Clinical Medicine Reviews in Vascular Health

Libertas Academica
FREEDOM TO RESEARCH

CMR
Clinical Medicine Reviews

REVIEW

A Review of the Structure, Pharmacokinetics, Pharmacodynamics, Efficacy and Safety of Insulin Glulisine in the Management of Diabetes Mellitus

Tang Wong[1], Christian M. Girgis[1], Nidhi Garg[1], Anna Lih[1] and John N. Carter[1,2]

[1]Department of Endocrinology and Metabolism, Concord Hospital, Concord, NSW, Australia 2139. [2]A/Professor of Medicine, University of Sydney, Sydney, NSW, Australia. Email: jcarter@bigpond.net.au

Abstract: Glulisine (Apidra™) is a rapid acting recombinant insulin analogue which differs from regular human insulin (RHI) by the substitution of lysine for asparagine at position B3 and glutamic acid for lysine at position B29. The chemical name is 3B-Lys-29-B-Glu-human insulin.The amino acid substitutions of glulisine and other rapid acting insulin analogues promote monomer stability, allowing for rapid dissociation and absorption after subcutaneous injection. It has a favourable pharmacokinetic and pharmacodynamic profile when compared with RHI, characterised by quicker absorption and a greater early disposal of glucose, thus replicating a more physiological response to a meal. It has been demonstrated to be superior to RHI in patients with Type 1 diabetes mellitus (DM) and at least non-inferior in the management of Type 2 DM with respect to reducing HbA1c and post-prandial glucose excursions, with a comparable safety profile.

In efficacy trials comparing glulisine with lispro in patients with type 1 DM, glulisine was non-inferior with no significant difference in change in HbA1c or post-prandial glucose levels. However, although glulisine and lispro have been demonstrated to induce comparable total glucose disposals in normal subjects, glulisine causes earlier glucose disposal in both lean and obese subjects, has significantly faster subcutaneous absorption along with similar rates of adverse events, hypoglycemia and weight gain. There are limited data comparing the pharmacokinetics, pharmacodynamics, efficacy and safety of glulisine and aspart insulins.

Keywords: glulisine, diabetes mellitus, lispro

Clinical Medicine Reviews in Vascular Health 2010:2 121–139

This article is available from http://www.la-press.com.

Introduction

The global pandemic of diabetes mellitus (DM) is projected to affect over 300 million people worldwide by 2025.[1] Glycemic control in combination with aggressive blood pressure and lipid control are pivotal in minimising the many complications associated with DM.[2–7]

In achieving glycemic control, all patients with type 1 DM and many patients with type 2 DM require insulin therapy. The gold standard for a rapid acting, meal time insulin was regular human insulin (RHI) up until the mid 1990s. Unfortunately, RHI fails to replicate physiological insulin levels during meal times due to a delayed peak of action. Subsequently there is insufficient early glucose disposal but a risk of late hypoglycemia. To avoid this, patients using RHI are instructed to administer it 30 minutes prior to a meal. However, this method of administration requires planning and is often impractical particularly in the pediatric population groups.

The rapid acting insulin analogues were genetically engineered with substitutions in their amino acid structure to facilitate a more rapid absorption of insulin following subcutaneous injection and to exhibit a more physiological insulin profile following a meal. There are currently three available rapid acting insulin analogues, lispro (Humalog™), aspart (Novolog, Novorapid™) and glulisine (Apidra™).

In this review, clinical trials with glulisine (blinded and open, parallel and cross-over designs) were included regardless of dose or schedule. The participants were of any age or sex with Type 1 or Type 2 DM on insulin using the diagnostic criteria (American Diabetes Association 1997). There were no studies on the use of glulisine in gestational diabetes. The primary outcome in studies of patients with Type 2 DM was the optimization of glycemic control as determined by improvements in HbA1c levels and improvements in fasting or postprandial blood glucose level.

