

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203314Orig1s000**

**LABELING**

1 **HIGHLIGHTS OF PRESCRIBING INFORMATION**  
2 **These highlights do not include all the information needed to use**  
3 **TRESIBA safely and effectively. See full prescribing information for**  
4 **TRESIBA.**

5 **TRESIBA® (insulin degludec injection), for subcutaneous use**  
6 **Initial U.S. Approval: 2015**

7 -----INDICATIONS AND USAGE-----

8 TRESIBA is a long-acting human insulin analog indicated to improve  
9 glycemic control in adults with diabetes mellitus (1).

10 **Limitations of Use:**

11 Not recommended for treating diabetic ketoacidosis.

12 -----DOSAGE AND ADMINISTRATION-----

- 13 • Individualize dose based on type of diabetes, metabolic needs, blood  
14 glucose monitoring results and glycemic control goal (2.1, 2.2, 2.3, 2.4).
- 15 • Rotate injection sites to reduce the risk of lipodystrophy (2.1).
- 16 • Do not dilute or mix with any other insulin or solution (2.1).
- 17 • Administer subcutaneously once daily at any time of day (2.2).
- 18 • Do NOT perform dose conversion when using the TRESIBA U-100 or U-  
19 200 FlexTouch pens. The TRESIBA U-100 and U-200 FlexTouch pens  
20 dose window shows the number of insulin units to be delivered and NO  
21 conversion is needed (2.2).

22 -----DOSAGE FORMS AND STRENGTHS-----

23 TRESIBA is available in the following package sizes:

- 24 • 100 units/mL (U-100): 3 mL FlexTouch® (3).
- 25 • 200 units/mL (U-200): 3 mL FlexTouch® (3).

26 -----CONTRAINDICATIONS-----

- 27 • During episodes of hypoglycemia (4).
- 28 • Hypersensitivity to TRESIBA or one of its excipients (4).

29 -----WARNINGS AND PRECAUTIONS-----

- 30 • *Never share* a TRESIBA FlexTouch pen between patients, even if the  
31 needle is changed (5.1).
- 32 • *Hyper- or hypoglycemia with changes in insulin regimen* Carry out under  
33 close medical supervision and increase frequency of blood glucose  
34 monitoring (5.2).

- 35 • *Hypoglycemia* May be life-threatening. Increase monitoring with  
36 changes to: insulin dosage, co-administered glucose lowering  
37 medications, meal pattern, physical activity; and in patients with renal  
38 impairment or hepatic impairment or hypoglycemia unawareness (5.3,  
39 5.4, 6.1).
- 40 • *Hypoglycemia due to medication errors* Accidental mix-ups between  
41 insulin products can occur. Instruct patients to check insulin labels before  
42 injection. DO NOT transfer TRESIBA into a syringe for administration as  
43 overdosage and severe hypoglycemia can result (5.4).
- 44 • *Hypersensitivity reactions* Severe, life-threatening, generalized allergy,  
45 including anaphylaxis, can occur. Discontinue TRESIBA, monitor and  
46 treat if indicated (5.5).
- 47 • *Hypokalemia* May be life-threatening. Monitor potassium levels in  
48 patients at risk for hypokalemia and treat if indicated (5.6).
- 49 • *Fluid retention and heart failure with concomitant use of*  
50 *Thiazolidinediones (TZDs)* Observe for signs and symptoms of heart  
51 failure; consider dosage reduction or discontinuation if heart failure  
52 occurs (5.7).

53 -----ADVERSE REACTIONS-----

54 Adverse reactions commonly associated with TRESIBA are:

- 55 • hypoglycemia, allergic reactions, injection site reactions, lipodystrophy,  
56 pruritus, rash, edema and weight gain (6.1).

57 **To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk**  
58 **at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

59 -----DRUG INTERACTIONS-----

- 60 • *Drugs that affect glucose metabolism* Adjustment of insulin dosage may  
61 be needed; closely monitor blood glucose (7).
- 62 • *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and*  
63 *reserpine)* Signs and symptoms of hypoglycemia may be reduced or  
64 absent (7).

65 **See 17 for PATIENT COUNSELING INFORMATION and FDA-**  
66 **approved patient labeling.**

67 **Revised: 09/2015**

68  
69  
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71

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116  
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118 listed.

119 **FULL PRESCRIBING INFORMATION**

120  
121 **1 INDICATIONS AND USAGE**

122 TRESIBA is indicated to improve glycemic control in adults with diabetes mellitus.

123  
124 Limitations of Use

125 TRESIBA is not recommended for the treatment of diabetic ketoacidosis.

126  
127 **2 DOSAGE AND ADMINISTRATION**

128  
129 **2.1 Important Administration Instructions**

- 130  
131 • Always check insulin labels before administration [*see Warnings and Precautions (5.4)*].
- 132 • Inspect visually for particulate matter and discoloration. Only use TRESIBA if the solution
- 133 appears clear and colorless.
- 134 • Train patients on proper use and injection technique before initiating TRESIBA. Training
- 135 reduces the risk of administration errors such as needle sticks and incomplete dosing.
- 136 • Inject TRESIBA subcutaneously into the thigh, upper arm, or abdomen.
- 137 • Rotate injection sites within the same region from one injection to the next to reduce the risk
- 138 of lipodystrophy [*see Adverse Reactions (6.1)*].
- 139 • DO NOT administer TRESIBA intravenously, intramuscularly or in an insulin infusion
- 140 pump.
- 141 • DO NOT dilute or mix TRESIBA with any other insulin products or solutions.
- 142 • DO NOT transfer TRESIBA from the TRESIBA pen into a syringe for administration [*see*
- 143 *Warnings and Precautions (5.4)*].
- 144

145 **2.2 General Dosing Instructions**

- 146  
147 • Inject TRESIBA subcutaneously once-daily at any time of day.
- 148 • Individualize and titrate the dose of TRESIBA based on the patient's metabolic needs, blood
- 149 glucose monitoring results, and glycemic control goal.
- 150 • The recommended days between dose increases is 3 to 4 days.
- 151 • Dose adjustments may be needed with changes in physical activity, changes in meal patterns
- 152 (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or
- 153 during acute illness to minimize the risk of hypoglycemia or hyperglycemia [*see Warnings*
- 154 *and Precautions (5.3)*].
- 155 • Instruct patients who miss a dose of TRESIBA to inject their daily dose during waking hours
- 156 upon discovering the missed dose. Instruct patients to ensure that at least 8 hours have
- 157 elapsed between consecutive TRESIBA injections.
- 158 • DO NOT perform dose conversion when using the TRESIBA U-100 or U-200 FlexTouch
- 159 pens. **The dose window for both the TRESIBA U-100 and U-200 FlexTouch pens shows**
- 160 **the number of insulin units to be delivered and NO conversion is needed.**
- 161
- 162
- 163
- 164

165 **2.3 Starting Dose in Insulin Naïve Patients**

166 *Type 1 Diabetes Mellitus:*

167 The recommended starting dose of TRESIBA in insulin naïve patients with type 1 diabetes is  
168 approximately one-third to one-half of the total daily insulin dose. The remainder of the total  
169 daily insulin dose should be administered as a short-acting insulin and divided between each  
170 daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used  
171 to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

172 *Type 2 Diabetes Mellitus:*

173 The recommended starting dose of TRESIBA in insulin naïve patients with type 2 diabetes  
174 mellitus is 10 units once daily.

175 **2.4 Starting Dose in Patients Already on Insulin Therapy**

176 *Type 1 and Type 2 Diabetes Mellitus:*

177 Start TRESIBA at the same unit dose as the total daily long or intermediate-acting insulin unit  
178 dose.

179

180

181 **3 DOSAGE FORMS AND STRENGTHS**

182 TRESIBA is available as a clear, and colorless solution for injection in:

183

- 184 • 100 units/mL (U-100): 3 mL FlexTouch disposable prefilled pen
- 185 • 200 units/mL (U-200): 3 mL FlexTouch disposable prefilled pen

186

187 **4 CONTRAINDICATIONS**

188 TRESIBA is contraindicated:

- 189 • During episodes of hypoglycemia [*see Warnings and Precautions (5.3)*].
- 190 • In patients with hypersensitivity to TRESIBA or one of its excipients [*see Warnings and*  
191 *Precautions (5.5)*].

192

193 **5 WARNINGS AND PRECAUTIONS**

194

195 **5.1 Never Share a TRESIBA FlexTouch Pen Between Patients**

196 TRESIBA FlexTouch disposable prefilled pens should never be shared between patients, even if  
197 the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

198

199 **5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen**

200 Changes in insulin, manufacturer, type, or method of administration may affect glycemic control  
201 and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously

202 and only under medical supervision and the frequency of blood glucose monitoring should be  
203 increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetic  
204 treatment may be needed. When converting from other insulin therapies to TRESIBA follow  
205 dosing recommendations [see *Dosage and Administration (2.4)*].

206

### 207 **5.3 Hypoglycemia**

208 Hypoglycemia is the most common adverse reaction of insulin, including TRESIBA [see  
209 *Adverse Reactions (6.1)*]. Severe hypoglycemia can cause seizures, may be life-threatening or  
210 cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an  
211 individual and others at risk in situations where these abilities are important (e.g., driving or  
212 operating other machinery). TRESIBA, or any insulin, should not be used during episodes of  
213 hypoglycemia [see *Contraindications (4)*].

214

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

220

#### 221 Risk Factors for Hypoglycemia

222 The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of  
223 hypoglycemia after an injection is related to the duration of action of the insulin [see *Clinical*  
224 *Pharmacology (12.2)*] and, in general, is highest when the glucose lowering effect of the insulin  
225 is maximal. As with all insulin preparations, the glucose lowering effect time course of  
226 TRESIBA may vary among different individuals or at different times in the same individual and  
227 depends on many conditions, including the area of injection as well as the injection site blood  
228 supply and temperature.

229

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

234

#### 235 Risk Mitigation Strategies for Hypoglycemia

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

241

### 242 **5.4 Hypoglycemia Due to Medication Errors**

243 Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting  
244 insulins, have been reported. To avoid medication errors between TRESIBA and other insulins,  
245 instruct patients to always check the insulin label before each injection.

246

247 Do not transfer TRESIBA from the TRESIBA pen to a syringe. The markings on the insulin

248 syringe will not measure the dose correctly and can result in overdosage and severe  
249 hypoglycemia [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.3)*].

250

### 251 **5.5 Hypersensitivity and Allergic Reactions**

252 Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin  
253 products, including TRESIBA. If hypersensitivity reactions occur, discontinue TRESIBA; treat  
254 per standard of care and monitor until symptoms and signs resolve. TRESIBA is contraindicated  
255 in patients who have had hypersensitivity reactions to insulin degludec or one of the excipients  
256 [see *Contraindications (4)*].

257

### 258 **5.6 Hypokalemia**

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

264

### 265 **5.7 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR 266 Gamma Agonist**

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

274

## 275 **6 ADVERSE REACTIONS**

276

277 The following adverse reactions are also discussed elsewhere:

278

- 279 • Hypoglycemia [see *Warnings and Precautions (5.3)*]
- 280 • Hypersensitivity and allergic reactions [see *Warnings and Precautions (5.5)*]
- 281 • Hypokalemia [see *Warnings and Precautions (5.6)*]

282

### 283 **6.1 Clinical Trial Experience**

284

285 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
286 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials  
287 of another drug and may not reflect the rates observed in practice.

288

289 The safety of TRESIBA was evaluated in nine treat to target trials of 6-12 months duration,  
290 conducted in subjects with type 1 diabetes or type 2 diabetes [see *Clinical Studies (14)*].

291

292 The data in Table 1 reflect the exposure of 1102 patients with type 1 diabetes to TRESIBA with  
293 a mean exposure duration to TRESIBA of 34 weeks. The mean age was 43 years and 1% were

294 older than 75 years. Fifty-seven percent were male, 81% were White, 2% were Black or African  
 295 American and 4% were Hispanic. The mean body mass index (BMI) was 26 kg/m<sup>2</sup>. The mean  
 296 duration of diabetes was 18 years and the mean HbA<sub>1c</sub> at baseline was 7.8%. A history of  
 297 neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in  
 298 11%, 16%, 7% and 0.5% respectively. The mean eGFR at baseline was 87 mL/min/1.73 m<sup>2</sup> and  
 299 7% of the patients had an eGFR less than 60 mL/min/1.73 m<sup>2</sup>.

300  
 301 The data in Table 2 reflect the exposure of 2713 patients with type 2 diabetes to TRESIBA with  
 302 a mean exposure duration to TRESIBA of 36 weeks. The mean age was 58 years and 3% were  
 303 older than 75 years. Fifty-eight percent were male, 71% were White, 7% were Black or African  
 304 American and 13% were Hispanic. The mean BMI was 30 kg/m<sup>2</sup>. The mean duration of diabetes  
 305 was 11 years and the mean HbA<sub>1c</sub> at baseline was 8.3 %. A history of neuropathy,  
 306 ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported for 14%, 10%,  
 307 6% and 0.6% of participants, respectively. At baseline, the mean eGFR was 83 mL/min/1.73m<sup>2</sup>  
 308 and 9% had an eGFR less than 60 mL/min/1.73 m<sup>2</sup>.

309  
 310 Common adverse reactions (excluding hypoglycemia) occurring in TRESIBA treated subjects  
 311 during clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are  
 312 listed in Table 1 and Table 2, respectively. Common adverse reactions were defined as reactions  
 313 occurring in ≥5% of the population studied. Hypoglycemia is not shown in these tables but  
 314 discussed in a dedicated subsection below.

315  
 316 **Table 1: Adverse Reactions Occurring in ≥5% of TRESIBA-Treated Patients with Type 1**  
 317 **Diabetes Mellitus**

Adverse Reaction	TRESIBA (n=1102)
Nasopharyngitis	23.9 %
Upper respiratory tract infection	11.9 %
Headache	11.8 %
Sinusitis	5.1 %
Gastroenteritis	5.1 %

319  
 320  
 321 **Table 2: Adverse Reactions Occurring in ≥5% of TRESIBA-Treated Patients with Type 2**  
 322 **Diabetes Mellitus**

Adverse Reaction	TRESIBA (n=2713)
Nasopharyngitis	12.9 %
Headache	8.8 %
Upper respiratory tract infection	8.4 %
Diarrhea	6.3 %

325 Hypoglycemia

326  
327 Hypoglycemia is the most commonly observed adverse reaction in patients using insulin,  
328 including TRESIBA [see *Warnings and Precautions (5.3)*]. The rate of reported hypoglycemia  
329 depends on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose  
330 control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons,  
331 comparing rates of hypoglycemia in clinical trials for TRESIBA with the incidence of  
332 hypoglycemia for other products may be misleading and also, may not be representative of  
333 hypoglycemia rates that will occur in clinical practice.

