

Insulin Glulisine: An Evaluation of Its Pharmacodynamic Properties and Clinical Application

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An estimated 171 million people worldwide and over 15 million adults in the US live with diabetes mellitus.^{1,2} By 2030, an estimated 366 million people worldwide will have diabetes. Long-term glycemic control in patients with diabetes can reduce and delay development of complications.^{3,4} Data suggest that intensive diabetes therapy decreases the risk of cardiovascular diseases, including nonfatal myocardial infarction (MI), stroke, and death, in patients with type 1 diabetes.³ Results from the United Kingdom Prospective Diabetes Study (UKPDS) Group suggest that oral antidiabetic (OAD) medications and insulin therapy will likely be required to maintain control in patients with type 2 diabetes.⁵ Further evidence suggests that early addition of insulin to patients receiving specific OAD drugs may provide significant long-term decreases in microvascular risk compared with OAD drugs alone in patients with type 2 diabetes.⁶ In addition, 10-year data support a significant decrease in the incidence of MI by 15% and all-cause mortality by 13% in patients receiving the combination of insulin and OAD medications.^{6,7}

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OBJECTIVE: To evaluate the pharmacodynamic properties, efficacy, safety, and clinical application of insulin glulisine, a rapid-acting insulin analog, in the treatment of diabetes mellitus in ambulatory and hospitalized patients.

DATA SOURCES: Searches were performed with the headings glulisine, insulin analog, [LysB3, GluB29] insulin, insulin glulisine, rDNA insulin, rapid-acting insulin, SoloStar, safety, efficacy, pharmacodynamics, and cost analysis within MEDLINE and PubMed, American Diabetes Association (ADA), the Food and Drug Administration (FDA), and Sanofi-aventis Pharmaceuticals (1990–August 2008).

STUDY SELECTION AND DATA EXTRACTION: Phase 1, Phase 2, Phase 3, and postmarketing trials examining the efficacy and safety of glulisine in type 1 or type 2 diabetes were reviewed. Studies published as abstracts and the manufacturer's product information supplemented data absent from clinical trials.

DATA SYNTHESIS: Insulin glulisine is a rapid-acting insulin with relative equivalence in efficacy and safety to other short- and rapid-acting insulins. Glulisine's onset of action of 20 minutes and 4-hour duration of action allow for bolus administration 15–20 minutes prior to or up to 20 minutes after meals. Clinical trials have demonstrated the safety and efficacy in adults with type 1 or type 2 diabetes. Several studies indicated a statistically significant decrease of hemoglobin A_{1c} (A1C) with glulisine compared with regular insulin (0.10 decrease); however, no difference in A1C control was found compared with insulin aspart or lispro. Significant adverse effects appear to be limited to localized and systemic allergic reactions and hypoglycemia.

CONCLUSIONS: Insulin glulisine is a safe and effective rapid-acting insulin analog for the treatment of adults with diabetes. Clinical benefit over other short- and rapid-acting insulin products is not established. Addition of insulin glulisine to a formulary should be based on institution-specific availability and cost differences between glulisine, lispro, and aspart in the absence of superiority of clinical efficacy or safety and data beyond 26 weeks.

KEY WORDS: diabetes mellitus, insulin analog, insulin glulisine.

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Since the first use of pancreatic extract to treat type 1 diabetes in 1922, numerous improvements have been made to insulin products to enhance glucose control while minimizing the risk of hypoglycemia.^{8,9} Development of rapid-acting insulin products allows for greater prandial glucose control and meal flexibility.⁹ Insulin glulisine is a human insulin analog with rapid-acting properties approved by the Food and Drug Administration (FDA) for the treatment of diabetes mellitus in adults in April 2004.¹⁰ Insulin glulisine, also known as glulisine, Apidra, HMR-1964, and LysB3 [and] GluB29 insulin, is manufactured by Sanofi-aventis.¹⁰⁻¹²

Therapy for insulin-requiring diabetes often requires use of a long-acting (basal) combined with a rapid-acting (bolus) insulin.^{8,9} Basal treatment provides continuous control of blood glucose levels, while bolus treatment minimizes postprandial glucose peaks. Compared with regular insulin, rapid-acting insulin may better mimic physiologic insulin release while decreasing hypoglycemia. In addition, rapid-acting insulin has been shown to potentially improve postprandial glucose control.

To determine the clinical application of insulin glulisine in patients with diabetes mellitus, clinical trials evaluating the pharmacodynamic properties, efficacy, and safety of glulisine in ambulatory and hospitalized patients with type 1 or type 2 diabetes and use in special populations are reviewed.

Study Selection and Data Extraction

A search of MEDLINE and PubMed (1990–August 2008) was performed using the key words glulisine, insulin analog, [LysB3, GluB29] insulin, insulin glulisine, rDNA insulin, rapid-acting insulin SoloStar, safety, efficacy, pharmacodynamics, costs, and cost analysis to identify clinical trials and review articles published in English. References of the identified articles were reviewed for additional citations. Phase 1, 2, and 3 clinical trials, as well as postmarketing trials examining the efficacy and safety of insulin glulisine were reviewed. Emphasis was placed on Phase 2, Phase 3, and postmarketing data. Studies published in abstract form and product information from the manufacturer were used to supplement data absent from the clinical trials. Additional sources included Sanofi-aventis Pharmaceuticals, FDA application and approval documents, and poster abstracts from the American Diabetes Association (ADA) Annual Scientific Sessions.