In patients with Type 1 DM, several authors.[8–10] have evaluated the pharmacodynamics and pharmacokinetics of glulisine when compared with RHI or lispro. There were limited data on the use of glulisine versus aspart in continous subcutaneous insulin infusion (CSII).[11] In addition there was one invitro study that compared the stability properties of glulisine to aspart[12] in a simulated CSII and concluded the physical stability was reduced for glulisine, but not for aspart, under these conditions. A higher rate of formation of biologically inactive high molecular weight proteins was observed for glulisine.

The published articles were identified by The Cochrane Library (issue 4, 2009), PUBMED, MEDLINE and EMBASE. Additional searching was done by cross-referencing from original articles and reviews. Abstracts were screened from major diabetes meeting and were published in Diabetologia, Diabetes and Diabetes Medicine. An inquiry was directed to Sanofi-Aventis on future research developments and articles pertaining to glulisine.

Table 1a. The baseline characteristics of type 1 diabetic patients participating in GLU trials.

	Author	Total no. (M:F)	Treatment regimen	Characteristics		
				Age	BMI	Duration of diabetes
cw RHI	Garg et al[1] (2005, 12 wks)	860 (1.12:1)	Basal GLA + PreGLU Basal GLA+ Post GLA Basal GLA + RHI	40.8 ± 11.9 39.8 ± 4.7 40.2 ± 11.4	27 ± 4.3 27.3 ± 4.7 27 ± 5	20 ± 11.4 20.2 ± 11.5 19.4 ± 11.2
cw IL	Dreyer et al[1] (2005, 26 wks)	672 (1.4:1)	GLA + GLU GLA + LIS	39.1 ± 12.1 37.9 ± 12.4	24.9 ± 12 37.9 ± 12	17.4 ± 11W 15.6 ± 10
	Kawamori et al[2] (2008, 28 wks)	267 (0.7:1)	GLA + GLU GLA + LIS	38.9 ± 14 38.8 ± 12	23.1 ± 3 22.8 ± 3	12.8 ± 10 11.1 ± 7.1
cw IL	Philotheou et al[2] (2008, 26 wks)	572	BasalNPH/Glargine + GLU Basal NPH /Glargine + IL	12.5 ± 3.1 12.6 ± 2.9	20.8 ± 3.4 20.5 ± 3.3	5.3 ± 3.6 5.2 ± 3.2

Table 1b. The baseline characteristics of type 2 diabetic patients participating in GLU trials.

	Author	Total No. (M:F)	Treatment regimen	Characteristics		
				Age	BMI	Duration of diabetes
cw RHI	Dailey et al[1] (2004, 26 wks)	876 (1.12:1)	Basal NPH + GLU Basal NPH + RHI	58.9 ± 10, 57.7 ± 9.9	34.6 ± 7 34.5 ± 7	14.7± 8 13.4 ± 7.6
	Rayman et al[1] (2007, 26 wks)	890 (0.98:1)	Basal NPH + GLU Basal NPH + RHI	59.8 ± 9, 60 ± 9.6	31.5 ± 5 31 ± 5	13.6 ± 8 13.4 ± 7.3
cw OAD	Kawamori et al[4] (2008,16 wks)	387	GLU + OAD GLU OAD	NR	BMI < 30	At least 1 year for all groups
Pre meal and Postmeal GLU	Lankisch[1] et al [OPAL] (2008, 26 wks)	393 (1.3:1)	Basal GLA + OAD + Pre B GLU Basal GLA + OAD + Pre M GLU	63.3[a] ± 9.2	31.3[a] ± 5.1	10.5[a] ± 7.1
	Wynne et al (2008, 52 wks)	330	Basal GLA + PreGLU Bsal GLA + PostGLU	54.1 ± 9.1, 53.7 ± 9.8	37.4 ± 8 36.9 ± 7.7	14 ± 8 13.9 ± 7
cw Premixed	Fritsche et al (2008, 52 wks)	310 (1:1)	Basal GLA + GLU Premixed Insulin[b]	12.5 ± 3.1 12.6 ± 2.9	20.8 ± 3.4 20.5 ± 3.3	5.3 ± 3.6 5.2 ± 3.2

[1]Open Labelled Multicentre Randomised Parallel Group.
[2]MultiCentre, Open, Randomised, Parallel Group non inferiority trial.
[3]Open Labelled Multicentre, Multinational, Randomised Controlled (1:1:1) Parallel Group.
[4]Open Lablled Randomised Parallel Group (Korea and Japan only).
[a]The mean values for all groups given.
[b]The type of pre-mixed insulin not specified.

