 usual subcutaneous dose could result in severe hypoglycemia.

147 **LANTUS must not be diluted or mixed with any other insulin or solution.** If LANTUS is diluted
148 or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g.,
149 onset of action, time to peak effect) of LANTUS and/or the mixed insulin may be altered in an
150 unpredictable manner. When LANTUS and regular human insulin were mixed immediately before
151 injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin
152 was observed. The total bioavailability of the mixture was also slightly decreased compared to
153 separate injections of LANTUS and regular human insulin. The relevance of these observations in
154 dogs to humans is not known.

155 As with all insulin preparations, the time course of LANTUS action may vary in different individuals
156 or at different times in the same individual and the rate of absorption is dependent on blood supply,
157 temperature, and physical activity.

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

160 **Hypoglycemia**

161 As with all insulin preparations, hypoglycemic reactions may be associated with the administration of
162 LANTUS. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of
163 hypoglycemia may be different or less pronounced under certain conditions, such as long duration of
164 diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes
165 control (see PRECAUTIONS, Drug interactions). Such situations may result in severe hypoglycemia
166 (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

167 The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may,
168 therefore, change when the treatment regimen is changed. Patients being switched from twice daily
169 NPH insulin to once-daily LANTUS should have their LANTUS dose reduced by 20% from the

170 previous total daily NPH dose to reduce the risk of hypoglycemia. (See DOSAGE AND
171 ADMINISTRATION: Changeover to LANTUS).

172 The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia.

173 In a clinical study, symptoms of hypoglycemia or counterregulatory hormone responses were similar
174 after intravenous insulin glargine and regular human insulin both in healthy subjects and patients with
175 type 1 diabetes.

176 **Renal impairment**

177 Although studies have not been performed in patients with diabetes and renal impairment, LANTUS
178 requirements may be diminished because of reduced insulin metabolism, similar to observations
179 found with other insulins. (See CLINICAL PHARMACOLOGY, Special Populations)

180 **Hepatic impairment**

181 Although studies have not been performed in patients with diabetes and hepatic impairment,
182 LANTUS requirements may be diminished due to reduced capacity for gluconeogenesis and reduced
183 insulin metabolism, similar to observations found with other insulins. (See CLINICAL
184 PHARMACOLOGY, Special Populations)

185 **Injection site and allergic reactions**

186 As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin
187 absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives,
188 swelling, and inflammation. Continuous rotation of the injection site within a given area may help to
189 reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a
190 few weeks.

191 Reports of injection site pain were more frequent with LANTUS than NPH human insulin (2.7%
192 insulin glargine versus 0.7% NPH). The reports of pain at the injection site were usually mild and did
193 not result in discontinuation of therapy.

194 Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or
195 the excipients may, for example, be associated with generalized skin reactions, angioedema,
196 bronchospasm, hypotension, or shock and may be life threatening.

197 **Intercurrent conditions**

198 Insulin requirements may be altered during intercurrent conditions such as illness, emotional
199 disturbances, or stress.

200 **Information for patients**

201 LANTUS must only be used if the solution is clear and colorless with no particles visible (See
202 DOSAGE and ADMINISTRATION, Preparation and Handling).

203 **Patients must be advised that LANTUS must not be diluted or mixed with any other insulin or**
204 **solution. (See PRECAUTIONS: General)**

205 Patients should be instructed on self-management procedures including glucose monitoring, proper
206 injection technique, and hypoglycemia and hyperglycemia management. Patients must be instructed
207 on handling of special situations such as intercurrent conditions (illness, stress, or emotional
208 disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased
209 insulin dose, inadequate food intake, or skipped meals. Refer patients to the LANTUS Information
210 for the Patient circular for additional information.

211 As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a
212 result of hypoglycemia or hyperglycemia.

213 Patients with diabetes should be advised to inform their doctor if they are pregnant or are
214 contemplating pregnancy.

215 **Drug interactions**

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

218 The following are examples of substances that may increase the blood-glucose-lowering effect and
219 susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates,
220 fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide),
221 sulfonamide antibiotics.

222 The following are examples of substances that may reduce the blood-glucose-lowering effect of
223 insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol,
224 terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens,
225 progestogens (e.g., in oral contraceptives).

226 Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-
227 glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be
228 followed by hyperglycemia.

229 In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine,
230 guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

231 **Carcinogenesis, mutagenesis, impairment of fertility**

232 In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at
233 doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse
234 approximately 5 times the recommended human subcutaneous starting dose of 10 IU (0.008
235 mg/kg/day), based on mg/m². The findings in female mice were not conclusive due to excessive
236 mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats
237 (statistically significant) and male mice (not statistically significant) in acid vehicle containing
238 groups. These tumors were not found in female animals, in saline control, or insulin comparator
239 groups using a different vehicle. The relevance of these findings to humans is unknown.