Chemistry and Pharmacology

Insulin glulisine lowers plasma glucose levels by stimulating glucose absorption in tissue and decreasing hepatic glucose release.^{13,14} Regular insulin can control glucose levels prandially; however, the absorption rate is limited by the slow dissociation of large insulin complexes into monomers in the subcutaneous tissues, resulting in an on-

set of action of 30 minutes and variable duration of action of 5–8 hours.^{10,15} Substitution of traditional amino acids for charged particles on the B1-8 and B26-30 regions of the insulin molecule has been shown to improve the rate of absorption by preventing the formation of insulin complexes.^{12,14,15} Glulisine is a human insulin analog created via recombinant DNA technology using nonpathogenic strains of *Escherichia coli* (K12).^{12,14} The asparagine at position B3 is replaced by lysine, and the lysine at B29 is replaced by glutamic acid, resulting in 3^B-lysine-29^B-glutamic acid human insulin.^{12,14,15} Insulin glulisine does not require stabilization with zinc; therefore, there is a faster rate of monomer formation on injection resulting in an increased rate of absorption.¹⁵

With modification of specific amino acids, undesirable pharmacodynamic changes may occur. Changes at the B10 position can cause increased affinity to the insulin growth factor receptor, resulting in neoplasm formation in mammary tissue of mice; however, this mitogenic potential has not been demonstrated with glulisine.¹⁵⁻¹⁷

Pharmacokinetics and Pharmacodynamics

Limited data are available on the pharmacokinetics of glulisine.¹⁶ Pharmacokinetic studies in patients with and without diabetes show a 42-minute half-life and volume of distribution after subcutaneous administration of 13 liters. The pharmacodynamic profile reflects a more rapid onset and a shorter duration of action than found with regular human insulin (Table 1).^{10,11,13,18,19}

Clinical Trials

Clinical trials have evaluated the efficacy and tolerability of insulin glulisine as monotherapy and in combination with basal insulin in patients with both type 1 and type 2 diabetes. Clinical trial results are summarized in Table 2,²⁰⁻²⁴ Table 3,²⁵⁻²⁸ and Table 4.²⁰⁻²⁸

TYPE 1 DIABETES

Study 3001 and Study 3011

A 26-week, Phase 3, noninferiority study evaluated changes in hemoglobin A_{1C} (A1C) in patients on basal glargine receiving preprandial glulisine or preprandial lispro (Table 2).²⁰ Goal A1C less than 7% was achieved in 35.6% of glulisine patients and 34.5% of lispro patients ($p = 0.9329$). No significant differences in self-monitored blood glucose levels were reported. Average daily glargine dose increased by 0.12 units with glulisine and 1.82 units with lispro ($p < 0.0001$). Overall rates of treatment-emergent adverse events (TEAEs) were similar (Table 4). There were no significant differences in insulin antibody formation or injection site reactions. Safety and efficacy appear

to be equivalent between glulisine and lispro in this study. In contrast to previous studies suggesting that insulin analogs require larger doses of basal insulin compared with regular insulin, glulisine appears to offer a basal insulin-sparing effect compared with lispro.^{20,29}

Study 3011, a 26-week unpublished extension including 87.6% of the original Study 3001 subjects, evaluated the long-term safety of glulisine (Table 2).^{21,22} Secondary endpoints examined efficacy. Mean A1C increased over 26 weeks in each group (0.14% glulisine vs 0.15% lispro). There were no significant differences in self-monitored blood glucose levels. The mean total daily dose of insulin increased during the extension in both groups (0.39 units glulisine vs 0.81 units lispro) and was primarily a result of differences in the mean increase in insulin glargine (0.21 units glulisine vs 2.01 units lispro). Differences in TEAEs over the 52 weeks were similar between groups; however, the rate of severe hypoglycemic events appears greater with glulisine (Table 4). This extension shows continued equivalency in efficacy between glulisine and lispro and the potential basal insulin-sparing effect of glulisine.

Study 3004

A 12-week noninferiority study compared patients on basal glargine who received preprandial glulisine, postprandial glulisine, or preprandial regular insulin (Table 2).²³ Postprandial administration was defined as either immediately following a meal (for meals lasting <20 min) or 20 minutes after starting a meal (for meals lasting >20 min). Self-monitored 2-hour postbreakfast glucose levels were significantly lower in patients receiving preprandial glulisine compared with regular insulin (difference 22.9 mg/dL; $p = 0.0001$) and postprandial glulisine (difference 13.4 mg/dL; $p = 0.0017$).

Similar trends were seen with 2-hour postdinner glucose levels (preprandial vs regular difference 19.9 mg/dL, $p = 0.0001$; preprandial vs postprandial difference 11.7 mg/dL, $p = 0.0137$). Incidence of overall TEAEs and hypoglycemic events was similar among groups (Table 4). No difference in insulin antibody formation or injection site reactions was found. Preprandial glulisine appears to offer a safe and significant advantage in A1C reduction compared with postprandial glulisine and preprandial regular insulin while requiring a lower total daily insulin dose.

TYPE 1 DIABETES WITH CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

Study 3006

Study 3006 compared the safety and compatibility of insulin glulisine with that of aspart when used as a bolus insulin in continuous subcutaneous insulin infusion (CSII) devices over 12 weeks (Table 2).²⁴ Efficacy parameters were secondary outcomes. Increases in A1C in both groups were attributed to declining adherence to diet, exercise, and medications. A greater number of subjects receiving glulisine compared with aspart (42.9% vs 40.7%) achieved an A1C less than 7%. All patients receiving glulisine achieved A1C less than 8% compared with 88.9% of those receiving aspart. No significant differences in self-reported 7-point blood glucose levels were found between groups, and glulisine patients had a mean decrease of 0.48 units of daily basal insulin compared with a mean increase of 0.09 units with aspart (95% CI -2.98 to 1.85). There was a greater number of TEAEs, including severe hypoglycemic events, in patients receiving aspart; however, general rates of hypoglycemic events were greater with

Table 1. Pharmacokinetic and Pharmacodynamic Comparison of Glulisine with Short- and Rapid-Acting Insulin Products