There were 108 articles in PUBMED with "glulisine" as the key word in patients with Type 1 DM. There have been four randomized non blinded, controlled studies, three of which investigated glulisine with lispro and one with RHI[13–17] Studies ranged in duration from 12–28 weeks (see Table 1a). The characteristics of the patients included in these studies were adults with Type 1 DM aged greater than 18 years, BMI < 35 kg/m^2 and younger than 40 years at the time of disease onset, whilst in the pediatric study 16 patients were aged 4–17 years. The HbA1c at entry in the studies for Type 1 DM patients were 6%–11%. The exclusion criteria included proliferative retinopathy, unstable diabetic retinopathy, hepatic or renal dysfunction, history of seizures, hypersensitivity to insulin, pancreatectomy, pancreatic islet cell transplantation and a history of alcohol/drug abuse.

In type 2 DM patients there have been 4 randomised non blinded studies, one single blinded study, one regimen controlled study[17–22] and one randomised, non blind regimen controlled safety trial.[23] The studies ranged in duration from 16–52 weeks (see Table 1b). The eligibility criteria included those patients with Type 2 DM who were aged greater than 18 years and had been on insulin therapy for greater than 6 months and/or were stable on a regimen of oral antidiabetic medication. The duration of diabetes was at least one year, BMI < 30 kg/m^2 with baseline HbA1c ranging from 6%–11% and fasting blood glucose (FBG) levels of ≤6.7 mmol/L.

Articles not pertaining to glulisine were omitted from this review, and the clinical trials selected were directly compared with RHI, oral therapy, insulin lispro, premixed insulin and glargine.

Structure and Pharmacokinetics

Glulisine (Apidra™) is a rapid acting recombinant insulin analogue which differs from RHI by the

Table 2. The pharmacokinetics of glulisine (GLU) versus RHI.[35] (no *P*-values reported).

	GLU	RHI
INS-AUCss (μIU.min/min)	2393 (CI 2059–2808)	1856 (1262–2201)
Insulin conc at steady state Css (μIU/min)	70	58
INS-AUC$_{0 \text{ to clamp end}}$ (μIU.min/min)	9262	7652
Volume of Distribution Vss (L)	13 (9–17)	22 (13–31)
$T_{1/2}$ 90 (min)	13 (9–26)	17 (9,26)
Cl total (ml/min)	927 (785–1046)	1084 (864–1600)
MRT (min)	14 (9–17)	19 (12,28)

substitution of lysine for asparagine at position B3 and glutamic acid for lysine at position B29.[24]

The chemical name of insulin glulisine is 3B-Lys-29B-Glu-human insulin.[25]

Glulisine is the newest addition to the class of rapid acting recombinant insulin analogues, which currently include lispro and aspart. Lispro is created by subsituting proline for lysine at position B28 and lysine for proline at position B29, effectively reversing the amino acids sequence at positions 28 and 29 of the insulin beta-chain.[26] Aspart is homologous to RHI except for the substitution of proline for aspartic acid at B28[27] (see Figs. 1–4).

In solution, insulin molecules exist in equilibrium among monomers, dimers, tetramers, hexamers and higher order aggregates. Human insulin is best absorbed in its monomeric form, however at physiologic pH normal insulin molecules tend to associate into dimers and subsequently hexamers in the presence of zinc. Consequently, the absorption of regular human insulin is limited by the degree and strength of self association of insulin molecules.[28]

Certain amino acid residues of the human insulin molecule are not required for full biological activity but have an effect on its self-association properties. For example, residues B28 and B29 are pivotal for dimer formation and B1–B8 have a role in hexamer formation.[29]