334  
335 The percent of participants randomized to TRESIBA who experienced at least one episode of  
336 hypoglycemia in adult clinical trials [see *Clinical Studies (14)*] of patients with type 1 and type 2  
337 diabetes respectively are shown in Table 3 and 4. No clinically important differences in risk of  
338 hypoglycemia between TRESIBA and comparators was observed in clinical trials.

339  
340 Severe hypoglycemia was defined as an episode requiring assistance of another person to  
341 actively administer carbohydrate, glucagon, or other resuscitative actions. A Novo Nordisk  
342 hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a  
343 laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a  
344 whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic  
345 symptoms).

346



347  
 348  
 349  
 350

**Table 3: Percent (%) of Type 1 Diabetes Patients Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia<sup>§</sup> on TRESIBA in Adult Clinical Trials**

	<b>Study A + insulin aspart 52 weeks</b>	<b>Study B + insulin aspart 26 weeks</b>	<b>Study C + insulin aspart 26 weeks</b>	
	<b>TRESIBA</b>	<b>TRESIBA</b>	<b>TRESIBA at the same time each day</b>	<b>TRESIBA at alternating times</b>
	<b>(N=472)</b>	<b>(N=301)</b>	<b>(N=165)</b>	<b>(N=164)</b>
<b>Severe hypoglycemia</b>				
Percent of patients	12.3%	10.6%	12.7%	10.4%
<b>Novo Nordisk hypoglycemia<sup>§</sup></b>				
Percent of patients	95.6%	93.0%	99.4%	93.9%

351 <sup>§</sup>Novo Nordisk hypoglycemia : a severe hypoglycemia episode or an episode where a laboratory or a self-measured  
 352 glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e.,  
 353 with or without the presence of hypoglycemic symptoms.)  
 354

355 **Table 4: Percent (%) of Patients with Type 2 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo**  
 356 **Nordisk Hypoglycemia<sup>§</sup> TRESIBA in Adult Clinical Trials**

	<b>Study D + 1-2 OADs* insulin naïve 52 weeks</b>	<b>Study E + 1-2 OAD*s insulin naïve 26 weeks</b>	<b>Study F ± 1-3 OADs* insulin naïve 26 weeks</b>	<b>Study G T2DM ± 0-3 OADs* 26 weeks</b>		<b>Study H T2DM ± 0-2 OADs* + insulin aspart 26 weeks</b>	<b>Study I T2DM ± 1-2 OADs* insulin naïve 26 weeks</b>
	<b>TRESIBA</b>	<b>TRESIBA</b>	<b>TRESIBA</b>	<b>TRESIBA</b>	<b>TRESIBA (alternating time)</b>	<b>TRESIBA</b>	<b>TRESIBA</b>
	<b>(N=766)</b>	<b>(N=228)</b>	<b>(N=284)</b>	<b>(N=226)</b>	<b>(N=230)</b>	<b>(N=753)</b>	<b>(N=226)</b>
<b>Severe Hypoglycemia</b>							
Percent of patients	0.3%	0	0	0.9%	0.4%	4.5%	0.4%
<b>Novo Nordisk Hypoglycemia<sup>§</sup></b>							
Percent of patients	46.5%	28.5%	50%	43.8%	50.9%	80.9%	42.5%

357 \*OAD: oral antidiabetic agent, <sup>§</sup>Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose  
 358 calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic  
 359 symptoms.  
 360

361  
362 Allergic Reactions  
363  
364 Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions,  
365 angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including  
366 TRESIBA and may be life threatening [see Warnings and Precautions (5.5)]. Hypersensitivity  
367 (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness, and itching) and  
368 urticaria were reported in 0.9% of patients treated with TRESIBA.

369  
370 Lipodystrophy

371  
372 Long-term use of insulin, including TRESIBA, can cause lipodystrophy at the site of repeated  
373 insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and  
374 lipoatrophy (thinning of adipose tissue) and may affect insulin absorption. Rotate insulin  
375 injection sites within the same region to reduce the risk of lipodystrophy [see Dosage and  
376 Administration (2.1)]. In the clinical program, lipodystrophy, lipohypertrophy, or lipoatrophy  
377 was reported in 0.3% of patients treated with TRESIBA.

378  
379 Injection Site Reactions

380  
381 Patients taking TRESIBA may experience injection site reactions, including injection site  
382 hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and  
383 injection site mass. In the clinical program, injection site reactions occurred in 3.8% of patients  
384 treated with TRESIBA.

385  
386 Weight Gain

387  
388 Weight gain can occur with insulin therapy, including TRESIBA, and has been attributed to the  
389 anabolic effects of insulin. In the clinical program after 52 weeks of treatment, patients with type  
390 1 diabetes treated with TRESIBA gained an average of 1.8 kg and patients with type 2 diabetes  
391 treated with TRESIBA gained an average of 3.0 kg.

392  
393 Peripheral Edema

394  
395 Insulin, including TRESIBA, may cause sodium retention and edema. In the clinical program,  
396 peripheral edema occurred in 0.9% of patients with type 1 diabetes mellitus and 3.0% of patients  
397 with type 2 diabetes mellitus treated with TRESIBA.

398  
399  
400 **6.2 Immunogenicity**

401 As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form.  
402 The detection of antibody formation is highly dependent on the sensitivity and specificity of the  
403 assay and may be influenced by several factors such as: assay methodology, sample handling,  
404 timing of sample collection, concomitant medication, and underlying disease. For these reasons,  
405 comparison of the incidence of antibodies to TRESIBA with the incidence of antibodies in other  
406 studies or to other products, may be misleading.

407  
 408 In studies of type 1 diabetes patients, 95.9% of patients who received TRESIBA once daily were  
 409 positive for anti-insulin antibodies (AIA) at least once during the studies, including 89.7% that  
 410 were positive at baseline. In studies of type 2 diabetes patients, 31.5% of patients who received  
 411 TRESIBA once daily were positive for AIA at least once during the studies, including 14.5%  
 412 that were positive at baseline. The antibody incidence rates for type 2 diabetes may be  
 413 underreported due to potential assay interference by endogenous insulin in samples in these  
 414 patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments  
 415 to correct for tendencies toward hyper- or hypoglycemia.

416  
 417 The incidence of anti-insulin degludec antibodies has not been established.

418  
 419 **7 DRUG INTERACTIONS**

420 Table 5 includes clinically significant drug interactions with TRESIBA.

421  
 422 **Table 5: Clinically Significant Drug Interactions with TRESIBA**

<b>Drugs That May Increase the Risk of Hypoglycemia</b>	
<i>Drugs:</i>	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DDP-4 inhibitors, SGLT-2 inhibitors
<i>Intervention:</i>	Dose reductions and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.
<b>Drugs That May Decrease the Blood Glucose Lowering Effect of TRESIBA</b>	
<i>Drugs:</i>	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
<i>Intervention:</i>	Dose increases and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.
<b>Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TRESIBA</b>	
<i>Drugs:</i>	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.
<b>Drugs That May Blunt Signs and Symptoms of Hypoglycemia</b>	

<i>Drugs:</i>	beta-blockers, clonidine, guanethidine, and reserpine
<i>Intervention:</i>	Increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.

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## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### **Pregnancy Category C**

There are no well-controlled clinical studies of the use of insulin degludec in pregnant women. Patients should be advised to discuss with their health care provider if they intend to or if they become pregnant. Because animal reproduction studies are not always predictive of human response, insulin degludec should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

Subcutaneous reproduction and teratology studies have been performed with insulin degludec and human insulin (NPH) as a comparator in rats and rabbits. In these studies, insulin was given to female rats before mating throughout pregnancy until weaning, and to rabbits during organogenesis. The effect of insulin degludec was consistent with those observed with human insulin as both caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at an insulin degludec dose of 21 U/kg/day (approximately 5 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day) and in rabbits at a dose of 3.3 U/kg/day (approximately 10 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day). The effects are probably secondary to maternal hypoglycemia.

### **8.3 Nursing Mothers**

It is unknown whether insulin degludec is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when insulin degludec is administered to a nursing mother. Women with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

In rats, insulin degludec was secreted in milk and the concentration in milk was lower than in plasma.

### **8.4 Pediatric Use**

The safety and efficacy of TRESIBA in children and adolescents under the age of 18 have not been established.

### **8.5 Geriatric Use**

464 In controlled clinical studies [see *Clinical Studies (14)*] a total of 77 (7%) of the 1102 TRESIBA  
465 -treated patients with type 1 diabetes were 65 years or older and 9 (1%) were 75 years or older.  
466 A total of 670 (25%) of the 2713 TRESIBA-treated patients with type 2 diabetes were 65 years  
467 or older and 80 (3%) were 75 years or older. Differences in safety or effectiveness were not  
468 suggested in subgroup analyses comparing subjects older than 65 years to younger subjects.

469  
470 Nevertheless, greater caution should be exercised when TRESIBA is administered to geriatric  
471 patients since greater sensitivity of some older individuals to the effects of TRESIBA cannot be  
472 ruled out. The initial dosing, dose increments, and maintenance dosage should be conservative to  
473 avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly.

474  
475 **8.6 Renal Impairment**  
476 In clinical studies [see *Clinical Studies (14)*] a total of 75 (7%) of the 1102 TRESIBA-treated  
477 patients with type 1 diabetes had an eGFR less than 60 mL/min/1.73 m<sup>2</sup> and 1(0.1%) had an  
478 eGFR less than 30 mL/min/1.73 m<sup>2</sup>. A total of 250 (9%) of the 2713 TRESIBA-treated patients  
479 with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m<sup>2</sup> and no subjects had an eGFR  
480 less than 30 mL/min/1.73 m<sup>2</sup>.

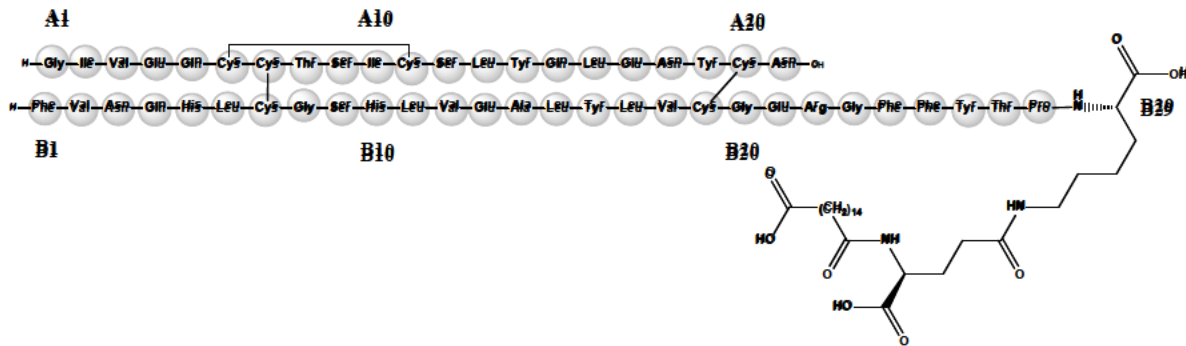
481  
482 No clinically relevant difference in the pharmacokinetics of TRESIBA was identified in a study  
483 comparing healthy subjects and subjects with renal impairment including subjects with end stage  
484 renal disease [see *Clinical Pharmacology (12.3)*]. However, as with all insulin products, glucose  
485 monitoring should be intensified and the TRESIBA dosage adjusted on an individual basis in  
486 patients with renal impairment.

487  
488 **8.7 Hepatic Impairment**  
489 No difference in the pharmacokinetics of TRESIBA was identified in a study comparing healthy  
490 subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment)  
491 [see *Clinical Pharmacology (12.3)*]. However, as with all insulin products, glucose monitoring  
492 should be intensified and the TRESIBA dosage adjusted on an individual basis in patients with  
493 hepatic impairment.

494  
495 **10 OVERDOSAGE**  
496 An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and  
497 sometimes prolonged and life-threatening hypoglycemia and hypokalemia [see *Warnings and*  
498 *Precautions (5.3,5.6)*]. Mild episodes of hypoglycemia usually can be treated with oral glucose.  
499 Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of  
500 hypoglycemia with coma, seizure, or neurologic impairment may be treated with  
501 intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent  
502 clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake  
503 may be necessary to avoid reoccurrence of hypoglycemia. Hypokalemia must be corrected  
504 appropriately.

505  
506 **11 DESCRIPTION**  
507 TRESIBA (insulin degludec injection) is a long-acting basal human insulin analog for  
508 subcutaneous injection. Insulin degludec is produced by a process that includes expression of  
509 recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

510  
 511 Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has  
 512 been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached  
 513 (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin). Insulin degludec  
 514 has a molecular formula of C<sub>274</sub>H<sub>411</sub>N<sub>65</sub>O<sub>81</sub>S<sub>6</sub> and a molecular weight of 6103.97. It has the  
 515 following structure:  
 516



517  
 518 **Figure 1: Structural Formula of TRESIBA**

519  
 520 TRESIBA is a sterile, aqueous, clear, and colorless solution that contains insulin degludec 100  
 521 units/mL (U-100) or 200 units/mL (U-200).

522  
 523 Inactive ingredients for the 100 units/mL are: glycerol 19.6 mg/mL, phenol 1.50 mg/mL,  
 524 metacresol 1.72 mg/mL, zinc 32.7 mcg/mL and water for injection.

525  
 526 Inactive ingredients for the 200 units/mL are glycerol 19.6 mg/mL, phenol 1.50 mg/mL,  
 527 metacresol 1.72 mg/mL, zinc 71.9 mcg/mL and water for injection.

528  
 529 TRESIBA has a pH of approximately 7.6. Hydrochloric acid or sodium hydroxide may be added  
 530 to adjust pH.