Parameter	Glulisine ^{10,13}	Regular Insulin ¹¹	Insulin Aspart ¹⁸	Insulin Lispro ¹⁹
Available as generic product	no	yes	no	no
Onset of action	20 min	30 min	immediate	5 min
Peak concentration	55 min	2–5 h	40–50 min	30–60 min
Duration of action	4 h	5–8 h	3–5 h	3 h
Dosing with meals ^a	15–20 min prior to meals or within 20 min of beginning a meal	30 min prior to meals	5–10 min prior to meals	15 min prior to or immediately after meals
Dosing route ^a	subcutaneous or intravenous	subcutaneous or intravenous	subcutaneous or intravenous	subcutaneous or intravenous
Use in insulin pumps	yes	yes	yes	yes
Compatible insulin products (in same syringe)	NPH insulin	NPH insulin	NPH insulin	NPH insulin, regular insulin
FDA pregnancy category	C	B	B	B
FDA approval in pediatrics	no	yes	no	yes

FDA = Food and Drug Administration.
^aReflects FDA-recommended dosing.

glulisine (Table 4). The monthly rate of catheter occlusions was lower with glulisine compared with aspart (0.08% vs 0.15%), and infusion site reactions were similar between groups (10.3% glulisine vs 13.3% aspart). This study suggests similar A1C-lowering effects between glulisine and aspart when administered via CSII and further basal insulin sparing with glulisine; however, hypoglycemia may be greater with glulisine.

TYPE 2 DIABETES

Study 3002 and Study 3012

Study 3002, a 26-week Phase 3 clinical trial, was designed to demonstrate noninferiority of glulisine to regular insulin given before breakfast and dinner in patients receiving basal NPH insulin (Table 3).²⁵ Subjects on insulin for 6 or more months prior to study initiation were permit-

ted to mix NPH with glulisine or regular insulin and continue OAD drugs. Similar numbers in each group (glulisine 53.5% vs regular 50.6%) reached an A1C less than 7%. Mean self-monitored fasting blood glucose levels (glulisine 142 mg/dL vs regular 151 mg/dL; $p = 0.006$) and 2-hour postprandial levels (188 mg/dL vs 200 mg/dL; $p = 0.012$) were significantly lower with glulisine. TEAEs were similar between groups (Table 4), but systemic hypersensitivity reactions were greater with glulisine (6.9% vs 5.2%). Mean changes in cross-reactive insulin antibody concentrations were not significantly different from baseline or between groups. This study reveals equivalent safety and a statistically significant decrease in A1C with glulisine compared with regular insulin; however, clinical significance of the A1C decrease is questionable.

Study 3012, a 26-week unpublished extension of Study 3002, evaluated the long-term safety of glulisine (Table

Table 2. Clinical Trial Summary: Type 1 Diabetes

Reference	Pts. (N)	Design	Duration (wk)	Objective, PE	Treatment	Change in A1C from Baseline	Mean Dose Changes (units)	
							Daily Short-Acting Insulin	Total Daily Insulin
Study 3001 ²⁰	672	R, MC, PG, OL, ITT	26	efficacy and tolerability PE = mean change in A1C	insulin glulisine ^a (n = 339)	-0.14 ^b	-1.07	-0.86 ^c
					or insulin lispro ^a (n = 333)	-0.14 ^b	-0.81	+1.01 $p = 0.0123$ between groups
Study 3011 ^{21,22} (extension of Study 3001)	589	R, MC, PG, OL, ITT	26	efficacy and tolerability PE = safety parameters	insulin glulisine ^a (n = 302)	-0.02 ^d	NR	+0.3 ^d
					or insulin lispro ^a (n = 297)	0 ^d	NR	+1.71 ^d
Study 3004 ²³	860	R, MC, OL, PG	12	efficacy and tolerability PE = mean change in A1C	insulin glulisine ^a (n = 286)	-0.26 ^{b,c}	-0.88 ^b	+2.35
					or insulin glulisine ^e (n = 296)	-0.11 ^b	-0.47 ^b	-0.22
					or regular insulin ^f (n = 278)	-0.13 ^b $p = 0.006$ (pre- vs postmeal)	+1.75 ^{b,c} $p = 0.0001$ (premeal vs regular)	+2.35 ^{b,c} $p = 0.0042$ (premeal vs regular)
						$p = 0.02$ (premeal vs regular)	$p = 0.0012$ (postmeal vs regular)	$p = 0.0014$ (postmeal vs regular)
Study 3006 ²⁴	59	R, MC, OL, PG, ITT	12	safety and compatibility with CSII PE = safety parameters	insulin glulisine ^g (n = 29)	+0.10	+1.0 ^c	+0.52
					insulin aspart ^g (n = 30)	+0.21 95% CI -0.09 to 0.31	+1.49 ^c 95% CI 3.04 to 2.06	+1.58 95% CI -4.8 to 2.7

A1C = hemoglobin A_{1c}; CSII = continuous subcutaneous insulin infusion; DB = double-blind; ITT = intent-to-treat; MC = multicenter; NR = not reported; OL = open-label; PE = primary endpoint; PG = parallel group; R = randomized.

^a0–15 minutes before meals.

^bStatistically significant change from baseline.

^cStatistically significant difference between groups.

^dChange from 52-week baseline.

^e0–20 minutes after meals.

^f30–45 minutes before meals.

^gVia external insulin pump.

3).^{21,26} Self-monitored fasting blood glucose levels were lower at all points with glulisine; however, results of statistical analyses were not reported. Rates of hypoglycemic events were similar between groups; however, slightly more patients using glulisine experienced severe hypoglycemia. There appears to be a continued decrease in A1C and a potential basal insulin-sparing effect with use of glulisine compared with regular insulin; however, clinical significance of the A1C reduction is unclear and increased rates of severe hypoglycemia may outweigh this benefit.