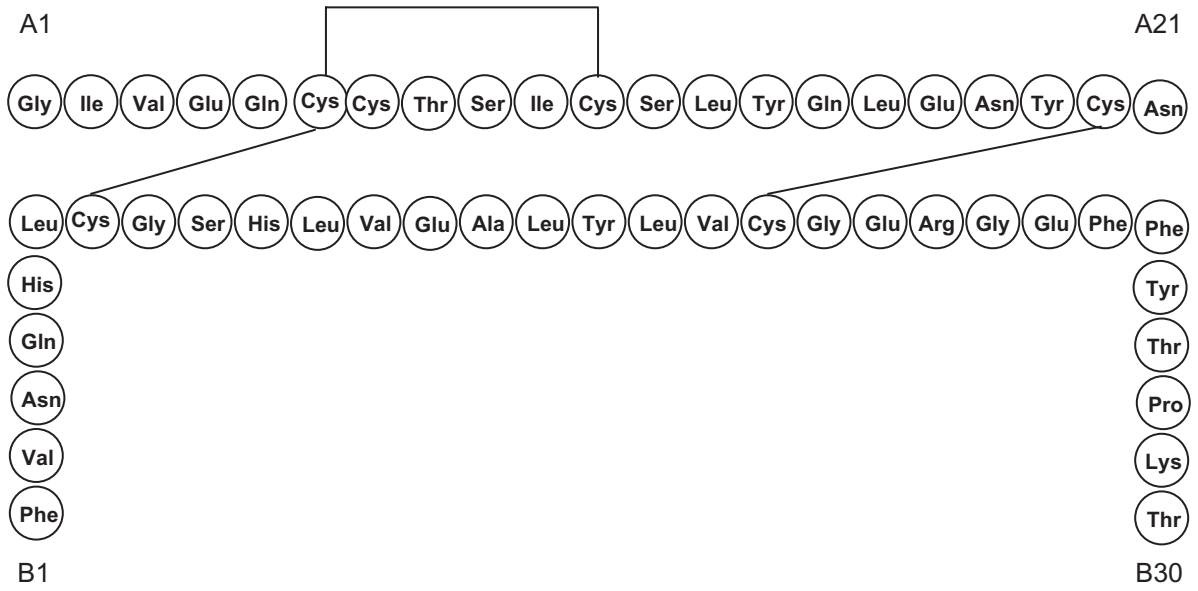

Figure 1. Regular human insulin.