240 Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and
241 mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations
242 (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

243 In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses
244 up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting
245 dose of 10 IU (0.008 mg/kg/day), based on mg/m², maternal toxicity due to dose-dependent
246 hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate
247 occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

248 **Pregnancy**

249 **Teratogenic effects: Pregnancy Category C.** Subcutaneous reproduction and teratology studies
250 have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits.
251 The drug was given to female rats before mating, during mating, and throughout pregnancy at doses
252 up to 0.36 mg/kg/day which is approximately 7 times the recommended human subcutaneous starting
253 dose of 10 IU (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is
254 approximately 2 times the recommended human subcutaneous starting dose of 10 IU (0.008
255 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin
256 glargine did not generally differ from those observed with regular human insulin in rats or rabbits.
257 However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the
258 cerebral ventricles. Fertility and early embryonic development appeared normal.

259 There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. It is
260 essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic
261 control before conception and throughout pregnancy. Insulin requirements may decrease during the
262 first trimester, generally increase during the second and third trimesters, and rapidly decline after
263 delivery. Careful monitoring of glucose control is essential in such patients. Because animal
264 reproduction studies are not always predictive of human response, this drug should be used during
265 pregnancy only if clearly needed.

266 **Nursing mothers**

267 It is unknown whether insulin glargine is excreted in significant amounts in human milk. Many
268 drugs, including human insulin, are excreted in human milk. For this reason, caution should be
269 exercised when LANTUS is administered to a nursing woman. Lactating women may require
270 adjustments in insulin dose and diet.

271 **Pediatric use**

272 Safety and effectiveness of LANTUS have been established in the age group 6 to 15 years with type 1
273 diabetes.

274 **Geriatric use**

275 In controlled clinical studies comparing insulin glargine to NPH human insulin, 593 of 3890 patients
276 with type 1 and type 2 diabetes were 65 years and older. The only difference in safety or
277 effectiveness in this subpopulation compared to the entire study population was an expected higher
278 incidence of cardiovascular events in both insulin glargine and NPH human insulin-treated patients.

279 In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should
280 be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the
281 elderly (See PRECAUTIONS, Hypoglycemia).

282 **ADVERSE REACTIONS**

283 The adverse events commonly associated with LANTUS include the following:

284 **Body as a whole:** allergic reactions (See PRECAUTIONS)

285 **Skin and appendages:** injection site reaction, lipodystrophy, pruritus, rash (See PRECAUTIONS)

286 **Other:** hypoglycemia (See WARNINGS and PRECAUTIONS)

287 In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site
288 pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The
289 reports of pain at the injection site were usually mild and did not result in discontinuation of therapy.
290 Other treatment-emergent injection site reactions occurred at similar incidences with both insulin
291 glargine and NPH human insulin.

292 Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and
293 fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH
294 treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy
295 was investigated by fundus photography using a grading protocol derived from the Early Treatment
296 Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with type 2 diabetes, a
297 difference in the number of subjects with ≥ 3 -step progression in ETDRS scale over a 6-month period
298 was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The
299 overall relevance of this isolated finding cannot be determined due to the small number of patients
300 involved, the short follow-up period, and the fact that this finding was not observed in other clinical
301 studies.

302 **OVERDOSAGE**

303 An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and
304 sometimes long-term and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually
305 be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be
306 needed.

307 More severe episodes with coma, seizure, or neurologic impairment may be treated with
308 intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical
309 recovery from hypoglycemia, continued observation and additional carbohydrate intake may be
310 necessary to avoid reoccurrence of hypoglycemia.

311 **DOSAGE AND ADMINISTRATION**

312 LANTUS is a recombinant human insulin analog. Its potency is approximately the same as human
313 insulin. It exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-
314 daily dosing.

315 LANTUS should be administered subcutaneously once a day at bedtime. LANTUS is not intended
316 for intravenous administration (See PRECAUTIONS). Intravenous administration of the usual
317 subcutaneous dose could result in severe hypoglycemia. The desired blood glucose levels as well as
318 the doses and timing of antidiabetic medications must be determined individually. Blood glucose

319 monitoring is recommended for all patients with diabetes. The prolonged duration of activity of
320 LANTUS is dependent on injection into subcutaneous space.

321 As with all insulins, injection sites within an injection area (abdomen, thigh or deltoid) must be
322 rotated from one injection to the next.

323 In clinical studies, there was no relevant difference in insulin glargine absorption after abdominal,
324 deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and
325 consequently the onset and duration of action, may be affected by exercise and other variables.