Study 3005

Study 3005 was a Phase 3 noninferiority trial designed similarly to Study 3002 except that participants used injection pens (Table 3).²⁷ Similar percentages of patients (glulisine 47.1% vs regular 48.5%) reached goal A1C of less than 7%. Subjects receiving glulisine had significantly lower self-reported 2-hour postprandial glucose levels ($p = 0.0010$) that were confirmed through preprandial ($p = 0.0488$) and postprandial ($p = 0.0010$) clinic testing. Rates of symptomatic and severe hypoglycemia were similar

(Table 4); however, nocturnal symptomatic hypoglycemia was less with glulisine compared with regular insulin (9.1% vs 14.5%; $p = 0.0290$). Incidence of severe nocturnal hypoglycemia was similar (0% vs 0.7%, respectively; $p = 0.1414$). These results suggest equivalent impact on A1C, better pre- and postprandial glucose control, and decreased risk of nocturnal hypoglycemia with glulisine compared with regular insulin.

RABBIT 2 Trial

The objective of the RABBIT 2 Trial was to compare the efficacy and safety of basal-bolus glargine/glulisine with sliding-scale regular insulin in non-critically ill, non-surgical, insulin-naïve hospitalized patients with type 2 diabetes (Table 3).²⁸ Goal fasting blood glucose levels were less than 140 mg/dL. Mean $\pm$ SD fasting blood glucose levels (147 ± 36 vs 165 ± 41 mg/dL; $p < 0.01$), mean $\pm$ SD random blood glucose levels (164 ± 35 vs 189 ± 42 mg/dL; $p < 0.001$), and mean $\pm$ SD blood glucose levels during the entire hospital stay (166 ± 32 vs 189 ± 42 mg/dL; $p < 0.001$) were significantly lower with glargine/glulisine compared

Table 3. Clinical Trial Summary: Type 2 Diabetes

Reference	Pts. (N)	Design	Duration	Objective, PE	Treatment	Change in A1C from Baseline	Mean Dose Changes (units)	
							Daily Short-Acting Insulin	Total Daily Insulin
Study 3002 ²⁵	876	R, MC, PG, OL, ITT	26 wk	efficacy and tolerability PE = mean change in A1C	insulin glulisine ^a (n = 435)	-0.46 ^{b,c}	+3.7	+9.3
					or regular insulin ^d (n = 441)	-0.30 ^{b,c} $p = 0.0029$ between groups	+5.0	+11.1
Study 3012 ²⁶ (extension of Study 3002)	709	R, MC, PG, OL, ITT	26 wk	efficacy and tolerability PE = safety parameters	insulin glulisine ^a (n = 357)	-0.23 ^e	+4.68 ^e	+10.79 ^e
					or regular insulin ^f (n = 352)	-0.13 ^e	+5.65 ^e	+14.83 ^e
Study 3005 ²⁷	890	R, MC, PG, OL, ITT	26 wk	efficacy and tolerability PE = mean change in A1C	insulin glulisine ^a (n = 448)	-0.32 ^e	+2.95	+7.56
					or regular insulin ^f (n = 442)	-0.35 ^b	+4.47	+9.36
RABBIT 2 Trial ²⁸	130	R, MC, OL, P	5.3 $\pm$ 6 days ^g	efficacy and tolerability PE = mean blood glucose	insulin glulisine ^d + glargine daily (n = 65)	NR	NR	NA
			5.1 $\pm$ 4 days ^g		or sliding scale regular insulin (n = 65)	NR	NR	NA

A1C = hemoglobin A_{1c}; ITT = intent-to-treat; MC = multicenter; NA = not applicable; NR = not reported; OL = open-label; P = prospective; PE = primary endpoint; PG = parallel group; R = randomized.

^a0–15 minutes before meals.

^bStatistically significant change from baseline.

^cStatistically significant difference between groups.

^dBefore meals (time undefined).

^eChange from 52-week baseline.

^f30–45 minutes before meals.

^gMean value.

with regular insulin. A significantly greater daily insulin dose was seen with basal bolus compared with sliding scale insulin (22 ± 2 units glargine plus 20 ± 1 units glulisine vs 12.5 ± 5 units regular insulin; $p < 0.001$). Hypoglycemia rates, defined as blood glucose less than 60 mg/dL, were similar (Table 4), with no other TEAEs reported. These results suggest greater blood glucose control with basal bolus therapy compared with sliding scale regular insulin with no increase in TEAEs.

LIMITATIONS OF CLINICAL TRIALS

In consideration of the safety and efficacy of glulisine, the quality and quantity of available data must be considered. There is a relative lack of published data establishing its long-term safety and efficacy in ambulatory patients with either type 1 or type 2 diabetes. Two pivotal trials,

Study 3001 and Study 3002, provide evidence suggesting equivalence of glulisine to lispro and regular insulin, respectively; however, both of these studies were limited to 26 weeks. The 26-week extensions of each of these studies used efficacy as a secondary endpoint, and no results have been published to date. Although portions of the data are available from the manufacturer and FDA, there is a lack of critical review that occurs with publication in peer-reviewed journals, including assessment of study design, data analysis, and potential author bias. Much of the unpublished information was summarized and lacked details to determine the impact of the findings. In addition, the clinical significance of the basal insulin-sparing effect with glulisine use is unclear. Statistical analyses were not defined and statistical results were not consistently reported. Although 2 other 12-week noninferiority studies were available, a rigorous assessment of long-term efficacy is