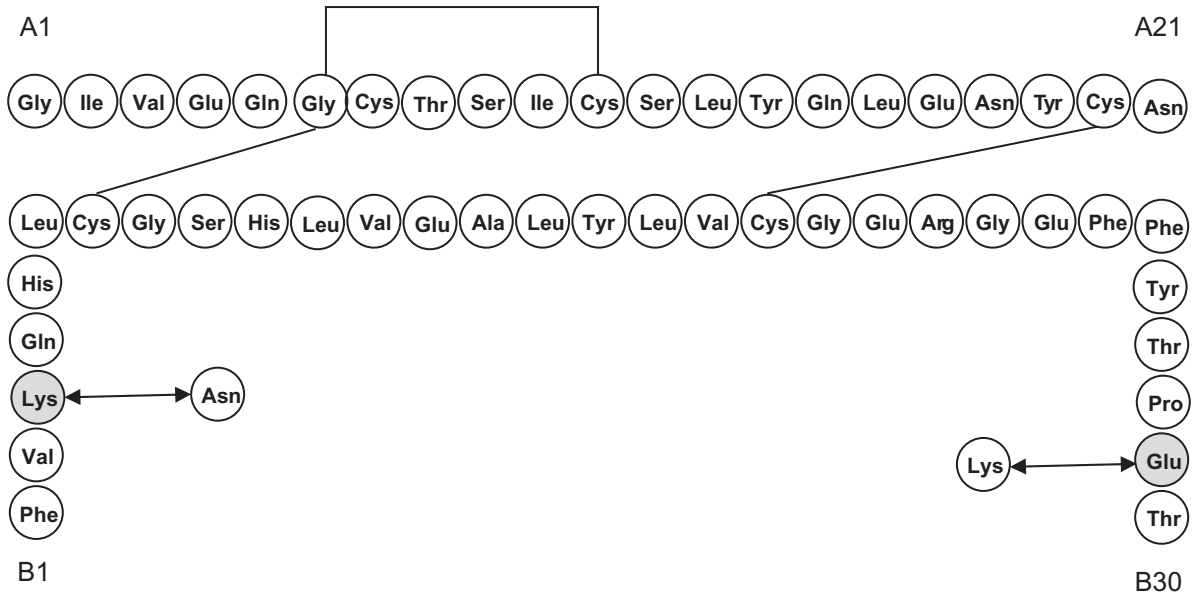

Figure 2. Glulisine Insulin.

The amino acid substitutions of glulisine and other rapid acting insulin analogues promote monomer stability, allowing for rapid dissociation and absorption after subcutaneous injection. In addition, the isolectric point (pI) is lowered to 5.1, enhancing solubility at physiological pH.[30]

Although human insulin is best absorbed in its monomeric form, the dimer and hexameric forms confer conformational stability and are less likely to denature in storage.[31] Hence zinc is added to aspart and lispro to stabilise the insulin molecules in hexamers to achieve a practical shelf-life.[32,33]

Unlike the other rapid acting insulin analogues, the oligomeric molecules of glulisine are stable without the addition of zinc, presumably because of the unaltered proline at position B28 thus allowing dimerization.[34] Instead, polysorbate 20, a surfactant is added to the product composition to prevent the irreversible formation of aggregates (fibrils) from monomers, further enhancing physical stability.[31]

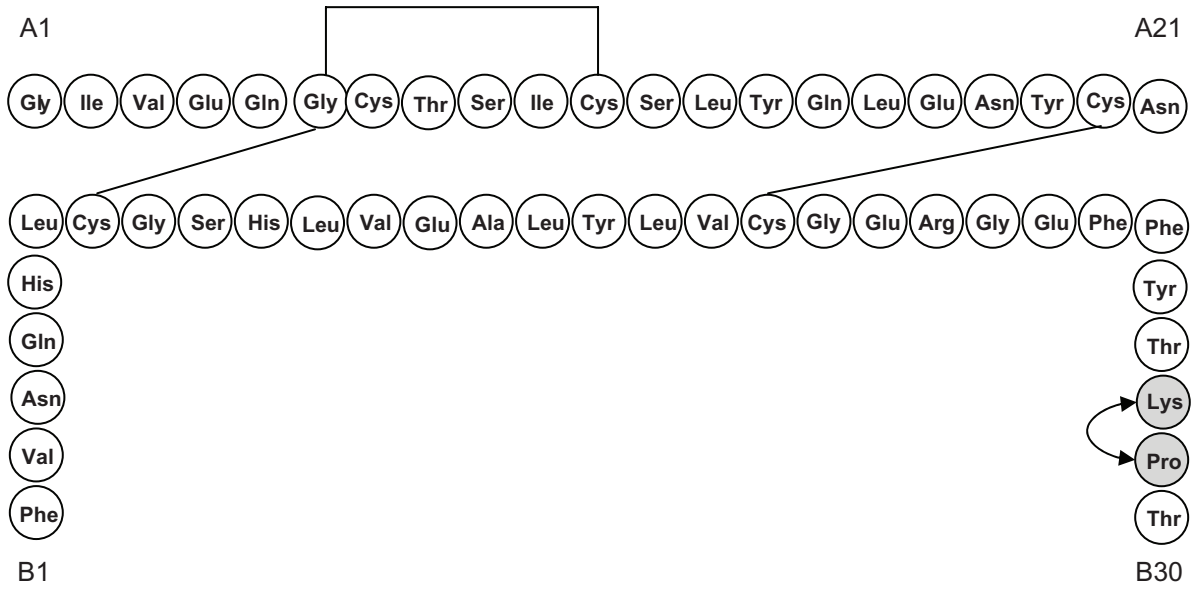

Figure 3. Lispro Insulin.