531  
 532 **12 CLINICAL PHARMACOLOGY**

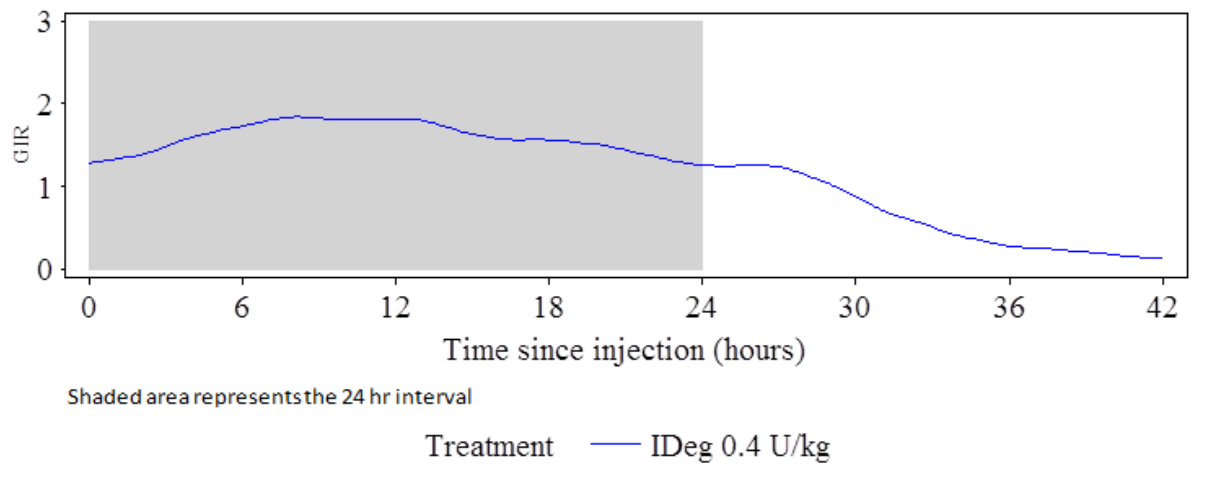
533  
 534 **12.1 Mechanism of Action**

535 The primary activity of insulin, including TRESIBA, is regulation of glucose metabolism.  
 536 Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially  
 537 by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits  
 538 lipolysis and proteolysis, and enhances protein synthesis. TRESIBA forms multi-hexamers  
 539 when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot.  
 540 The protracted time action profile of TRESIBA is predominantly due to delayed absorption of  
 541 insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent  
 542 due to binding of insulin-degludec to circulating albumin.

543  
 544 **12.2 Pharmacodynamics**

545 The glucose-lowering effect of TRESIBA after 8 days of once-daily dosing was measured in a  
 546 euglycemic glucose clamp study enrolling 21 patients with type 1 diabetes. Figure 2 shows the

547 pharmacodynamic effect of TRESIBA over time following 8 once-daily subcutaneous injections  
548 of 0.4 U/kg of TRESIBA in patients with type 1 diabetes.  
549



550  
551  
552  
553 **Figure 2: Mean GIR profile for 0.4 U/kg dose of TRESIBA (steady state) in patients with**  
554 **Type 1 diabetes mellitus**

555  
556 The mean maximum glucose lowering effect ( $GIR_{max}$ ) of a 0.4 U/kg dose of TRESIBA was 2.0  
557 mg/kg/min, which was observed at a median of 12 hours post-dose. The glucose lowering effect  
558 of TRESIBA lasted at least 42 hours after the last of 8 once-daily injections.

559  
560 In patients with type 1 diabetes mellitus, the steady-state, within subjects, day-to-day variability  
561 in total glucose lowering effect was 20% with TRESIBA (within-subject coefficient of variation  
562 for  $AUC_{GIR,t,SS}$ ).

563  
564 The total glucose-lowering effect of TRESIBA over 24 hours measured in a euglycemic clamp  
565 study after 8 days of once-daily administration in patients with type 1 diabetes increases  
566 approximately in proportion to the dose for doses between 0.4 U/kg to 0.8 U/kg.

567  
568 The total glucose-lowering effect of 0.4 U/kg of TRESIBA U-100 and 0.4 U/kg of TRESIBA U-  
569 200, administered at the same dose, and assessed over 24 hours in a euglycemic clamp study  
570 after 8 days of once-daily injection was comparable.

### 571 12.3 Pharmacokinetics

#### 572 Absorption

573  
574 In patients with type 1 diabetes, after 8 days of once daily subcutaneous dosing with 0.4 U/kg of  
575 TRESIBA, maximum degludec concentrations of 4472 pmol/L were attained at a median of 9  
576 hours ( $t_{max}$ ). After the first dose of TRESIBA, median onset of appearance was around one hour.

577  
578 Total insulin degludec concentration (i.e., exposure) increased in a dose proportional manner  
579 after subcutaneous administration of 0.4 U/kg to 0.8 U/kg TRESIBA. Total and maximum



580 insulin degludec exposure at steady state are comparable between TRESIBA U-100 and  
581 TRESIBA U-200 when each is administered at the same U/kg dose.

582  
583 Insulin degludec concentration reach steady state levels after 3-4 days of TRESIBA  
584 administration [*see Dosage and Administration (2.2)*].

585  
586 *Distribution*

587 The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of  
588 >99% in human plasma. The results of the *in vitro* protein binding studies demonstrate that there  
589 is no clinically relevant interaction between insulin degludec and other protein bound drugs.

590  
591 *Elimination*

592 The half-life after subcutaneous administration is determined primarily by the rate of absorption  
593 from the subcutaneous tissue. On average, the half-life at steady state is approximately 25 hours  
594 independent of dose. Degradation of TRESIBA is similar to that of insulin human; all  
595 metabolites formed are inactive. The mean apparent clearance of insulin degludec is 0.03 L/kg  
596 (2.1 L/h in 70 kg individual) after single subcutaneous dose of 0.4 U/kg.

597  
598 **Specific Populations**

599  
600 As with other insulin preparations, TRESIBA should always be titrated according to individual  
601 requirements.

602  
603 *Geriatrics-*

604 Pharmacokinetic and pharmacodynamic response of TRESIBA in 13 younger adult (18–35  
605 years) and 14 geriatric ( $\geq 65$  years) subjects with type 1 diabetes following two 6 day periods of  
606 once-daily subcutaneous dosing with 0.4 U/kg dose of TRESIBA or insulin glargine. On  
607 average, the pharmacokinetic and pharmacodynamic properties of TRESIBA at steady state were  
608 similar in younger adult and geriatric subjects, albeit with greater between subject variability  
609 among the geriatric subjects.

610  
611 *Gender-*

612 The effect of gender on the pharmacokinetics of TRESIBA was examined in an across-trial  
613 analysis of the pharmacokinetic and pharmacodynamic studies. Overall, there were no clinically  
614 relevant differences in the pharmacokinetic properties of insulin degludec between female and  
615 male subjects.

616  
617 *Obesity-*

618 The effect of BMI on the pharmacokinetics of TRESIBA was explored in a cross-trial analysis of  
619 pharmacokinetic and pharmacodynamic studies. For subjects with type 1 diabetes, no  
620 relationship between exposure of TRESIBA and BMI was observed. For subjects with type 1 and  
621 type 2 diabetes a trend for decrease in glucose-lowering effect of TRESIBA with increasing BMI  
622 was observed.

623  
624  
625

626 *Race and Ethnicity-*  
627 TRESIBA has been studied in a pharmacokinetic and pharmacodynamic study in Black or  
628 African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic  
629 or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2  
630 diabetes mellitus. There were no statistically significant differences between the racial and  
631 ethnic groups investigated.

632  
633 *Pregnancy-*  
634 The effect of pregnancy on the pharmacokinetics and pharmacodynamics of TRESIBA has not  
635 been studied [*see Use in Specific Populations (8.1)*].

636  
637 *Renal Impairment-*  
638 TRESIBA pharmacokinetics was studied in 32 subjects (n=4-8/group) with normal or impaired  
639 renal function/end-stage renal disease following administration of a single subcutaneous dose  
640 (0.4U/kg) of TRESIBA. Renal function was defined using creatinine clearance (Cl<sub>cr</sub>) as follows:  
641  $\geq 90$  mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and  $< 30$  mL/min  
642 (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD).  
643 Total (AUC<sub>IDeg,0-120h,SD</sub>) and peak exposure of TRESIBA were on average about 10-25% and 13-  
644 27% higher, respectively in subjects with mild to severe renal impairment except subjects with  
645 ESRD who showed similar exposure as compared to subjects with normal renal function. No  
646 systematic trend was noted for this increase in exposure across different renal impairment  
647 subgroups. Hemodialysis did not affect clearance of TRESIBA (CL/F<sub>IDeg,SD</sub>) in subjects with  
648 ESRD [*see Use in Specific Populations (8.6)*].

649  
650 *Hepatic Impairment-*  
651 TRESIBA has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal  
652 or impaired hepatic function (mild, moderate, and severe hepatic impairment) following  
653 administration of a single subcutaneous dose (0.4U/kg) of TRESIBA. Hepatic function was  
654 defined using Child-Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic  
655 impairment). No differences in the pharmacokinetics of TRESIBA were identified between  
656 healthy subjects and subjects with hepatic impairment [*see Use in Specific Populations (8.7)*].

## 657 658 **13 NONCLINICAL TOXICOLOGY**

### 659 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

660 Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the  
661 carcinogenic potential of insulin degludec. In a 52-week study including human insulin (NPH  
662 insulin) as comparator (6.7 U/kg/day), Sprague-Dawley rats were dosed subcutaneously with  
663 insulin degludec at 3.3, 6.7, and 10 U/kg/day, resulting in 5 times the human exposure (AUC)  
664 when compared to a human subcutaneous dose of 0.75 U/kg/day. Human insulin was dosed at  
665 6.7 U/kg/day. No treatment-related increases in incidences of hyperplasia, benign or malignant  
666 tumors were recorded in female mammary glands from rats dosed with insulin degludec and no  
667 treatment related changes in the female mammary gland cell proliferation were found using  
668 BrdU incorporation. Further no treatment related changes in the occurrence of hyperplastic or  
669 neoplastic lesions were seen in other tissues in animals dosed with insulin degludec when  
670 compared to vehicle or human insulin.

671

672 Genotoxicity testing of insulin degludec was not performed.

673  
674 In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin  
675 degludec up to 21 U/kg/day (approximately 5 times the human subcutaneous dose of 0.75  
676 U/kg/day, based on U/body surface area) prior to mating and in female rats during gestation had  
677 no effect on mating performance and fertility.

678

## 679 **14 CLINICAL STUDIES**

680

681 The efficacy of TRESIBA administered once-daily either at the same time each day or at any  
682 time each day in patients with type 1 diabetes and used in combination with a mealtime insulin  
683 was evaluated in three randomized, open-label, treat-to-target, active-controlled, trials. The  
684 efficacy of TRESIBA administered once-daily either at the same time each day or at any time  
685 each day in patients with type 2 diabetes and used in combination with a mealtime insulin or in  
686 combination with common oral anti-diabetic agents was evaluated in six randomized, open-label,  
687 treat-to-target active-controlled trials.

688

689 Patients treated with TRESIBA achieved levels of glycemic control similar to those achieved  
690 with LANTUS (insulin glargine 100 U/mL) and LEVEMIR (insulin detemir) and achieved  
691 statistically significant improvements compared to sitagliptin.

692

### 693 **14.1 Type 1 Diabetes – Adult**

694

695 *TRESIBA Administered at the Same Time each Day in Combination with a Rapid-Acting Insulin*  
696 *Analog at Mealtimes*

697

#### 698 *Study A*

699

700 The efficacy of TRESIBA was evaluated in a 52-week randomized, open-label, multicenter trial  
701 in 629 patients with type 1 diabetes mellitus (Study A). Patients were randomized to TRESIBA  
702 once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved  
703 labeling. Insulin aspart was administered before each meal in both treatment arms.

704

705 The mean age of the trial population was 43 years and mean duration of diabetes was 18.9 years.  
706 58.5% were male. 93% were White, 1.9% Black or African American. 5.1% were Hispanic.  
707 8.6% of patients had eGFR<60 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately 26.3 kg/m<sup>2</sup>.

708

709 At week 52, the difference in HbA<sub>1c</sub> reduction from baseline between TRESIBA and insulin  
710 glargine U-100 was -0.01% with a 95% confidence interval of [-0.14%; 0.11%] and met the pre-  
711 specified non-inferiority margin (0.4%). See Table 6, Study A.

712

#### 713 *Study B*

714

715 The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial  
716 in 455 patients with type 1 diabetes mellitus (Study B). Patients were randomized to TRESIBA  
717 or insulin detemir once-daily in the evening. After 8 weeks, insulin detemir could be dosed

718 twice-daily. 67.1% used insulin detemir once daily at end of trial. 32.9% used insulin detemir  
 719 twice daily at end of trial. Insulin aspart was administered before each meal in both treatment  
 720 arms.

721  
 722 The mean age of the trial population was 41.3 years and mean duration of diabetes was 13.9  
 723 years. 51.9% were male. 44.6% were White, 0.4% Black or African American. 4.4% were  
 724 Hispanic. 4.4% of patients had eGFR<60 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately  
 725 23.9 kg/m<sup>2</sup>.

726  
 727 At week 26, the difference in HbA<sub>1c</sub> reduction from baseline between TRESIBA and insulin  
 728 detemir was -0.09% with a 95% confidence interval of [-0.23%; 0.05%] and met the pre-  
 729 specified non-inferiority margin (0.4%). See Table 6, Study B.

730  
 731 **TABLE 6: Results at Week 52 in a Trial Comparing TRESIBA to Insulin glargine U-100**  
 732 **(Study A) and Week 26 in a Trial Comparing TRESIBA to Insulin detemir (Study B) in**  
 733 **Patients with Type 1 Diabetes Mellitus receiving Insulin aspart at Mealtimes**

	Study A		Study B	
	TRESIBA + Insulin aspart	Insulin glargine U- 100 + Insulin aspart	TRESIBA + Insulin aspart	Insulin detemir + Insulin aspart
<b>N</b>	<b>472</b>	<b>157</b>	<b>302</b>	<b>153</b>
<b>HbA<sub>1c</sub> (%)</b>				
Baseline	7.7	7.7	8.0	8.0
End of trial	7.3	7.3	7.3	7.3
Adjusted mean change from baseline*	-0.36	-0.34	-0.71	-0.61
Estimated treatment difference [95%CI] TRESIBA - Insulin glargine U-100	-0.01 [-0.14;0.11]		-0.09 [-0.23;0.05]	
<b>Proportion Achieving HbA<sub>1c</sub> &lt; 7% at Trial End</b>	39.8%	42.7%	41.1%	37.3%
<b>FPG (mg/dL)</b>				
Baseline	165	174	178	171
End of trial	141	149	131	161
Adjusted mean change from baseline	-27.6	-21.6	-43.3	-13.5
<b>Daily basal insulin dose</b>				
Baseline mean	28 U	26 U	22 U	22 U
Mean dose at end of study	29 U <sup>1</sup>	31 U <sup>1</sup>	25 U <sup>2</sup>	29 U <sup>2</sup>
<b>Daily bolus insulin dose</b>				
Baseline mean	29 U	29 U	28 U	31 U

Mean dose at end of study	32 U <sup>1</sup>	35 U <sup>1</sup>	36 U <sup>2</sup>	41 U <sup>2</sup>
---------------------------	-------------------	-------------------	-------------------	-------------------

<sup>1</sup>At Week 52

<sup>2</sup>At Week 26

\*The change from baseline to end of treatment visit in HbA<sub>1c</sub> was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA<sub>1c</sub> as covariates. In Study A, there were 14.8% of subjects in the TRESIBA and 11.5% Insulin glargine arms for whom data was missing at the time of the HbA<sub>1c</sub> measurement. In Study B, there were 6.3% of subjects in the TRESIBA and 9.8% Insulin detemir arms for whom data was missing at the time of the HbA<sub>1c</sub> measurement.