Table 4. Summary of Treatment-Emergent Adverse Effects^a

Trial/ Duration	Treatment Groups (n)	TEAEs, n pts. (%)	Nonhypoglycemic Serious TEAEs, n pts. (%)	Treatment Discontinued, n pts. (%)	Symptomatic Hypoglycemia, n pts. (%)	Severe Hypoglycemia, n pts. (%)
Study 3001 ²⁰ 26 wk	insulin glulisine (339) insulin lispro (333)	219 (64.6) 206 (61.9)	NR NR	10 (2.9) 13 (3.9)	3.64 ^a 3.48 ^a	0.03 ^a 0.02 ^a
Study 3011 ²¹ 26 wk	insulin glulisine (302) insulin lispro (287)	NR NR	NR NR	5 (1.7) 5 (1.7)	NR NR	NR NR
Total of Study 3001 and Study 3011 ²⁰⁻²² 52 wk	insulin glulisine (339) insulin lispro (333)	245 (72.3) 229 (68.8)	33 (9.7) 21 (6.3)	15 (4.4) 18 (5.4)	NR NR	48 (14.2) 38 (11.4)
Study 3004 ²³ 12 wk	insulin glulisine ^c (286) insulin glulisine ^d (296) regular insulin (278)	174 (60.8) 196 (66.2) 174 (62.6) $p = \text{NR}$	29 (10.1) 28 (9.5) 35 (12.6) $p = \text{NR}$	3 (1.0) 3 (1.0) 4 (1.4) $p = \text{NR}$	234 (81.8) 248 (83.8) 228 (82.0) $p = \text{NR}$	24 (8.4) ^b 25 (8.4) ^b 28 (10.1) ^d $p = \text{NR}$
Study 3006 ²⁴ 12 wk	insulin glulisine (29) insulin aspart (30)	14 (48.3) 20 (66.7) $p = \text{NR}$	5 (17.2) 4 (13.3) $p = \text{NR}$	1 (3.4) 1 (3.3) $p = \text{NR}$	26 (89.7) 24 (80.0) $p = \text{NR}$	1 (3.4) ^d 2 (6.7) ^d $p = \text{NR}$
Study 3002 ²⁵ 26 wk	insulin glulisine (435) regular insulin (441)	358 (82.3) 351 (79.6) $p = \text{NR}$	40 (9.2) 40 (9.1) $p = \text{NR}$	28 (6.4) 36 (8.2) $p = \text{NR}$	225 (51.7) 236 (53.6) $p = 0.600$	6 (1.4) ^d 5 (1.2) ^d $p = 0.645$
Study 3012 ^{21,26} 26 wk	insulin glulisine (357) regular insulin (352)	NR NR	NR NR	28 (7.8) 14 (4.0) $p = \text{NR}$	192 (53.8) 180 (51.1) $p = \text{NR}$	6 (1.7) ^d 1 (0.3) ^d $p = \text{NR}$
Total of Study 3002 and Study 3012 ^{21,25,26} 52 wk	insulin glulisine (435) regular insulin (441)	384 (88.3) 288 (65.3)	75 (17.2) 67 (15.2)	56 (12.9) 50 (11.3) $p = \text{NR}$	336 (77.2) 338 (76.6) $p = \text{NR}$	21 (4.8) ^d 13 (2.9) ^d $p = \text{NR}$
Study 3005 ²⁷ 26 wk	insulin glulisine ^b (448) regular insulin ^e (442)	260 (58) 260 (58.8) $p = \text{NR}$	43 (9.6) 52 (11.8) $p = \text{NR}$	NR NR	140 (32.8) 144 (33.2) $p = 0.9888$	2 (0.5) ^d 7 (1.6) ^d $p = 0.1726$
RABBIT 2 Study ²⁸ average 5 days	insulin glulisine/glargine (65) regular insulin (65)	NR NR	NR NR	NR NR	2 (3.1) 2 (3.1) $p = \text{NR}$	0 0

NR = not reported; TEAEs = treatment-emergent adverse effects.
^aReported as mean rate/month.
^b0–15 minutes before meals.
^c0–20 minutes after meals.
^dDefined as an episode requiring assistance and confirmed by blood glucose level <36 mg/dL or prompt response to glucose or glucagon.
^eBefore meals (time undefined).

difficult. In addition, there are limited data assessing the safety and efficacy of glulisine in patients using CSII devices or in hospitalized patients.

Contraindications, Warnings, and Precautions

Glulisine is contraindicated in patients with hypoglycemia or hypersensitivity to glulisine or excipients.¹⁰ As with all insulin products, patients may experience localized allergic injection site reactions including itching, erythema, and swelling, which should subside within a few days to weeks. Systemic allergic reactions, including diffuse rash, shortness of breath, hypotension, tachycardia, and/or anaphylaxis may occur with use of glulisine.

Pregnancy and Lactation

Glulisine is FDA pregnancy category C, with no well-controlled clinical trials to date. Rodent reproduction studies showed no toxic effects on fetal development, except for fetal loss secondary to hypoglycemia. Results were similar to those seen with regular insulin.^{10,30} Human insulin is excreted in human milk; there are no studies evaluating this with glulisine.^{10,11}

Special Populations

GERIATRICS

Of the 2408 patients who received glulisine in Phase 3 clinical trials, 6.1% (147) were greater than 65 years of age and 1.12% (27) were greater than age 75 years.¹⁰ A majority of these patients had type 2 diabetes. Study results suggest no difference in frequency of hypoglycemia or average A1C in this population compared with other age groups.

PEDIATRICS

The safety and efficacy of glulisine have not been established in pediatric patients, with only one published study evaluating its use in adolescents.³¹ In 20 subjects ranging from 12 to 17 years of age with type 1 diabetes, no significant differences in pharmacokinetic parameters were found; however, more data are needed to determine the drug's overall safety and efficacy in this population.

RENAL IMPAIRMENT

Nondiabetic patients with moderate (creatinine clearance [CrCl] 30–50 mL/min) and severe (CrCl <30 mL/min) renal impairment demonstrated increased exposure to glulisine by 29–40% and decreased clearance of glulisine by 20–25%.¹⁰ No guidelines for dose adjustment in patients with renal impairment are provided; however, glulisine dose requirements may be less in this population.

HEPATIC IMPAIRMENT

No studies have assessed the effects of hepatic impairment on glulisine pharmacokinetics. Use of other insulin products in patients with impaired hepatic function has led to decreased insulin metabolism, gluconeogenesis, and insulin requirements; therefore, glulisine requirements may also be decreased.¹⁰

OBESITY

One study published in abstract form evaluated the use of glulisine in 18 obese patients without diabetes.^{32,33} Patients were categorized based on body mass index (BMI): 30.0–34.9 kg/m² or 35.0–40.0 kg/m². Results demonstrated that BMI had no impact on pharmacokinetic or pharmacodynamic properties of glulisine.