326

327 LANTUS is not the insulin of choice for the treatment of diabetic ketoacidosis. Intravenous short-
328 acting insulin is the preferred treatment.

329 **Pediatric use**

330 LANTUS can be safely administered to pediatric patients ≥ 6 years of age. Administration to
331 pediatric patients < 6 years has not been studied. Based on the results of a study in pediatric patients,
332 the dose recommendation for changeover to LANTUS is the same as described for adults in
333 DOSAGE AND ADMINISTRATION, Changeover to LANTUS.

334 **Initiation of LANTUS therapy**

335 In a clinical study with insulin naïve patients with type 2 diabetes already treated with oral
336 antidiabetic drugs, LANTUS was started at an average dose of 10 IU once daily, and subsequently
337 adjusted according to the patient's need to a total daily dose ranging from 2 to 100 IU.

338 **Changeover to LANTUS**

339 If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with
340 LANTUS, the amount and timing of short-acting insulin or fast-acting insulin analog or the dose of
341 any oral antidiabetic drug may need to be adjusted. In clinical studies, when patients were transferred
342 from once-daily NPH human insulin or ultralente human insulin to once-daily LANTUS, the initial
343 dose was usually not changed. However, when patients were transferred from twice-daily NPH
344 human insulin to LANTUS once daily at bedtime, to reduce the risk of hypoglycemia, the initial dose
345 (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin)
346 within the first week of treatment and then adjusted based on patient response. (See
347 PRECAUTIONS, Hypoglycemia)

348 A program of close metabolic monitoring under medical supervision is recommended during transfer
349 and in the initial weeks thereafter. The amount and timing of short-acting insulin or fast-acting
350 insulin analog may need to be adjusted. This is particularly true for patients with acquired antibodies
351 to human insulin needing high-insulin doses and occurs with all insulin analogs. Dose adjustment of
352 LANTUS and other insulins or oral antidiabetic drugs may be required; for example, if the patient's
353 weight or lifestyle changes or other circumstances arise that increase susceptibility to hypoglycemia
354 or hyperglycemia (See PRECAUTIONS, Hypoglycemia).

355 The dose may also have to be adjusted during intercurrent illness (See PRECAUTIONS, Intercurrent
356 conditions).

357 **Preparation and handling**

358 Parenteral drug products should be inspected visually prior to administration whenever the solution
359 and the container permit. LANTUS must only be used if the solution is clear and colorless with no
360 particles visible.

361 **The syringes must not contain any other medicinal product or residue.**

362 **Mixing and diluting. LANTUS must not be diluted or mixed with any other insulin or solution**
363 **(See PRECAUTIONS: General).**

364 Cartridge version only: If the OptiPen One Insulin Delivery Device malfunctions, LANTUS may be
365 drawn from the cartridge into a U 100 syringe and injected.

366 **HOW SUPPLIED**

367 LANTUS 100 units per mL (U 100) is available in the following package sizes:

368

369 5 mL vials (NDC 0088-2220-32)

370 10 mL vials (NDC 0088-2220-33)

371 3 mL cartridges*, package of 5 (NDC 0088-2220-52)

372 *Cartridges are for use only in the OptiPen™ One Insulin Delivery Device

373 **Storage**

374 Unopened LANTUS vials and cartridges should be stored in a refrigerator, 36°F - 46°F (2°C - 8°C).
375 LANTUS should not be stored in the freezer and it should not be allowed to freeze.

376 If refrigeration is not possible, the 10 mL vial or cartridge of LANTUS in use can be kept
377 unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not
378 greater than 86°F (30°C). Unrefrigerated 10 mL vials and cartridges must be used within the 28-day
379 period or they must be discarded.

380 If refrigeration is not possible, 5 mL vials of LANTUS in use can be kept unrefrigerated for up to 14
381 days away from direct heat and light, as long as the temperature is not greater than 86°F (30°C).
382 Unrefrigerated 5 mL vials must be used within the 14-day period or they must be discarded. If
383 refrigerated, the 5 mL vial of LANTUS in use can be kept for up to 28 days.

384 Once the cartridge is placed in an OptiPen One, it should not be put in the refrigerator.

385 Rx only

386 Prescribing Information as of April 2000

387 Manufactured by:

388 Hoechst Marion Roussel Deutschland GmbH

389 D-65926 Frankfurt am Main

390 Germany

Page 14 of 14
NDA 21-081
DRAFT package insert (Sponsor revision #5)
Date of submission: April 20, 2000

391 **Manufactured for:**
392 **Aventis Pharmaceuticals Inc.**
393 **Kansas City, MO 64137 USA**
394 **US Patents 5,656,722, 5,370,629, and 5,509,905**
395 **Made in Germany**

396 www.aventispharma-us.com