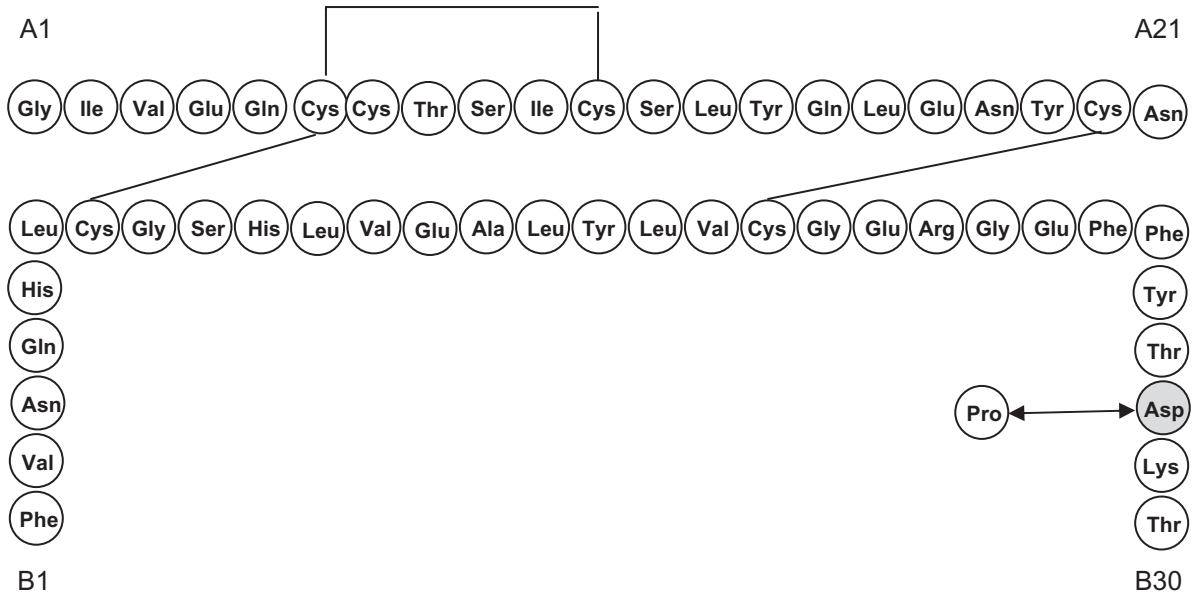

Figure 4. Aspart Insulin.

Potency

The potency of glulisine was compared with RHI in a single-centre, randomised, open-label, two-way crossover, euglycemic clamp study of 16 healthy male subjects administered either 0.8 mIU/min/kg of glulisine or RHI intravenously over 2 hours. Glucose disposal at steady state (area under the GIR curves [GIR-AUCss]) were 209 mg/kg and 214 mg/kg for glulisine and RHI respectively. The GIR profiles of both treatments were super-imposable, indicating equal onset of action and effectiveness for glucose disposal and thus equipotency on a molar basis of the two insulins studied.[35]

Mechanism of Action

Insulin and its analogues lower serum glucose levels by facilitating glucose uptake in skeletal muscle and fat, and by inhibiting gluconeogenesis, glycogenolysis, lipolysis and proteolysis through its effect on the insulin receptor. Compared with RHI, there are no differences in association, dissociation or receptor binding affinity.[36]

Biovailability, Half life, Volume of Distribution and Clearance

The main factor affecting the bioavailability of insulin administered subcutaneously is absorption, which can be influenced by the site and depth of injection, insulin dose, insulin mixing, exercise and local temperature. Glulisine, when administered subcutaneously, has a bioavailability of approximately 70%, and this parameter does not vary significantly between the different injection sites (e.g. abdomen, deltoid and thigh),[37] and is comparable to other rapid acting insulin products.[26,27]

The half lives of glulisine and regular human insulin were 42 minutes and 86 minutes respectively following subcutaneous administration,[38]

The pharmacokinetic parameters of glulisine following intravenous administration was evaluated in a euglycemic clamp study of 16 healthy subjects randomised to receive an intravenous infusion of 0.8 mU/kg/min of either glulisine or RHI.[35] The results are summarised in Table 2.