A second randomized, open-label, crossover study compared the use of preprandial glulisine with use of lispro in 18 obese insulin-naïve patients with type 2 diabetes (males 36.7 kg/m² [33.2–43.8], females 40.0 kg/m² [35.7–46.5]).³⁴ Patients received 0.15 units/kg of glulisine or lispro within 2 minutes of 3 standardized meals over 12 hours. No significant differences in plasma glucose levels were found; however, mean maximum glucose concentrations were 12% lower with glulisine compared with lispro ($p < 0.01$), and mean insulin concentrations postprandially were higher with glulisine ($p < 0.01$). Post hoc analysis revealed an increased rate of absorption in the first 30 minutes for glulisine compared with lispro ($p < 0.0001$). The authors concluded that obese patients had more rapid absorption and sustained insulin concentrations with glulisine than with lispro.

Drug Interactions

Drug interactions with glulisine are thought to be similar to those seen with other insulin products and are pharmacodynamic in nature.¹⁰ Medications may blunt the blood glucose-lowering response to insulin, including corticosteroids, diuretics, sympathomimetics, thyroid hormone, estrogen and progestin, protease inhibitors, and antipsychotics.³ Other drugs enhance hypoglycemic effects, including angiotensin-converting enzyme inhibitors, fibrates, fluoxetine, and sulfonamide antibiotics.¹⁰ Additionally, β -blockers, clonidine, guanethidine, and reserpine may reduce signs and symptoms of hypoglycemia.

Safety and Tolerability

ADVERSE EFFECTS

Most clinical trials published to date report favorable tolerability with glulisine (Table 4).^{20–28} In studies involving type 1 diabetes, 66.2% of patients who received glulisine reported at least one TEAE compared with 66.0% of pa-

tients receiving lispro or regular insulin. Infection and nervous system disorders were most common.²¹ A greater incidence of cardiac-related TEAEs were seen with glulisine (1.6%) compared with lispro or regular insulin (0.6%); however, this difference was observed only in Study 3001 and likely reflects the significantly greater number of cardiac risk factors at baseline in patients receiving glulisine compared with those receiving lispro.

Serious TEAEs occurred in 14.4% of glulisine patients with type 1 diabetes and 14.7% of patients receiving lispro or regular insulin, with hypoglycemia most commonly reported (10.4% vs 10.8%, respectively).²¹ Serious, nonhypoglycemic TEAEs most commonly included injection-site reactions (4.2% vs 5.0%), systemic hypersensitivity reactions (2.1% vs 1.7%), and cardiac disorders (1.5% vs 0.5%).

In studies with type 2 diabetes, at least one TEAE was reported by 82.3% of glulisine patients and 79.1% of patients receiving regular insulin.²¹ The most commonly reported TEAEs were not delineated. Serious TEAEs were reported in 15.4% and 14.8% of glulisine and regular insulin patients, respectively, with the most common being systemic hypersensitivity reactions (6.7% vs 5.3%, respectively), cardiac disorders (3.4% vs 4.1%), and injection site reactions (2.6% in both groups). Hypoglycemia-related TEAEs occurred in 3.1% of both groups.

HYPOGLYCEMIA

The most commonly reported serious TEAE across all treatment groups was severe hypoglycemia.²¹ Severe hypoglycemia was defined as an episode requiring assistance and confirmed by blood glucose levels less than 36 mg/dL or prompt response to glucose or glucagon. Although trial results from Study 3001 lead to concern of an increased incidence of hypoglycemia with glulisine compared with lispro, this disparity between groups narrows with the combined results from Study 3011. Of additional concern is the increased risk of severe hypoglycemia seen with glulisine compared with regular insulin in Study 3012. These results were not supported by the results of Study 3004 or Study 3005. In addition, the pooled results from all trials suggest that the overall risk with glulisine is similar to that with aspart, lispro, and regular insulin (6.9% vs 6.3%, respectively); however, no *p* values were provided.

HYPERSENSITIVITY REACTIONS

Because glulisine is a protein, there is concern of increased rates of hypersensitivity reactions; however, the rates of TEAEs are similar to those of lispro and regular insulin.²¹ Study 3002/3012 found a slight increase in cross-reactive insulin antibodies at week 12; however, similar increases were seen with use of regular insulin and levels returned to baseline by week 52.^{25,26} No relationship was

seen between antibody concentration and incidence of hypoglycemia, dose changes, or A1C.^{21,25,26} To date, there has only been a case report on the use of glulisine in combination with glargine in a patient who had developed symptoms on previous insulins—lispro, NPH, regular, and aspart. This preliminary report indicates that glulisine may be worth trying in patients who have had allergy symptoms with other insulins.³⁵

Approved Labeling/Off-Label Uses

Glulisine is approved by the FDA for subcutaneous use through injection or CSII in the treatment of hyperglycemia in adults with diabetes mellitus.¹⁰ The use of glulisine has been investigated in ambulatory adults with type 1 diabetes and in ambulatory and hospitalized patients with type 2 diabetes. Glulisine has additional approval for intravenous dosing under strict medical supervision. Use in pediatric, pregnant, or nursing patients would be considered off-label.

Dosage and Administration

Glulisine is available as 100 units/mL in 10-mL vials and 3-mL cartridges for use with Aventis OptiClik (insulin delivery device) or insulin pump/infusion set.¹⁰ In addition, the FDA has approved a disposable insulin pen, SoloStar, for administration of insulin glulisine. Initial data show increased patient preference for this device compared with 3 other insulin pen devices.³⁶ The manufacturer recommends that subcutaneous glulisine be administered in the abdominal wall, thigh, or deltoid as early as 15 minutes before or up to 20 minutes after beginning a meal. Although the results from Study 3004 suggest the potential for greater A1C reduction with premeal administration, the clinical significance of this finding is not established (Table 2).^{10,14} Further, Lankisch et al. found no difference in A1C reduction in patients receiving a bolus dose of glulisine with breakfast compared with patients receiving glulisine bolus with an evening meal when utilized in combination with insulin glargine and an OAD (*p* = 0.0481).³⁷

As with all insulin products, the dose of glulisine should be adjusted to meet the needs of the individual patient. In clinical trials, 1 unit of glulisine has been shown to lower blood glucose readings to a similar extent as 1 unit of regular human insulin, with differing times to onset.¹⁰ Glulisine should generally be used in regimens with a long-acting basal insulin (eg, NPH or insulin glargine). Glulisine may be mixed with NPH in the same syringe and should be drawn into the syringe prior to NPH. Due to lack of data, glulisine should not be mixed with other insulin products.