*Study C: TRESIBA Administered at the Same Time each Day or at Any Time each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes*

The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial in 493 patients with type 1 diabetes mellitus. Patients were randomized to TRESIBA injected once-daily at the same time each day (with the main evening meal), to TRESIBA injected once daily at any time each day or to insulin glargine U-100 injected once-daily according to the approved labeling. The any time each day TRESIBA arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily, dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 43.7 years and mean duration of diabetes was 18.5 years. 57.6% were male. 97.6% were White, 1.8% Black or African American. 3.4% were Hispanic. 7.4% of patients had eGFR<60 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately 26.7 kg/m<sup>2</sup>.

At week 26, the difference in HbA<sub>1c</sub> reduction from baseline between TRESIBA administered at alternating times and insulin glargine U-100 was 0.17% with a 95% confidence interval of [0.04%; 0.30%] and met the pre-specified non-inferiority margin (0.4%). See Table 7.

**Table 7: Results at Week 26 in a Trial Comparing TRESIBA Dosed Once Daily at the Same and at Alternating Times Each Day to Insulin glargine U-100 in Patients with Type 1 Diabetes Mellitus receiving Insulin aspart at mealtimes**

	TRESIBA at the same time each day + Insulin aspart	TRESIBA at alternating times + Insulin aspart	Insulin glargine U-100 + Insulin aspart
N	165	164	164
<b>HbA<sub>1c</sub>(%)</b>			
Baseline	7.7	7.7	7.7
End of trial	7.3	7.3	7.1
Adjusted mean change from baseline*	-0.41	-0.40	-0.57

Estimated treatment difference [95%CI]		0.17 [0.04;0.30]	
TRESIBA alternating - Insulin glargine U-100			
<b>Proportion Achieving HbA<sub>1c</sub> &lt; 7% at Trial End</b>	37.0%	37.2%	40.9%
<b>FPG (mg/dL)</b>			
Baseline	179	173	175
End of trial	133	149	151
Adjusted mean change from baseline	-41.8	-24.7	-23.9
<b>Daily basal insulin dose</b>			
Baseline mean	28 U	29 U	29 U
Mean dose at end of study	32 U	36 U	35 U
<b>Daily bolus insulin dose</b>			
Baseline mean	29 U	33 U	32 U
Mean dose at end of study	27 U	30 U	35 U

The change from baseline to end of treatment visit in HbA<sub>1c</sub> was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA<sub>1c</sub> as covariates. In Study C, there were 15.8% and 15.9% of subjects in the TRESIBA (same time and alternating times respectively) and 7.9% Insulin glargine arms for whom data was missing at the time of the HbA<sub>1c</sub> measurement.

## 14.2 Type 2 Diabetes – Adult

*Study D: TRESIBA Administered at the Same Time each Day as an Add-on to Metformin with or without a DPP4-inhibitor in Insulin Naïve Patients*

The efficacy of TRESIBA was evaluated in a 52-week randomized, open-label, multicenter trial that enrolled 1030 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs). Patients were randomized to TRESIBA once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Metformin alone (82.5%) or in combination with a DPP4 inhibitor (17.5%) was used as background therapy in both treatment arms.

The mean age of the trial population was 59.1 years and mean duration of diabetes was 9.2 years. 61.9% were male. 88.4% were White, 7.1% Black or African American. 17.2% were Hispanic. 9.6% of patients had eGFR < 60 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately 31.1 kg/m<sup>2</sup>.

At week 52, the difference in HbA<sub>1c</sub> reduction from baseline between TRESIBA and insulin glargine U-100 was 0.09% with a 95% confidence interval of [-0.04%; 0.22%] and met the pre-specified non-inferiority margin (0.4%); See Table 8.

**Table 8: Results at Week 52 in a Trial Comparing TRESIBA to Insulin glargine U-100 in Patients with Type 2 Diabetes Mellitus on OAD(s)\***

	TRESIBA + OAD(s)*	Insulin glargine U-100 + OAD(s)*
--	-------------------	----------------------------------

<b>N</b>	<b>773</b>	<b>257</b>
<b>HbA<sub>1c</sub> (%)</b>		
Baseline	8.2	8.2
End of trial	7.1	7.0
Adjusted mean change from baseline <sup>**</sup>	-1.06	-1.15
Estimated treatment difference [95%CI] TRESIBA - Insulin glargine U-100	0.09 [-0.04;0.22]	
<b>Proportion Achieving HbA<sub>1c</sub> &lt; 7% at Trial End</b>	51.7%	54.1%
<b>FPG (mg/dL)</b>		
Baseline	174	174
End of trial	106	115
Adjusted mean change from baseline	-68.0	-60.2
<b>Daily insulin dose</b>		
Baseline mean (starting dose)	10 U	10 U
Mean dose after 52 weeks	56 U	58 U

795 \* OAD: oral antidiabetic agent

796 \*\* The change from baseline to end of treatment visit in HbA<sub>1c</sub> was analysed using ANOVA with treatment,  
797 region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA<sub>1c</sub> as covariates.  
798 In Study D, there were 20.6% of subjects in the TRESIBA and 22.2% Insulin glargine arms for whom data was  
799 missing at the time of the HbA<sub>1c</sub> measurement.

800

801 *Study E: TRESIBA U-200 Administered at the Same Time each Day as an Add-on to Metformin*  
802 *with or without a DPP4-inhibitor in Insulin Naïve Patients*

803

804 The efficacy of TRESIBA U-200 was evaluated in a 26-week randomized, open-label,  
805 multicenter trial in 457 insulin naïve patients with type 2 diabetes mellitus inadequately  
806 controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized  
807 to TRESIBA U-200 once-daily with the evening meal or insulin glargine U-100 once-daily  
808 according to the approved labeling. Both treatment arms were receiving metformin alone (84%)  
809 or in combination with a DPP4 inhibitor (16%) as background therapy.

810

811 The mean age of the trial population was 57.5 years and mean duration of diabetes was 8.2 years.  
812 53.2% were male. 78.3% were White, 13.8% Black or African American. 7.9% were Hispanic.  
813 7.5% of patients had eGFR <60 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately 32.4 kg/m<sup>2</sup>.

814

815 At week 26, the difference in HbA<sub>1c</sub> reduction from baseline between TRESIBA U-200 and  
816 insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.11%; 0.19%] and met  
817 the pre-specified non-inferiority margin (0.4%). See Table 9.

818

819

820 **Table 9: Results at Week 26 in a Trial Comparing TRESIBA U-200 to Insulin glargine U-**  
 821 **100 in Patients with Type 2 Diabetes Mellitus on OAD(s)\***

	<b>TRESIBA U-200 + Met ± DPP-4</b>	<b>Insulin glargine U-100 + Met ± DPP-4</b>
<b>N</b>	<b>228</b>	<b>229</b>
<b>HbA<sub>1c</sub> (%)</b>		
Baseline	8.3	8.2
End of trial	7.0	6.9
Adjusted mean change from baseline**	-1.18	-1.22
Estimated treatment difference [95%CI] TRESIBA - Insulin glargine U-100	0.04 [-0.11;0.19]	
<b>Proportion Achieving HbA<sub>1c</sub> &lt; 7% at Trial End</b>	52.2%	55.9%
<b>FPG (mg/dL)</b>		
Baseline	172	174
End of trial	106	113
Adjusted mean change from baseline	-71.1	-63.5
<b>Daily insulin dose</b>		
Baseline mean	10 U	10 U
Mean dose after 26 weeks	59 U	62 U

822 \*OAD: oral antidiabetic agent

823 \*\* The change from baseline to end of treatment visit in HbA<sub>1c</sub> was analysed using ANOVA with treatment,  
 824 region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA<sub>1c</sub> as covariates.  
 825 In Study E, there were 12.3% of subjects in the TRESIBA and 12.7% Insulin glargine arms for whom data was  
 826 missing at the time of the HbA<sub>1c</sub> measurement.

827  
 828 *Study F: TRESIBA Administered at the Same Time each Day in Insulin Naïve Patients as an*  
 829 *Add-on to One or More of the Following Oral Agents: Metformin, Sulfonylurea, Glinides or*  
 830 *Alpha-Glucosidase inhibitors*

831  
 832 The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial  
 833 in Asia in 435 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one  
 834 or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA  
 835 once-daily in the evening or insulin glargine U-100 once-daily according to the approved  
 836 labeling. Pre-trial oral antidiabetes agents were continued as background therapy except for  
 837 DPP-4 inhibitors or thiazolidinediones in both treatment arms.

838  
 839 The mean age of the trial population was 58.6 years and mean duration of diabetes was 11.6  
 840 years. 53.6% were male. All patients were Asian. 10.9% of patients had eGFR<60  
 841 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately 25.0 kg/m<sup>2</sup>.



843 At week 26, the difference in HbA<sub>1c</sub> reduction from baseline between TRESIBA and insulin  
 844 glargine U-100 was 0.11% with a 95% confidence interval of [-0.03%; 0.24%] and met the pre-  
 845 specified non-inferiority margin (0.4%). See Table 10.

846 **Table 10: Results at Week 26 in a Trial Comparing TRESIBA to Insulin glargine U-100 in**  
 847 **Patients with Type 2 Diabetes Mellitus on OAD(s)\***

	<b>TRESIBA + OAD(s)*</b>	<b>Insulin glargine U-100 + OAD(s)*</b>
<b>N</b>	<b>289</b>	<b>146</b>
<b>HbA<sub>1c</sub> (%)</b>		
Baseline	8.4	8.5
End of trial	7.2	7.1
Adjusted mean change from baseline**	-1.42	-1.52
Estimated treatment difference [95%CI] TRESIBA - Insulin glargine U-100	0.11 [-0.03 ; 0.24]	
<b>Proportion Achieving HbA<sub>1c</sub> &lt; 7% at Trial End</b>	40.8%	48.6%
<b>FPG (mg/dL)</b>		
Baseline	152	156
End of trial	100	102
Adjusted mean change from baseline	-54.6	-53.0
<b>Daily insulin dose</b>		
Baseline mean (starting dose)	9 U	9 U
Mean dose after 26 weeks	19 U	24 U

848 \*OAD: oral antidiabetic agent

849 \*\* The change from baseline to end of treatment visit in HbA<sub>1c</sub> was analysed using ANOVA with treatment,  
 850 region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA<sub>1c</sub> as covariates.  
 851 In Study F, there were 10% of subjects in the TRESIBA and 6.8% Insulin glargine arms for whom data was  
 852 missing at the time of the HbA<sub>1c</sub> measurement.

853 *Study G: TRESIBA Administered at the Same Time each Day or Any Time each Day as an Add-*  
 854 *on to One and up to Three of the Following Oral Agents: Metformin, Sulfonylurea or Glinides or*  
 855 *Pioglitazone*

856  
 857 The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial  
 858 in 687 patients with type 2 diabetes mellitus inadequately controlled on basal insulin alone, oral  
 859 antidiabetic agents (OADs) alone or both basal insulin and OAD. Patients were randomized to  
 860 TRESIBA injected once-daily at the same time each day (with the main evening meal), to  
 861 TRESIBA injected once daily at any time each day or to insulin glargine U-100 injected once-  
 862 daily according to the approved labeling. The any time each day TRESIBA arm was designed to  
 863 simulate a worst-case scenario injection schedule of alternating short and long, once daily,

864 dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA in this arm  
 865 was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday,  
 866 Thursday, Saturday, and Sunday. Up to three of the following oral antidiabetes agents  
 867 (metformin, sulfonylureas, glinides or thiazolidinediones) were administered as background  
 868 therapy in both treatment arms.

869  
 870 The mean age of the trial population was 56.4 years and mean duration of diabetes was 10.6  
 871 years. 53.9% were male. 66.7% were White, 2.5% Black or African American. 10.6% were  
 872 Hispanic. 5.8% of patients had eGFR<60 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately  
 873 29.6 kg/m<sup>2</sup>.

874  
 875 At week 26, the difference in HbA<sub>1c</sub> reduction from baseline between TRESIBA at alternating  
 876 times and insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.12%; 0.20%].  
 877 This comparison met the pre-specified non-inferiority margin (0.4%). See Table 11.  
 878

879 **Table 11: Results at Week 26 in a Trial Comparing TRESIBA at same and alternating**  
 880 **times to Insulin glargine U-100 in Patients with Type 2 Diabetes Mellitus on OAD(s)\*\***

	<b>TRESIBA at the same time each day ± OAD(s)*</b>	<b>TRESIBA at alternating times ± OAD(s)*</b>	<b>Insulin glargine U-100 ± OAD(s)*</b>
<b>N</b>	<b>228</b>	<b>229</b>	<b>230</b>
<b>HbA<sub>1c</sub> (%)</b>			
Baseline	8.4	8.5	8.4
End of trial	7.3	7.2	7.1
Adjusted mean change from baseline**	-1.03	-1.17	-1.21
Estimated treatment difference [95%CI] TRESIBA alternating- Insulin glargine U-100		0.04 [-0.12;0.20]	
Estimated treatment difference TRESIBA alternating – TRESIBA same	-0.13		
<b>Proportion Achieving HbA<sub>1c</sub> &lt; 7% at Trial End</b>	40.8%	38.9%	43.9%
<b>FPG (mg/dL)</b>			
Baseline	158	162	163
End of trial	105	105	112
Adjusted mean change from baseline	-54.2	-55.0	-47.5
<b>Daily insulin dose</b>			
Baseline mean	21 U	19 U	19 U
Mean dose after 26 weeks	45 U	46 U	44 U

881 OAD: oral antidiabetic agent

882       \*\* The change from baseline to end of treatment visit in HbA<sub>1c</sub> was analysed using ANOVA with treatment,  
 883       region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA<sub>1c</sub> as covariates.  
 884       In Study G, there were 11.4% subjects for TRESIBA (both same time and alternating times) and 11.7% Insulin  
 885       glargine arms for whom data was missing at the time of the HbA<sub>1c</sub> measurement.

887       *Study H: TRESIBA Administered at the Same Time each Day in Combination with a Rapid-*  
 888       *Acting Insulin Analog at Mealtimes*

890       The efficacy of TRESIBA was evaluated in a 52-week randomized, open-label, multicenter trial  
 891       in 992 patients with type 2 diabetes mellitus inadequately controlled on premix insulin, bolus  
 892       insulin alone, basal insulin alone, oral antidiabetic agents (OADs) alone or any combination  
 893       thereof. Patients were randomized to TRESIBA once-daily with the main evening meal or insulin  
 894       glargine U-100 once-daily according to the approved labeling. Insulin aspart was administered  
 895       before each meal in both treatment arms. Up to two of the following oral antidiabetes agents  
 896       (metformin or pioglitazone) were used as background therapy in both treatment arms.