The manufacturer states that glulisine may also be administered through CSII in the abdomen; however, *in vitro* data suggest that there is significant degradation of glulisine when placed in contact with tubing or reservoirs.^{10,38}

When compared with aspart administered through CSII, glulisine was found to have twice the amount of biologically inactive insulin proteins compared with aspart after 10 days, suggesting a greater loss of stability for glulisine compared with aspart.³⁸ Although Study 3006 found no difference in efficacy compared with aspart with use in CSII, tubing and glulisine were replaced every 2 days in this study population.²⁴ Based on this study protocol, the manufacturer recommends that tubing and glulisine be replaced at least every 48 hours. Other insulin products should not be combined with glulisine in external infusion devices due to lack of stability data.^{10,38} Due to limited long-term data and compelling in vitro data, use of glulisine in a CSII should be avoided until further evidence is available.

Patient Counseling

Glulisine should be inspected prior to administration to ensure that the product is clear, colorless, and free of particulate matter.¹⁰ An unopened vial or cartridge of glulisine should be stored in the refrigerator, protected from light, and used prior to the expiration date. Opened vials of glulisine can be stored in the refrigerator or at room temperatures below 25 °C and must be used within 28 days. Opened cartridges of glulisine inserted into OptiClick insulin pen should be stored at room temperature below 25 °C and used within 28 days.

Therapeutic Controversies and Discussion

Comparison trials in ambulatory patients with type 1 diabetes and in patients with type 2 diabetes yield relative equivalence in efficacy between glulisine and other rapid- and short-acting insulin products (Tables 2 and 3). Although several studies indicate a statistically significant difference in control of A1C with glulisine compared with regular insulin, the clinical significance of this difference is not clear. No studies showed greater A1C control with glulisine compared with aspart or lispro. Use of glulisine in combination with glargine in the general inpatient setting appears to offer greater blood glucose control compared with sliding scale regular insulin; however, the small study population and lack of replication warrant further investigation before widespread use.

Use of glulisine in special populations must be based on the evidence with glulisine and other rapid-acting insulin products. At this time, no human data support the safe use of glulisine in pregnant or nursing women. As both aspart and lispro are pregnancy category B and have been shown to be safe in these populations, these agents may be safer alternatives until further data are available.^{10,18,30,38} Similar to aspart and lispro, glulisine use in geriatric patients has shown no difference in frequency of hypoglycemia or difference in average A1C values when compared with other

age groups.^{10,18,38} Glulisine may be used in geriatric patients with appropriate administration and monitoring for hypoglycemia unless future studies with insulin products suggest otherwise. Limited data support the overall safety and efficacy of glulisine in children and adolescents; therefore, its use in this population should be cautiously considered. Alternatively, use of aspart, which is approved for children, may be considered.^{31,38}

Data suggest that glulisine dose requirements may be less in patients with renal impairment.¹⁰ Further evidence supports that changes in dose requirements may be warranted with all rapid-acting insulin products; therefore, glulisine may be used with frequent monitoring of both blood glucose and renal function.^{18,38} No data are available regarding the use of glulisine in hepatic impairment; however, data on aspart and lispro show changes in pharmacokinetic parameters regardless of the level of impairment.^{9,18,38} Until data are available, aspart and lispro may be safer alternatives than glulisine in patients with hepatic dysfunction.

Studies with glulisine have demonstrated lack of impact of BMI on pharmacokinetic and pharmacodynamic properties of glulisine.^{32,33} When glulisine was compared with lispro, obese patients had more rapid absorption and more sustained insulin concentrations with glulisine compared with lispro.³⁴ While this information suggests a potential benefit with use of glulisine in obese patients, close monitoring of blood glucose levels should be considered. With all special populations, appropriate administration techniques and timing with regard to meals, as well as close monitoring of blood glucose levels, should be a part of any recommendation for use of glulisine.

Outside of efficacy, there does appear to be the potential that insulin glulisine allows for lower doses of the basal insulin and, in some cases, total insulin dose (eg, 1.7 units less in Study 3001); however, the clinical significance of these small differences is debatable. Currently, there have been no cost analyses reported or published regarding glulisine; therefore, overall cost-effectiveness with the potential decrease in basal insulin dose is unavailable.¹⁹ The safety of insulin glulisine compared with other insulin therapies appears to be comparable. Although data are mixed, TEAEs, including those related to hypoglycemia, show rates similar to those of other short- or rapid-acting insulin therapies. With regard to dosing, the stability of insulin glulisine in CSII devices is not clear. Although 12-week data show improved glycemic control compared with insulin aspart, in vitro findings raise doubts regarding long-term stability.

Summary/Formulary Recommendations

Insulin glulisine offers an alternative to other rapid-acting insulin products, which allows for preprandial or postprandial administration. Studies have demonstrated that glulisine is equivalent in efficacy and safety to other short- and

rapid-acting insulin products; however, the clinical benefit of this agent over other insulin products is unclear. Glulisine appears to offer little or no significant advantage to other rapid-acting insulin products. Addition of insulin glulisine to a formulary should be based on institution-specific availability and cost differences among glulisine, lispro, and aspart in the absence of clear superiority of clinical efficacy or safety.

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Insulina Glulisina: Evaluación de sus Propiedades
Farmacodinámicas y Aplicación Clínica

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EXTRACTO

OBJETIVO: Evaluar las propiedades farmacodinámicas, eficacia, seguridad, y aplicación clínica de insulina glulisina, un análogo de insulina de acción rápida en el manejo de pacientes ambulatorios y hospitalizados con diabetes mellitus.

FUENTES DE DATOS: En la búsqueda de la literatura se utilizaron los términos glulisina, análogo de insulina, insulina [LysB3, GluB29], insulina glulisina, insulina rDNA, insulina de acción rápida, SoloStar, seguridad, eficacia, farmacodinámica, y análisis de costo. La búsqueda se realizó mediante el uso de los sistemas de MEDLINE y PubMed, la información publicada de la Asociación Americana de Diabetes (ADA), la Administración de Drogas y Alimentos (FDA), y la compañía Sanofi Aventis Pharmaceuticals. La búsqueda de información incluyó el período desde 1990 al 2008.

SELECCIÓN DE LOS ESTUDIOS Y OBTENCIÓN DE LOS DATOS: Se revisaron los estudios de fase 1, fase 2, fase 3, y post-mercado que evaluaron la eficacia y seguridad de glulisina en pacientes con diabetes tipo 1 y tipo 2. Se suplementaron los datos obtenidos en los estudios clínicos con la información publicada en forma de resumen y con la información del producto que provee la compañía manufacturera.

SÍNTESIS DE LOS DATOS: La insulina glulisina es una insulina de acción rápida con equivalencia relativa a las otras insulinas de acción rápida y corta en relación a su eficacia y seguridad. El inicio de acción de glulisina es de 20 minutos y dura 4 horas. Esto permite que se pueda administrar como bolo 15–20 minutos previo a la ingesta de comida o hasta 20 minutos después de comer. Los estudios clínicos han demostrado que es un medicamento seguro y eficaz en pacientes adultos con diabetes tipo 1 y tipo 2. Algunos estudios señalan que glulisina provee una reducción de la hemogloblinemia A_{1c} (A1C) estadísticamente significativa cuando se compara con insulina regular (disminución de 0.10) y que no presenta diferencia en A1C cuando se compara con las insulinas aspart o lispro. Los efectos adversos más importantes aparentan limitarse a reacciones alérgicas localizadas y sistémicas y a hipoglucemia. El medicamento no está aprobado por el FDA para uso en pediatría, embarazo o lactancia.

CONCLUSIONES: Insulina glulisina es una insulina de acción rápida, segura, y efectiva para el tratamiento de pacientes adultos con diabetes. No se ha demostrado un beneficio clínico mayor a los otros productos de insulina de acción rápida o corta. La decisión de añadir insulina glulisina en el formulario se debe basar en la disponibilidad del medicamento en la institución y las diferencias en costo entre los productos glulisina, lispro y aspart, ya que no hay superioridad en términos de eficacia clínica o seguridad del medicamento en comparación a otras insulinas y porque no hay suficiente información publicada sobre su uso por períodos mayores de 26 semanas.

Traducido por Mirza D Martínez

Insuline Glulisine: une Évaluation de ses Propriétés
Pharmacodynamiques et de ses Applications Cliniques

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RÉSUMÉ

OBJECTIF: Évaluer les propriétés pharmacodynamiques, l'efficacité, la sécurité, et les applications cliniques de l'insuline glulisine, une insuline analogue d'action ultra rapide, dans le traitement du diabète mellitus chez les patients hospitalisés ou ambulatoires.

REVUE DE LITTÉRATURE: Des recherches ont été réalisées pour la période s'étendant de 1990 à 2008 au niveau de MEDLINE, PubMed, l'Association Américaine de Diabète, l'Administration des Drogues et Alimentaires, et la compagnie pharmaceutique Sanofi Aventis en utilisant les mots clé suivants: glulisine, analogue d'insuline, [LysB3, GluB29] insuline, insuline glulisine, rDNA insuline, insuline de action rapide, SoloStar, sécurité, efficacité, pharmacodynamies, et l'analyse de coûts.

SÉLECTION DES ÉTUDES ET SÉLECTION DE L'INFORMATION: Les études de phase 1, de phase 2 et de phase 3 de même que les essais réalisés après la mise en marché du produit ont été révisés. Les études publiées sous forme de résumés et l'information sur le produit obtenue du manufacturier ont permis de compléter les données manquantes des essais cliniques.

RÉSUMÉ: L'insuline glulisine est une insuline d'action ultra rapide dont l'efficacité et la sécurité est relativement équivalente aux autres insulines d'action rapide ou ultra rapide. Son début d'action en 20 minutes et sa durée d'action de 4 heures permettent son administration dans les 15–20 minutes avant ou jusqu'à 20 minutes après les repas. Les essais cliniques ont démontré son efficacité et sa sécurité chez les diabétiques adultes de type 1 ou de type 2. Plusieurs études indiquent une diminution statistiquement significative de l'hémoglobine A_{1c} (A1C) (diminution de 0.10) avec l'insuline glulisine en comparaison avec l'insuline régulière; cependant, aucune différence au niveau du contrôle de l'A1C n'a été démontrée en comparaison avec l'insuline aspart ou l'insuline lispro. Les effets indésirables significatifs semblent se limiter aux réactions allergiques localisées et généralisées et à l'hypoglycémie.

CONCLUSIONS: L'insuline glulisine est une insuline analogue d'action ultra rapide sécuritaire et efficace dans le traitement du diabète chez l'adulte. Les avantages cliniques sur les autres insulines d'action rapide ou ultra rapide n'ont pas été établis. L'ajout de l'insuline glulisine au formulaire devrait se faire selon les politiques de l'institution et selon les différences de coûts entre les insulines glulisine, aspart et lispro étant donné l'absence de supériorité au niveau de l'efficacité et de la sécurité et l'absence de données cliniques au-delà de 26 semaines.

Traduit par Marie Larouche