898       The mean age of the trial population was 58.9 years and mean duration of diabetes was 13.5  
 899       years. 54.2% were male. 82.9% were White, 9.5% Black or African American. 12.0% were  
 900       Hispanic. 12.4% of patients had eGFR < 60 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately  
 901       32.2 kg/m<sup>2</sup>.

903       At week 52, the difference in HbA<sub>1c</sub> reduction from baseline between TRESIBA and insulin  
 904       glargine U-100 was 0.08% with a 95% confidence interval of [-0.05%; 0.21%] and met the pre-  
 905       specified non-inferiority margin (0.4%). See Table 12.

906       **Table 12: Results at Week 52 in a Trial Comparing TRESIBA to Insulin glargine U-100 in**  
 907       **Patients with Type 2 Diabetes Mellitus receiving Insulin aspart at mealtimes and OADs\***  
 908

	<b>TRESIBA + Insulin aspart ± OAD(s)*</b>	<b>Insulin glargine U- 100 + Insulin aspart ± OAD(s)*</b>
<b>N</b>	<b>744</b>	<b>248</b>
<b>HbA<sub>1c</sub> (%)</b>		
Baseline	8.3	8.4
End of trial	7.1	7.1
Adjusted mean change from baseline**	-1.10	-1.18
Estimated treatment difference [95% CI] TRESIBA - Insulin glargine U-100	0.08 [-0.05;0.21]	
<b>Proportion Achieving HbA<sub>1c</sub> &lt; 7% at Trial End</b>	49.5%	50.0%
<b>FPG (mg/dL)</b>		
Baseline	166	166
End of trial	122	127
Adjusted mean change	-40.6	-35.3

from baseline		
<b>Daily basal insulin dose</b>		
Baseline mean	42 U	41 U
Mean dose after 52 weeks	74 U	67 U
<b>Daily bolus insulin dose</b>		
Baseline mean	33 U	33 U
Mean dose after 52 weeks	70 U	73 U

\*OAD: oral antidiabetic agent

\*\* The change from baseline to end of treatment visit in HbA<sub>1c</sub> was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA<sub>1c</sub> as covariates.

In Study H, there were 16.1% of subjects in the TRESIBA and 14.5% Insulin glargine arms for whom data was missing at the time of the HbA<sub>1c</sub> measurement.

*Study I: TRESIBA Administered at Any Time each Day as an Add-on to One or Two of the Following Oral Agents: Metformin, Sulfonylurea, or Pioglitazone*

The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial in 447 patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agent (OADs) at baseline. Patients were randomized to TRESIBA once-daily at any time of day or sitagliptin once-daily according to the approved labeling. One or two of the following oral antidiabetes agents (metformin, sulfonylurea or pioglitazone) were also administered in both treatment arms.

The mean age of the trial population was 55.7 years and mean duration of diabetes was 7.7 years. 58.6% were male. 61.3% were White, 7.6% Black or African American. 21.0% were Hispanic. 6% of patients had eGFR<60 mL/min/1.73m<sup>2</sup>. The mean BMI was approximately 30.4 kg/m<sup>2</sup>.

At the end of 26 weeks, TRESIBA provided greater reduction in mean HbA<sub>1c</sub> compared to sitagliptin (p < 0.001). See Table 13.

**Table 13: Results at Week 26 in a Trial Comparing TRESIBA to Sitagliptin in Patients with Type 2 Diabetes Mellitus on OADs\***

	<b>TRESIBA + OAD(s)*</b>	<b>Sitagliptin + OAD(s)*</b>
<b>N</b>	<b>225</b>	<b>222</b>
<b>HbA<sub>1c</sub> (%)</b>		
Baseline	8.8	9.0
End of trial	7.2	7.7
Adjusted mean change from baseline **	-1.52	-1.09
Estimated treatment difference [95% CI] TRESIBA - Sitagliptin	-0.43 [-0.61;-0.24] <sup>1</sup>	
<b>Proportion Achieving HbA<sub>1c</sub> &lt; 7% at Trial End</b>	40.9%	27.9%
<b>FPG (mg/dL)</b>		

Baseline	170	179
End of trial	112	154
Adjusted mean change from baseline	-61.4	-22.3
<b>Daily insulin dose</b>		
Baseline mean	10 U	N/A
Mean dose after 26 weeks	43 U	N/A

935  
936  
937  
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940  
941  
942

\* OAD: oral antidiabetic agent

\*\* The change from baseline to end of treatment visit in HbA<sub>1c</sub> was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA<sub>1c</sub> as covariates.

In Study I, there were 20.9% of subjects in the TRESIBA and 22.5% Sitagliptin arms for whom data was missing at the time of the HbA<sub>1c</sub> measurement.

<sup>1</sup>p <0.001; 1-sided p-value evaluated at 2.5% level for superiority

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

TRESIBA is available as a clear and colorless solution in the following package sizes (see Table 14).

947  
948

**Table 14 Presentations of TRESIBA**

TRESIBA	Total volume	Concentration	Total units available in presentation	NDC number	Max dose per injection	Dose increment	Pack Size
U-100 FlexTouch	3 mL	100 units/mL	300 Units	0169-2660-15	80 Units	1 Unit	5 pens.
U-200 FlexTouch	3 mL	200 units/mL	600 Units	0169-2550-13	160 Units	2 Unit	3 pens.

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### 16.2 Recommended Storage

Unused TRESIBA should be stored between 36°F to 46°F (2°C and 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use TRESIBA if it has been frozen.

#### Unopened FlexTouch disposable prefilled pen:

Not in-use (unopened) TRESIBA disposable prefilled pen should be stored in a refrigerator (36°F - 46°F [2°C - 8°C]). Discard after expiration date.

958

#### Open (In-Use) FlexTouch disposable prefilled pen:

The in-use TRESIBA FlexTouch pen should NOT be refrigerated but should be kept at room temperature (below 86°F [30°C]) away from direct heat and light. The opened (in-use) TRESIBA FlexTouch pen may be used for up to 56 days (8 weeks) after being opened, if it is kept at room temperature.

964

965 The storage conditions are summarized in Table 15:

966 **Table 15: Storage Conditions for TRESIBA FlexTouch**

	<b>Not in-use (unopened)</b>  <b>Refrigerated</b> <b>(36°F - 46°F [2°C - 8°C])</b>	<b>Not in-use (unopened)</b>  <b>Room Temperature</b> <b>(below 86°F [30°C])</b>	<b>In-use (opened)</b>  <b>Room Temperature</b> <b>(below 86°F [30°C])</b>
3 mL TRESIBA U-100 FlexTouch	Until expiration date	56 days (8 weeks)	56 days (8 weeks) <b>(Do not refrigerate)</b>
3 mL TRESIBA U-200 FlexTouch	Until expiration date	56 days (8 weeks)	56 days (8 weeks) <b>(Do not refrigerate)</b>

967

968

969

970 **17 PATIENT COUNSELING INFORMATION**

971 See FDA-Approved Patient Labeling (Patient Information and Instructions for Use)

972

973 **Never Share a TRESIBA FlexTouch Pen Between Patients**

974 Advise patients that they should never share a TRESIBA FlexTouch, pen device with another  
975 person, even if the needle is changed, because doing so carries a risk for transmission of blood-  
976 borne pathogens [see *Warnings and Precautions (5.1)*].

977

978 **Hyperglycemia or Hypoglycemia**

979 Inform patients that hypoglycemia is the most common adverse reaction with insulin. Inform  
980 patients of the symptoms of hypoglycemia. Inform patients that the ability to concentrate and  
981 react may be impaired as a result of hypoglycemia. This may present a risk in situations where  
982 these abilities are especially important, such as driving or operating other machinery. Advise  
983 patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to  
984 use caution when driving or operating machinery.

985

986 Advise patients that changes in insulin regimen can predispose to hyper- or hypoglycemia.

987 Advise patients that changes in insulin regimen should be made under close medical supervision  
988 [see *Warnings and Precautions (5.2)*].

989

990 **Medication errors**

991 Inform patients to always check the insulin label before each injection [see *Warnings and*  
992 *Precautions (5.4)*]. TRESIBA FlexTouch pen is available in concentrations of 100 units/mL or  
993 200 units/mL.

994

995 Inform patients that the dose counter of TRESIBA FlexTouch pen shows the number of units of  
996 TRESIBA to be injected. NO dose re-calculation is required [see *Dosage and Administration*  
997 *(2.2)*].

998 Instruct patients that when injecting TRESIBA, they must press and hold down the dose button  
999 until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6. When  
1000 the dose counter returns to 0, the prescribed dose is not completely delivered until 6 seconds  
1001 later. If the needle is removed earlier, they may see a stream of insulin coming from the needle  
1002 tip. If so, the full dose will not be delivered (a possible under-dose may occur by as much as  
1003 20%), and they should increase the frequency of checking their blood glucose levels and possible  
1004 additional insulin administration may be necessary.  
1005

- 1006 • If 0 does not appear in the dose counter after continuously pressing the dose button, the  
1007 patient may have used a blocked needle. In this case they would **not** have received **any**  
1008 insulin – even though the dose counter has moved from the original dose that was set.
- 1009 • If the patient did have a blocked or damaged needle, instruct them to change the needle as  
1010 described in Step 15 of the Instructions for Use and repeat all steps in the IFU starting  
1011 with a new needle and the Section Preparing your TRESIBA FlexTouch Pen. **Make sure**  
1012 **the patient selects the full dose needed.**  
1013

1014 If patients routinely do not hold the needle under the skin as recommended, the patient may need  
1015 to slightly increase the dialed insulin dose to achieve the patient’s glycemic targets.  
1016

1017 Instruct patients to not re-use needles. A new needle must be attached before each injection.  
1018 Reuse of needles increases the risk of blocked needles which may cause under-dosing or  
1019 overdosing.  
1020

1021 Instruct Patients to never use a syringe to remove TRESIBA from the FlexTouch disposable  
1022 insulin prefilled pen.  
1023

### 1024 **Administration**

1025 TRESIBA must only be used if the solution is clear and colorless with no particles visible.  
1026 Patients must be advised that TRESIBA must NOT be diluted or mixed with any other insulin or  
1027 solution [*see Dosage and Administration (2.1)*].  
1028

### 1029 **Management of Hypoglycemia and Handling of Special Situations**

1030 Patients should be instructed on self-management procedures including glucose monitoring,  
1031 proper injection technique, and management of hypoglycemia and hyperglycemia. Patients must  
1032 be instructed on handling of special situations such as intercurrent conditions (illness, stress, or  
1033 emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an  
1034 increased insulin dose, inadequate food intake, and skipped meals [*see Warnings and*  
1035 *Precautions (5.3)*].  
1036

1037 Refer patients to the TRESIBA “Patient Information” for additional information about the  
1038 potential side effects of insulin therapy, including lipodystrophy (and the need to rotate injection  
1039 sites within the same body region), weight gain, allergic reactions, and hypoglycemia.  
1040

### 1041 **Women of Reproductive Potential**

1042 Advise patients to inform their health care professional if they are pregnant or are contemplating  
1043 pregnancy.

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**Rx Only**

Date of Issue:

Version:

*Novo Nordisk*<sup>®</sup>, *TRESIBA*<sup>®</sup>, *FlexTouch*<sup>®</sup>, *LEVEMIR*<sup>®</sup>, *NOVOLOG*<sup>®</sup>, *NovoFine*<sup>®</sup> and *NovoTwist*<sup>®</sup> are registered trademarks of Novo Nordisk A/S.

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TRESIBA<sup>®</sup> is covered by US Patent No. 7,615,532 and other patents pending.

FlexTouch<sup>®</sup> is covered by US Patent Nos. 6,899,699, 7,686,786, 8,672,898, 8,684,969, 8,920,383, D724,721, D734,450 and other patents pending.

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**Patient Information**  
**TRESIBA® (tre-SI-bah)**  
(insulin degludec injection)

**Do not share your TRESIBA FlexTouch insulin delivery device with other people, even if the needle has changed. You may give other people a serious infection, or get a serious infection from them.**

**What is TRESIBA?**

- TRESIBA is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus.
- TRESIBA is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- TRESIBA is available in 2 concentrations: The 100 units/mL pen can be injected from 1 to 80 units in a single injection, in increments of 1 unit. The 200 units/mL pen can be injected from 2 to 160 units in a single injection, in increments of 2 units.
- It is not known if TRESIBA is safe and effective in children under 18 years of age.

**Who should not take TRESIBA?**

**Do not take TRESIBA if you:**

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to TRESIBA or any of the ingredients in TRESIBA.

**Before taking TRESIBA, tell your healthcare provider about all your medical conditions including, if you are:**

- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

**Before you start taking TRESIBA, talk to your healthcare provider about low blood sugar and how to manage it.**

**How should I take TRESIBA?**

- **Read the Instructions for Use** that come with your TRESIBA.
- Take TRESIBA exactly as your healthcare provider tells you to.
- **Do not do any conversion of your dose. The dose counter always shows the selected dose in units.** Both the 100 units/mL and 200 units/mL TRESIBA FlexTouch pens are made to deliver your insulin dose in units.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- If you miss or are delayed in taking your dose of TRESIBA:
  - Take your dose as soon as you remember then continue with your regular dosing schedule.
  - Make sure there are at least **8** hours between your doses.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **Do not reuse or share your needles with other people.** You may give other people a serious infection or get a serious infection from them.
- **Never** inject TRESIBA into a vein or muscle.
- **Never** use a syringe to remove TRESIBA from the FlexTouch pen.

**What should I avoid while taking TRESIBA?**

**While taking TRESIBA do not:**

- Drive or operate heavy machinery, until you know how TRESIBA affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

**What are the possible side effects of TRESIBA?**

**TRESIBA may cause serious side effects that can lead to death, including:**

- **Low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness    ○ blurred vision    ○ anxiety, irritability, or mood changes
  - sweating    ○ slurred speech    ○ hunger
  - confusion    ○ shakiness    ○ headache
  - fast heart beat
- **Low potassium in your blood (hypokalemia).**
- **Heart failure.** Taking certain diabetes pills called thiazolidinediones or “TZDs” with TRESIBA may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure, it may get worse while you take TZDs with TRESIBA. Your healthcare provider should monitor you closely while you are taking TZDs with TRESIBA. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, tiredness, swelling of your ankles or feet and sudden weight gain. Treatment with TZDs and TRESIBA may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

**Your insulin dose may need to change because of:**

- change in level of physical activity or exercise
- weight gain or loss
- increased stress
- illness
- change in diet

**Common side effects of TRESIBA may include:**

- serious allergic reactions (whole body reactions), reactions at the injection site, skin thickening or pits at the injection site (lipodystrophy), itching, rash, swelling of your hands and feet, and weight gain.

**Get emergency medical help if you have:**

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of TRESIBA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of TRESIBA.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about TRESIBA that is written for health professionals. Do not use TRESIBA for a condition for which it was not prescribed. Do not give TRESIBA to other people, even if they have the same symptoms that you have. It may harm them.

**What are the ingredients in TRESIBA?**

**Active Ingredient:** insulin degludec

**Inactive Ingredients:** zinc, metacresol, glycerol, phenol, and water for injection. Hydrochloric acid or sodium hydroxide may be added.

**Manufactured by:** Novo Nordisk A/S DK-2880 Bagsvaerd, Denmark

For more information, go to [www.novonordisk-us.com](http://www.novonordisk-us.com) or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: 09/2015

**Instructions for Use**  
**TRESIBA® (tre-SI-bah) FlexTouch® Pen 100 units/mL**  
(insulin degludec injection)

- **Do not share your TRESIBA FlexTouch Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.**
- **TRESIBA FlexTouch Pen 100 units/mL (“Pen”) is a prefilled disposable pen containing 300 units of TRESIBA (insulin degludec injection) 100 units/mL insulin. You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.**
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

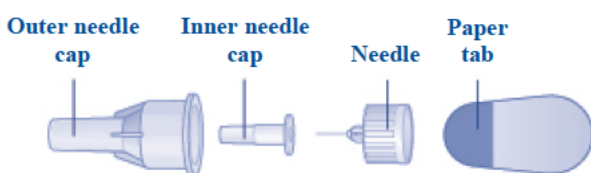
**Supplies you will need to give your TRESIBA injection:**

- TRESIBA FlexTouch Pen
- a new NovoFine or NovoTwist needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. See “After your injection” at the end of these instructions.

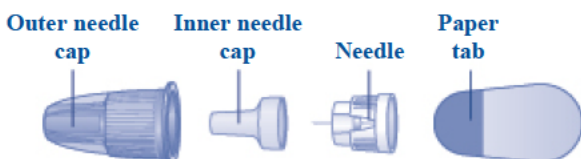
**Preparing your TRESIBA FlexTouch Pen:**

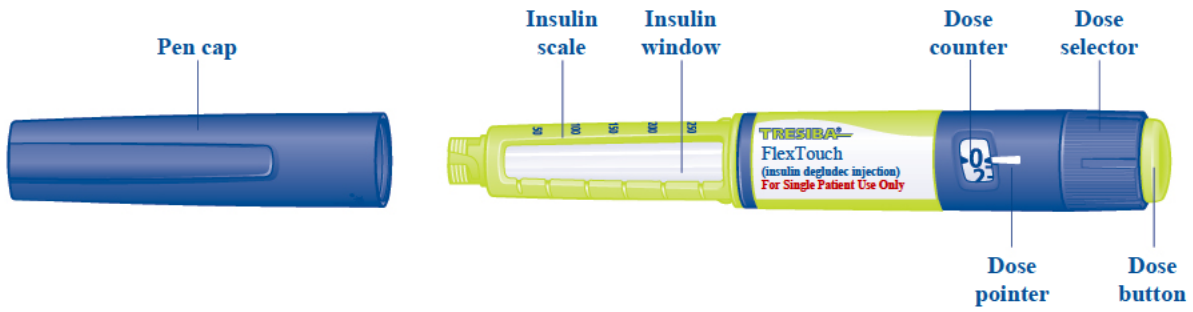
- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the TRESIBA FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- TRESIBA should look clear and colorless. **Do not use TRESIBA if it is cloudy or colored.**
- **Do not use TRESIBA past the expiration date printed on the label or 56 days after you start using the Pen.**
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.**

**NovoFine®**



**NovoTwist®**

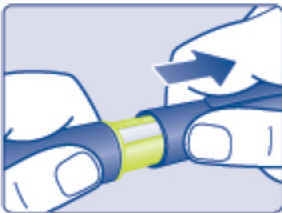




(Figure A)

**Step 1:**

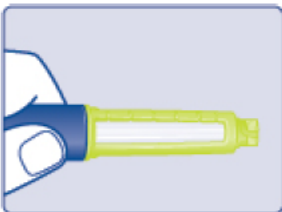
- Pull Pen cap straight off (See Figure B).



(Figure B)

**Step 2:**

- **Check the liquid in the Pen** (See Figure C). TRESIBA should look clear and colorless. **Do not** use it if it looks cloudy or colored.



(Figure C)

**Step 3:**

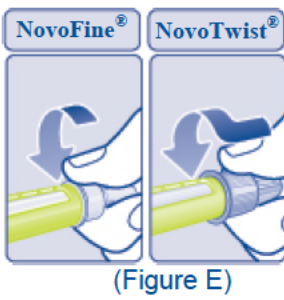
- **Select a new needle.**
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

**Step 4:**

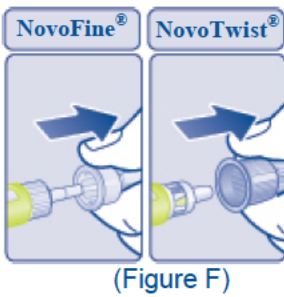
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

**Step 5:**

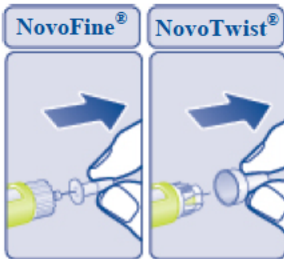
- Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

**Step 6:**

- Pull off the inner needle cap and throw it away (See Figure G).

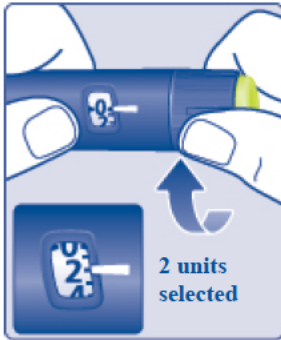


(Figure G)

## Priming your TRESIBA FlexTouch Pen:

### Step 7:

- Turn the dose selector to **select 2 units** (See Figure H).



(Figure H)

### Step 8:

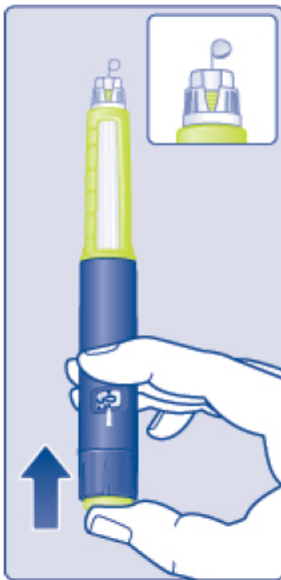
- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



(Figure I)

### Step 9:

- **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
  - o If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
  - o If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.



(Figure J)

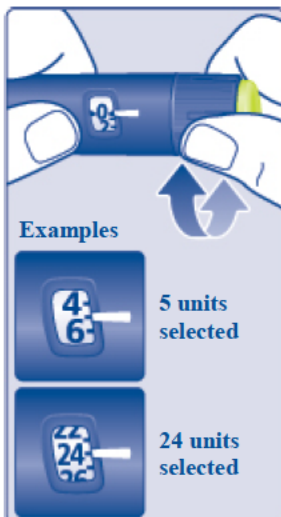
### Selecting your dose:

#### Step 10:

TRESIBA FlexTouch Pen 100 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. **Do not perform any dose conversion.**

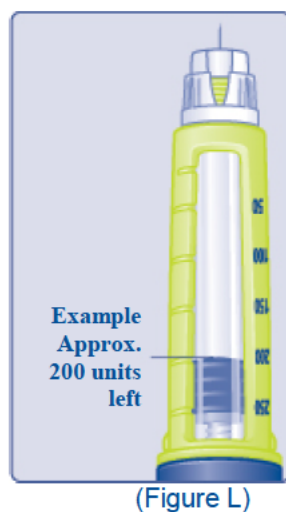
**Check to make sure the dose selector is set at 0.**

- **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).
  - o If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - o The **even** numbers are printed on the dial.
  - o The **odd** numbers are shown as lines.



(Figure K)

- The TRESIBA FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



- **To see how much insulin is left in your TRESIBA FlexTouch Pen:**

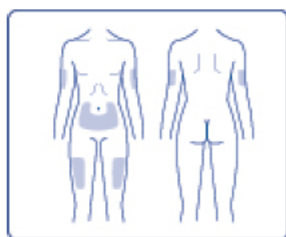
- o Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen.
- o If the dose counter shows **less than 80**, the number shown in the dose counter is the number of units left in your Pen.

**Giving your injection:**

- Inject your TRESIBA exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- TRESIBA can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

**Step 11:**

- Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.

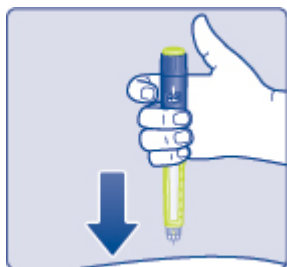


(Figure M)



**Step 12:**

- **Insert the needle into your skin** (See Figure N).
  - **Make sure you can see the dose counter.** **Do not** cover it with your fingers, this can stop your injection.



(Figure N)

**Step 13:**

- **Press and hold down the dose button until the dose counter shows “0”** (See Figure O).
  - The “0” must line up with the dose pointer. You may then hear or feel a click.



(Figure O)

- **Keep the needle in your skin after the dose counter has returned to “0” and slowly count to 6** (See Figure P).
  - **When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.**
  - **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
  - **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**

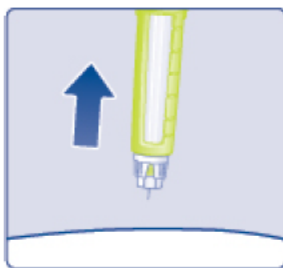


(Figure P)

**Step 14:**

- **Pull the needle out of your skin** (See Figure Q).

o If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.

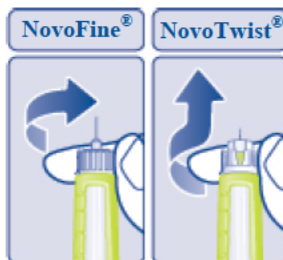


(Figure Q)

**Step 15:**

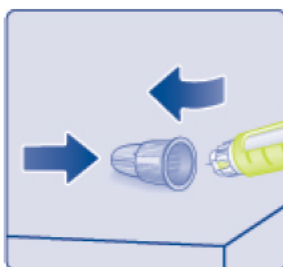
- **Carefully remove the needle from the Pen and throw it away** (See Figure R).

o **Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.

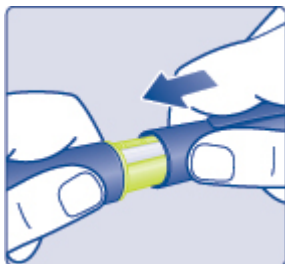


(Figure S)

- o **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

#### Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

#### After your injection:

- Put your used TRESIBA FlexTouch Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - o made of a heavy-duty plastic
  - o can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - o upright and stable during use
  - o leak-resistant
  - o properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

#### How should I store my TRESIBA FlexTouch Pen?

##### Before use:

- Store unused TRESIBA FlexTouch Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze TRESIBA. **Do not** use TRESIBA if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

##### Pen in use:

- Store the Pen you are currently using out of the refrigerator below 86°F.
- Keep TRESIBA away from heat or light.

- The TRESIBA FlexTouch Pen you are using should be thrown away after 56 days, even if it still has insulin left in it and the expiration date has not passed.

**General Information about the safe and effective use of TRESIBA.**

- **Keep TRESIBA FlexTouch Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not** share TRESIBA FlexTouch Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

**Manufactured by:**

Novo Nordisk A/S  
DK-2880 Bagsvaerd, Denmark

**Revised: 09/2015**



For more information go to [www.TRESIBA.com](http://www.TRESIBA.com)

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## Instructions for Use

### TRESIBA<sup>®</sup> (tre-SI-bah) FlexTouch<sup>®</sup> Pen 200 units/mL

(insulin degludec injection)

- **Do not share your TRESIBA FlexTouch Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.**
- **TRESIBA FlexTouch Pen 200 units/mL (“Pen”) is a prefilled disposable pen containing 600 units of TRESIBA (insulin degludec injection) 200 units/mL insulin. You can inject from 2 to 160 units in a single injection. The units can be increased by 2 units at a time.**
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

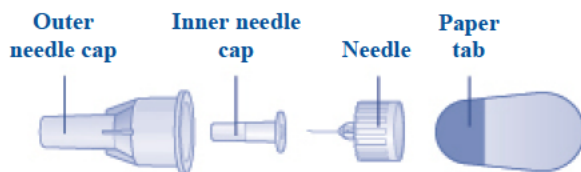
#### Supplies you will need to give your TRESIBA injection:

- TRESIBA FlexTouch Pen
- a new NovoFine or NovoTwist needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. See “After your injection” at the end of these instructions.

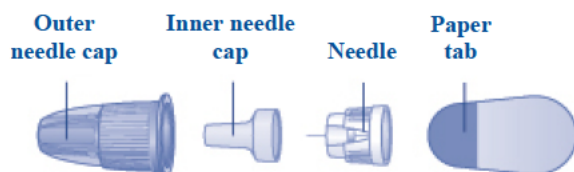
#### Preparing your TRESIBA FlexTouch Pen:

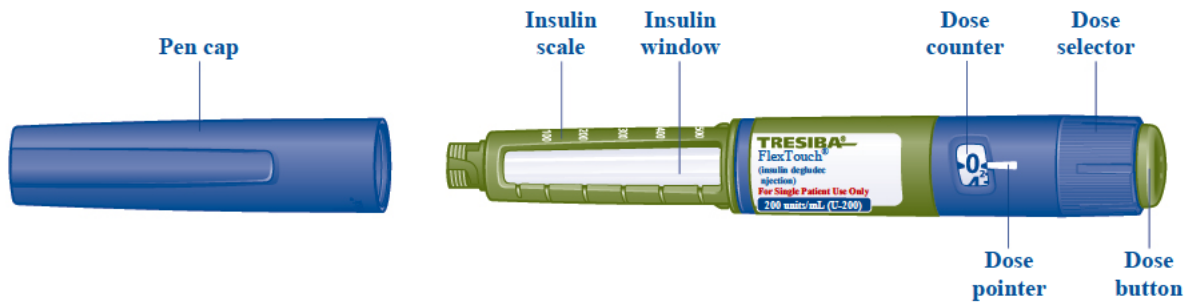
- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the TRESIBA FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- TRESIBA should look clear and colorless. **Do not** use TRESIBA if it is cloudy or colored.
- **Do not** use TRESIBA past the expiration date printed on the label or 56 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.**

#### NovoFine<sup>®</sup>



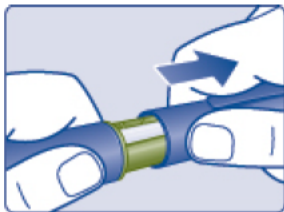
#### NovoTwist<sup>®</sup>





**Step 1:**

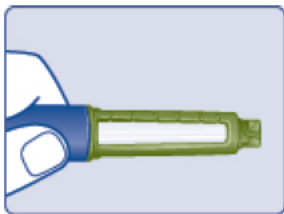
- Pull Pen cap straight off (See Figure B).



(Figure B)

**Step 2:**

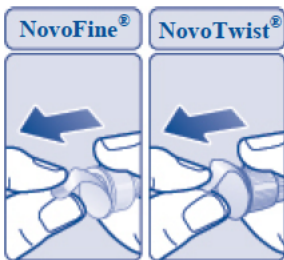
- **Check the liquid in the Pen** (See Figure C). TRESIBA should look clear and colorless. **Do not** use it if it looks cloudy or colored.



(Figure C)

**Step 3:**

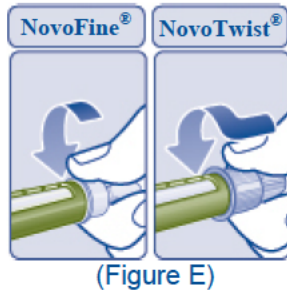
- **Select a new needle.**
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

**Step 4:**

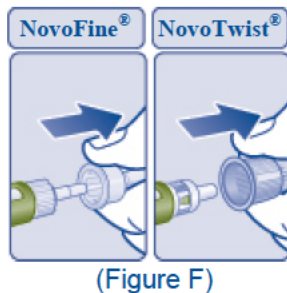
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

**Step 5:**

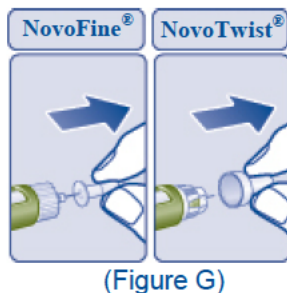
- Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

**Step 6:**

- Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

## Priming your TRESIBA FlexTouch Pen:

### Step 7:

- Turn the dose selector to **select 2 units** (See Figure H).



(Figure H)

### Step 8:

- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



(Figure I)

### Step 9:

- **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
  - If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
  - If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.





(Figure J)

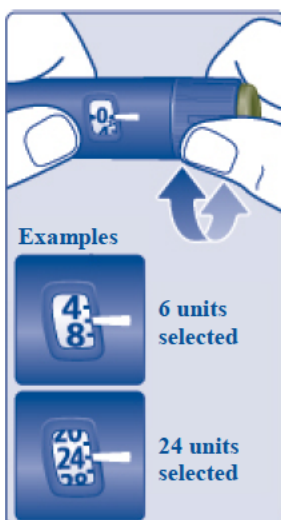
### Selecting your dose:

#### Step 10:

TRESIBA FlexTouch Pen 200 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. **Do not perform any dose conversion.**

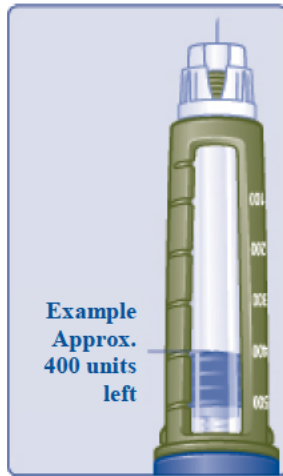
**Check to make sure the dose selector is set at 0.**

- **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - Each line on the dial is an even number.



(Figure K)

- The TRESIBA FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



(Figure L)

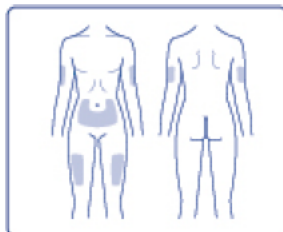
- **To see how much insulin is left in your TRESIBA FlexTouch Pen:**
  - Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 160, there are **at least 160** units left in your Pen.
  - If the dose counter shows **less than 160**, the number shown in the dose counter is the number of units left in your Pen.

#### Giving your injection:

- Inject your TRESIBA exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- TRESIBA can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

#### Step 11:

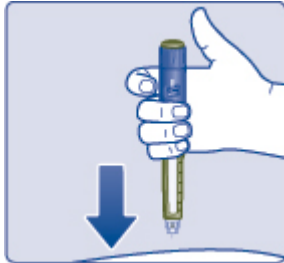
- Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.



(Figure M)

**Step 12:**

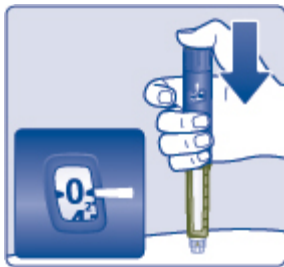
- **Insert the needle into your skin** (See Figure N).
  - **Make sure you can see the dose counter. Do not** cover it with your fingers, this can stop your injection.



(Figure N)

**Step 13:**

- **Press and hold down the dose button until the dose counter shows “0”** (See Figure O).
  - The “0” must line up with the dose pointer. You may then hear or feel a click.



(Figure O)

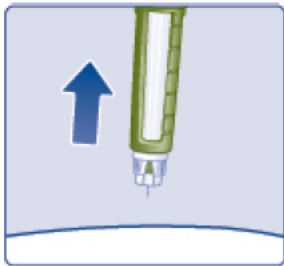
- **Keep the needle in your skin after** the dose counter has returned to “0” and **slowly count to 6** (See Figure P).
  - **When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.**
  - **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
  - **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**



(Figure P)

**Step 14:**

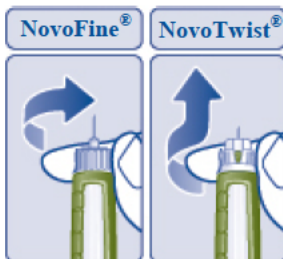
- **Pull the needle out of your skin** (See Figure Q).
  - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



(Figure Q)

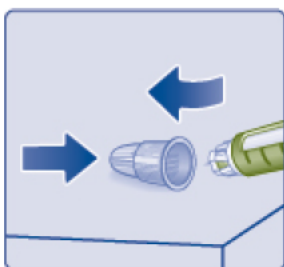
**Step 15:**

- **Carefully remove the needle from the Pen and throw it away** (See Figure R).
  - **Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.

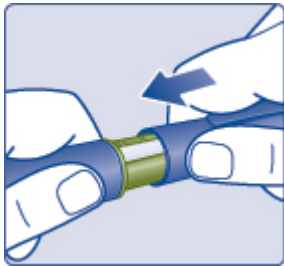


(Figure S)

- **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

**Step 16:**

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

**After your injection:**

- Put your used TRESIBA FlexTouch Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

**How should I store my TRESIBA FlexTouch Pen?**

**Before use:**

- Store unused TRESIBA FlexTouch Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze TRESIBA. **Do not** use TRESIBA if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

**Pen in use:**

- Store the Pen you are currently using out of the refrigerator below 86°F.
- Keep TRESIBA away from heat or light.
- The TRESIBA FlexTouch Pen you are using should be thrown away after 56 days, even if it still has insulin left in it and the expiration date has not passed.

**General Information about the safe and effective use of TRESIBA.**

- **Keep TRESIBA FlexTouch Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not** share TRESIBA FlexTouch Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

**Manufactured by:**

Novo Nordisk A/S  
DK-2880 Bagsvaerd, Denmark

**Revised: 09/2015**



For more information go to [www.TRESIBA.com](http://www.TRESIBA.com)

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Code centre line  
Code: 100% Dispersion  
Length: Max 29 mm (100%)

(b) (4)

2  
8



22-521-00

NDC 0169-2660-15 List: 266015  
**TRESIBA<sup>®</sup>**  
**FlexTouch<sup>®</sup>**  
(insulin degludec injection)  
**100 units/mL (U-100)**  
5x3 mL Prefilled Pens

8-9560-31-301-1

**Warning**  
Any change of insulin should be made cautiously and only under medical supervision. Tresiba<sup>®</sup> FlexTouch<sup>®</sup> 100 units/mL is for single person use only. See accompanying literature for dosage. Needles not included. For subcutaneous use.

Each mL contains 100 Units of insulin degludec (600 nmol/mL); glycerol, 19.6 mg; metacresol, 1.72 mg; phenol, 1.50 mg; zinc, 32.7 mcg, and water for injection.

Novo Nordisk<sup>®</sup>, Tresiba<sup>®</sup>, FlexTouch<sup>®</sup>, NovoFine<sup>®</sup>, and NovoTwist<sup>®</sup> are registered trademarks of Novo Nordisk A/S. Tresiba<sup>®</sup> is covered by US Patent No. 7,615,532 and other patents pending. FlexTouch<sup>®</sup> is covered by US Patent Nos. 6,899,699, 7,686,786, 8,672,898, 8,684,969, 8,920,383, D724,721, D734,450 and other patents pending.



3 01692 66015 3

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Novo Nordisk Inc.  
Plainsboro, NJ 08536  
www.novonordisk-us.com  
1-800-727-6500

(Se habla español)

Manufactured by:  
Novo Nordisk A/S  
DK-2880 Bagsvaerd  
Denmark



**TRESIBA<sup>®</sup>**  
**FlexTouch<sup>®</sup>**  
(insulin degludec injection)  
**100 units/mL (U-100)**  
5x3 mL Prefilled Pens



NDC 0169-2660-15 List: 266015  
**TRESIBA<sup>®</sup>**  
**FlexTouch<sup>®</sup>**  
(insulin degludec injection)  
**For Single Patient Use Only**  
**100 units/mL (U-100)**

5x 3 mL Prefilled Pens

For subcutaneous use only  
Rx Only

Recommended for use with NovoFine<sup>®</sup>,  
NovoFine<sup>®</sup> Plus or NovoTwist<sup>®</sup>  
disposable needles.  
Keep in a cold place until first use.  
Store at 36°F - 46°F (2°C - 8°C).  
Do not freeze.  
Protect from light.

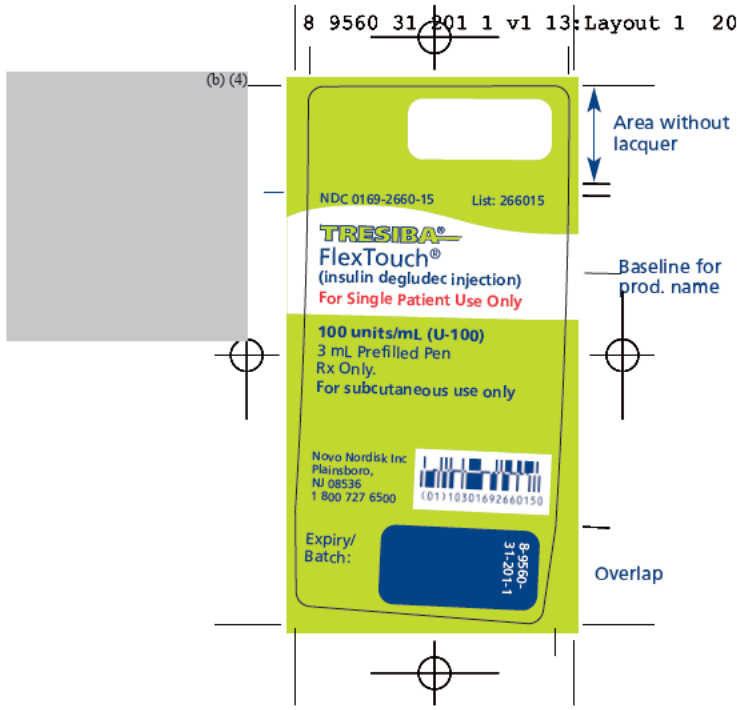


Expiry/Batch:

**TRESIBA<sup>®</sup>**  
**FlexTouch<sup>®</sup>**  
(insulin degludec injection)  
**100 units/mL (U-100)**  
5x 3 mL Prefilled Pens

**TRESIBA<sup>®</sup>**  
**FlexTouch<sup>®</sup>**  
(insulin degludec injection)  
**100 units/mL (U-100)**  
5x3 mL Prefilled Pens



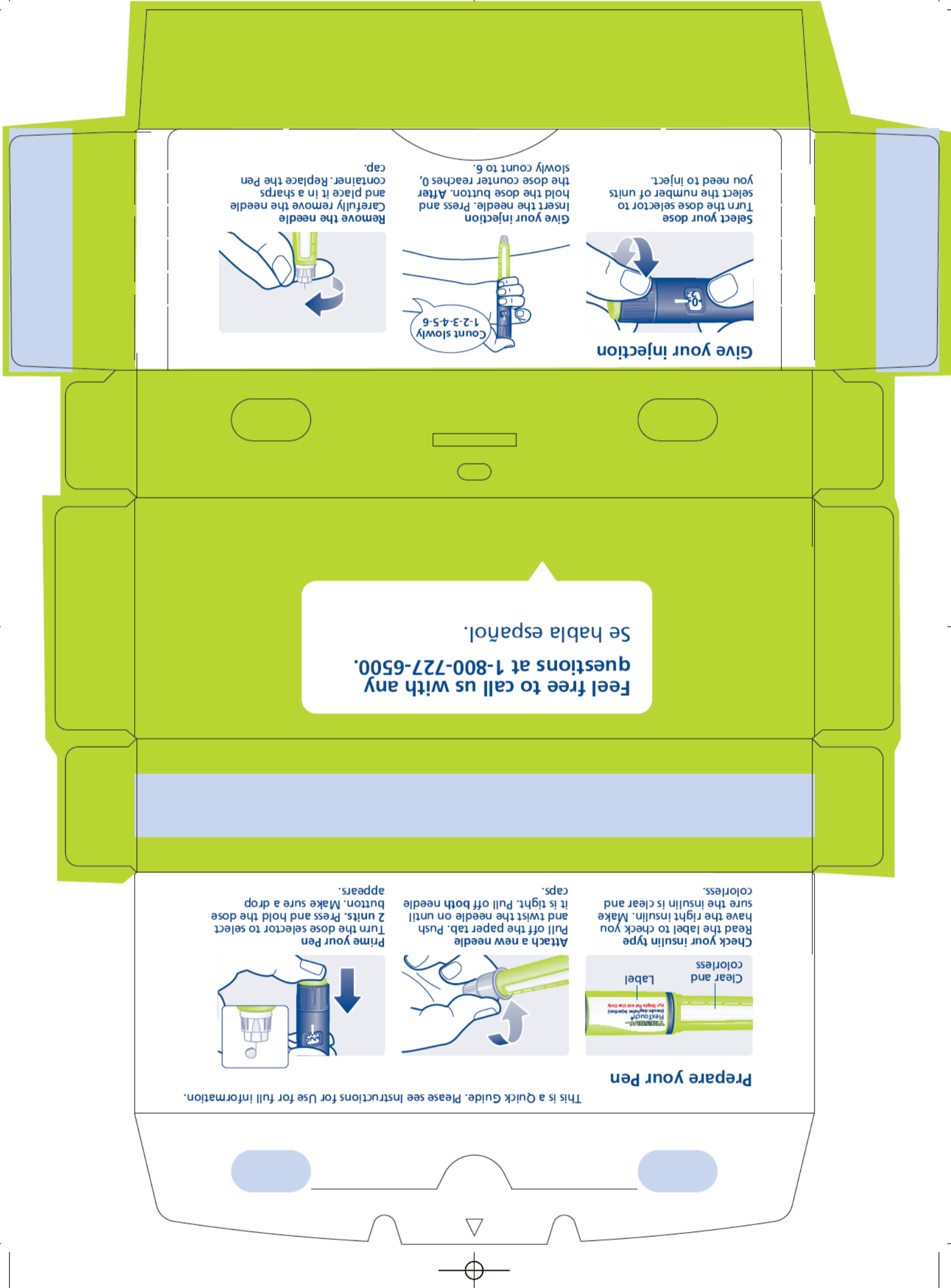




(b) (4)



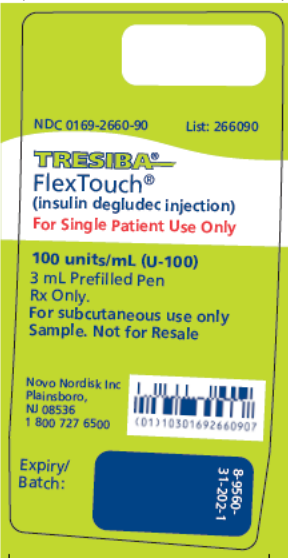
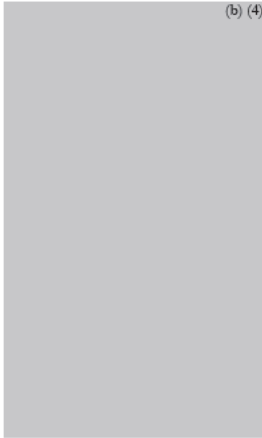
(b) (4)



(b) (4)

8 9560 31 202 1 v1 17

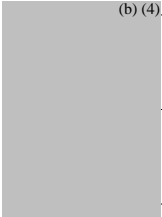
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Baseline for prod. name

Overlap



(b) (4)

Rx:  
Tresiba® FlexTouch®  
(insulin degludec injection)  
100 units/mL (U-100)  
■ 1 box (5x3 mL)  
(NDC 0169-2660-15)  
■ NovoFine® Plus 32G  
disposable needles  
1 box (#100)  
(NDC 0169-1855-50)

8-9560-31-220-1

Code: 100% Direction - Code centreline - Length: Max 29 mm (100%)



**Warning**  
 Any change of insulin should be made cautiously and only under medical supervision. TRESIBA FlexTouch 200 units/mL is for single person use only. See accompanying literature for dosage. Needles not included. For subcutaneous use.

Each mL contains 200 Units of insulin degludec (1200 nmol/mL); glycerol, 19.6 mg; metacresol, 1.72 mg; phenol, 1.50 mg; zinc, 71.9 mcg, and water for injection.

Novo Nordisk, TRESIBA, FlexTouch, NovoFine, and NovoTwist are registered trademarks of Novo Nordisk A/S. TRESIBA is covered by US Patent No. 7,615,532 and other patents pending. FlexTouch is covered by US Patent Nos. 6,899,699, 7,686,786, 8,672,898, 8,684,969, 8,920,383, D724,721, D734,450 and other patents pending.



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 Plainsboro, NJ 08536  
 www.novonordisk-us.com  
 1-800-727-6500  
 (Se habla español)  
 Manufactured by:  
 Novo Nordisk A/S  
 DK-2880 Bagsvaerd  
 Denmark



NDC 0169-2550-13 List: 255013  
**TRESIBA**  
 FlexTouch  
 (insulin degludec injection)  
**200 units/mL (U-200)**  
 3x3 mL Prefilled Pens

NDC 0169-2550-13 List: 255013  
**TRESIBA**  
 FlexTouch  
 (insulin degludec injection)  
**For Single Patient Use Only**  
**200 units/mL (U-200)**

3x3 mL Prefilled Pens  
 For subcutaneous use only  
 Rx Only

Recommended for use with NovoFine, NovoFine Plus or NovoTwist disposable needles. Keep in a cold place until first use. Store at 36°F - 46°F (2°C - 8°C). Do not freeze. Protect from light.



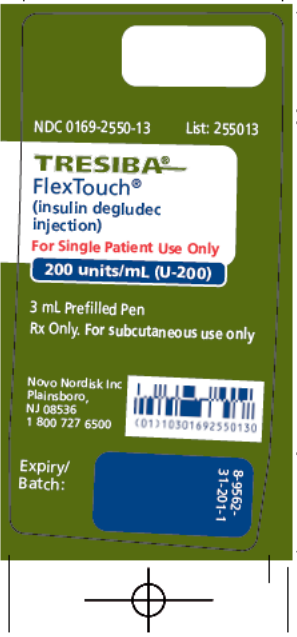
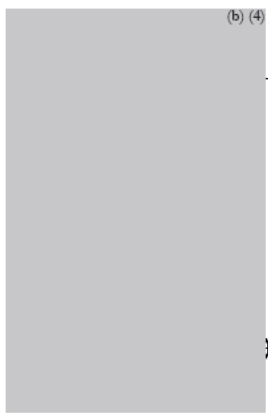
Expiry/Batch:



(b) (4)

8 9562 31 201 1 v1 15

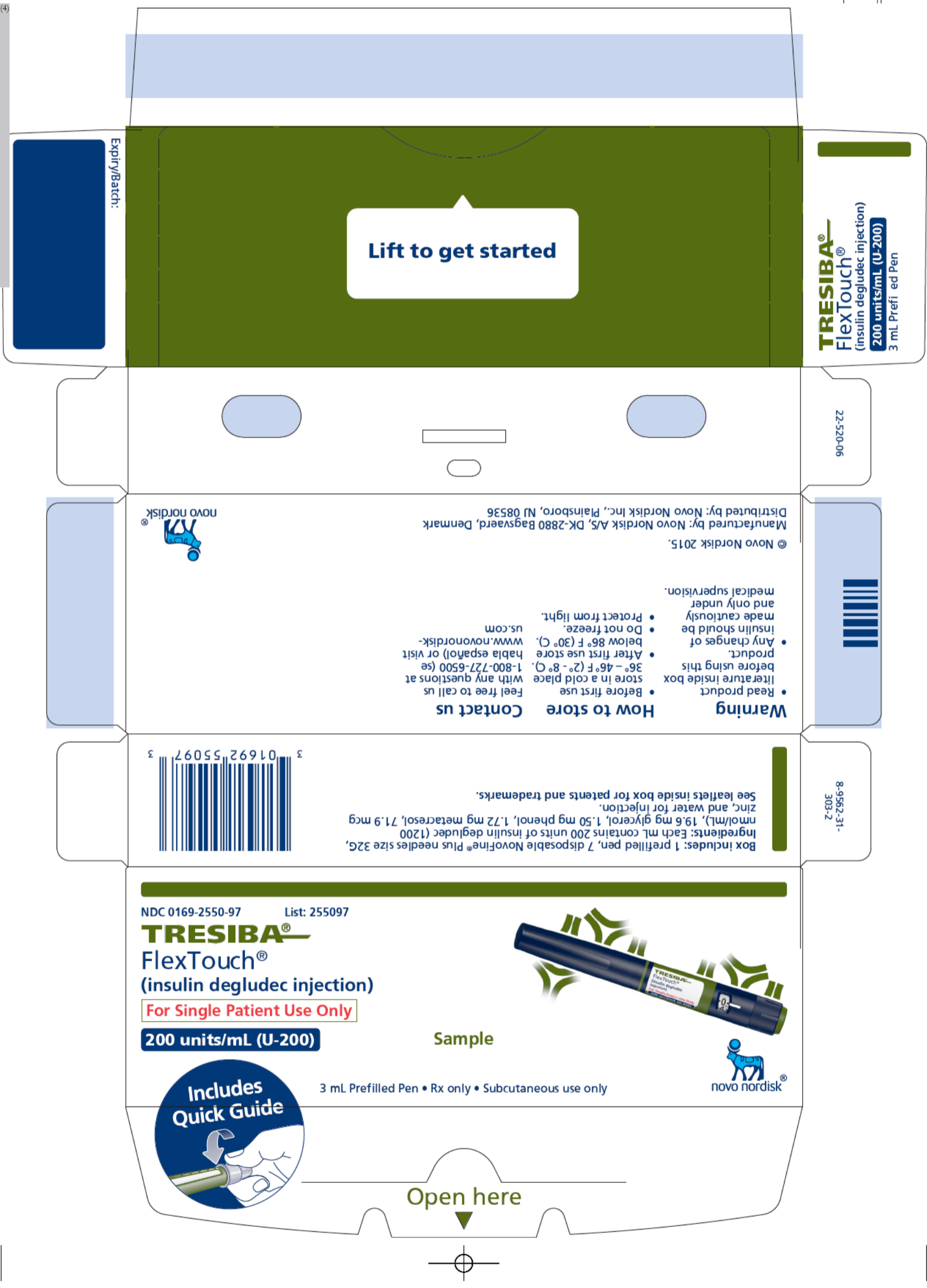
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Area without lacquer

Center for prod. name

Overlap



Lift to get started

**TRESIBA®**  
**FlexTouch®**  
(insulin degludec injection)  
**200 units/mL (U-200)**  
3 mL Prefilled Pen

Expiry/Batch:

22-520-06



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Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark  
Distributed by: Novo Nordisk Inc., Plainsboro, NJ 08536

**Warning**  
• Read product literature inside box before using this product.  
• Any changes of insulin should be made cautiously and only under medical supervision.  
• Insulin should be stored in a cold place with any questions at 36° - 46° F (2° - 8° C).  
• After first use store below 86° F (30° C).  
• Do not freeze. Protect from light.  
**How to store**  
• Before first use store in a cold place with any questions at 36° - 46° F (2° - 8° C).  
• After first use store below 86° F (30° C).  
• Do not freeze. Protect from light.



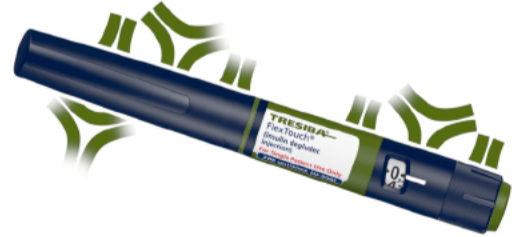
Code centre line  
Code: 100% Direction →  
Length: Max 29mm (100%)



Box includes: 1 prefilled pen, 7 disposable NovoFine® Plus needles size 32G, zinc, and water for injection.  
Ingredients: Each mL contains 200 units of insulin degludec (1200 nmol/mL), 19.6 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 71.9 mcg

8-9562-31-303-2

NDC 0169-2550-97 List: 255097  
**TRESIBA®**  
**FlexTouch®**  
(insulin degludec injection)  
**For Single Patient Use Only**  
**200 units/mL (U-200)**



Sample

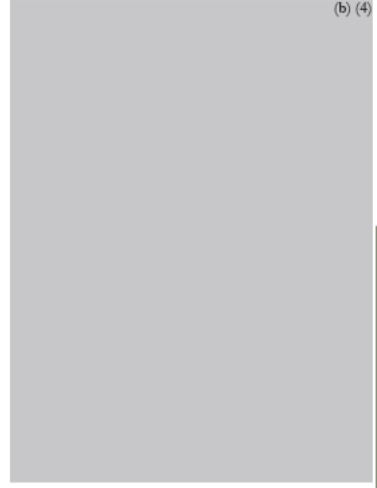


3 mL Prefilled Pen • Rx only • Subcutaneous use only



Open here


(b) (4)



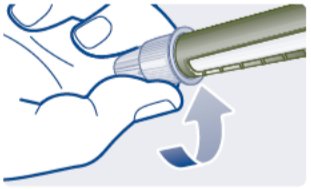
**Feel free to call us with any questions at 1-800-727-6500.**  
Se habla español.

**Prepare your Pen**


This is a Quick Guide. Please see Instructions for Use for full information.



**Prime your Pen**  
Turn the dose selector to select 2 units. Press and hold the dose button. Make sure a drop appears.

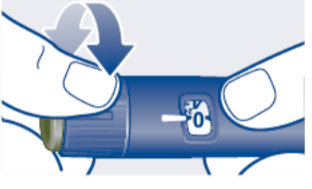


**Attach a new needle**  
Pull off the paper tab. Push and twist the needle on until it is tight. Pull off both needle caps.

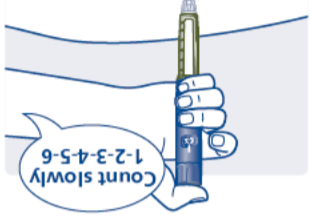


**Check your insulin type**  
Read the label to check you have the right insulin. Make sure the insulin is clear and colorless.


**Give your injection**



**Select your dose**  
Turn the dose selector to select the number of units you need to inject.



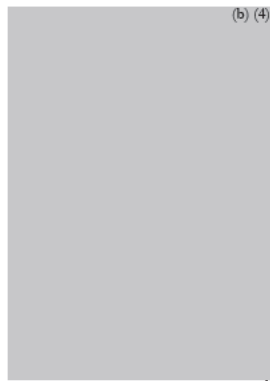
**Give your injection**  
Insert the needle. Press and hold the dose button. After the dose counter reaches 0, slowly count to 6.



**Remove the needle**  
Carefully remove the needle and place it in a sharps container. Replace the Pen cap.

Count slowly 1-2-3-4-5-6





Area without lacquer

Center for prod. name

Overlap

(b) (4)

**Rx:**  
**Tresiba® FlexTouch®**  
(insulin degludec injection)  
200 units/mL (U-200)  
■ **1 box (3×3 mL)**  
(NDC 0169-2550-13)  
■ **NovoFine® Plus 32G**  
disposable needles  
1 box (#100)  
(NDC 0169-1855-50)

8-9562-31-220-1

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/s/  
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CURTIS J ROSEBRAUGH  
09/25/2015