Metabolism

Biodegradation of insulin is most importantly regulated by insulin protease enzymes. The peptide bonds within the structure of glulisine do not alter its sensitivity to the same pathways of metabolism and degradation as RHI.[39] Modifications of the primary structure of glulisine do not involve the peptide bonds that are sensitive to this degradation and thus glulisine undergoes the same pathways of metabolism and degradation as RHI.

Pre-Mixing with Intermediate Acting Insulin

Pre-mixing of glulisine with intermediate acting insulin (such as neutral protamine Hagedorn [NPH]) is

practiced in pediatric and occasionally adult patients. A randomised, open-label, two-way crossover study of 32 healthy male subjects compared the effects of injecting a single subcutaneous dose of 0.1 U/kg dose of insulin glulisine immediately after pre-mixing with a 0.2 U/kg dose of NPH insulin with glulisine alone using the manual euglycemic clamp technique. Total glulisine exposure was similar, although some attenuation of C_{max} was noted after premixing (51 versus 70 μIU.ml $P < 0.05$). The T_{max} was not affected by mixing.[40]

There are no studies available on the mixing of glulisine with other insulins. When mixing with NPH, it has been suggested that glulisine should be drawn first into the syringe immediately prior to the injection.[25]

Intravenous Administration of Glulisine

Glulisine can be administered by intravenous infusion at concentrations of 0.05 units/ml to 1 unit/ml, using polyvinyl chloride (PVC) bags. Glulisine has been shown to be stable in normal saline solution (0.9% normal saline)[38] but it is not compatible with dextrose or Ringer's solution.[38]

Special Patient Groups

Obese patients

In a euglycemic clamp study, 18 obese patients without diabetes were stratified into two groups (BMI 30–34.9 and 35–40 kg/m^2) and were randomised to 0.3 U/kg of glulisine, lispro or RHI subcutaenously. There was no significant correlation between skin thickness, BMI and the pharmacokinetic or pharmacodynamic parameters with glulisine. There was a positive correlation for lispro and RHI between skin thickness, BMI and time to maximal insulin concentration (T_{max}).[41]

Japanese patients

Although not statistically significant, a Japanese population demonstrated slightly faster absorption and action compared with BMI-matched Caucasian men, in a euglycemic clamp study with a single 0.2 U/kg dose of glulisine, lispro or RHI.[42]

Renal failure

Patients with moderately (eGFR 30–50 ml/min) and severely impaired renal function (<30 ml/min) may require dose reduction due to observed increases in insulin exposure (29%–40%) and decreases in clearance (20%–25%) when compared with healthy individuals.[38] Twenty-four non-diabetic patients with normal renal function ($n = 8$, eGFR >80 ml/min), moderate renal impairment ($n = 8$, eGFR 30–50 ml/min) and severe renal impairment ($n = 8$, eGFR < 30 ml/min), were administered a single dose of 0.15 U/kg of glulisine subcutaneously. There was a weak correlation between renal function and total glulisine exposure ($AUC_{0\text{-end}}$), but no correlation between the creatinine clearance and the parameters characterising the rapid acting properties of glulisine ($AUC_{0–1h}$, $AUC_{0–2h}$, T_{max} or C_{max}). Even though the author suggested that dose reduction of insulin in patients with renal impairment was not warranted,[43] we would recommend caution until more clinical data are obtained.

Children

A double blind, randomised, cross-over study of 20 pediatric patients with type 1 diabetes (10 children of ages 5–11 and 10 adolescents of ages 12–17 yrs) incorporated a single-dose (0.15 U/kg) of either glulisine or RHI two minutes before a standardised meal. Similar to adults with type 1 DM, glulisine demonstrated greater early insulin exposure, earlier time to maximal insulin concentration and lower blood glucose excursion compared with RHI. The pharmacokinetic profiles were similar in both the children and adolescent groups.[9]

Table 3. Pharmacodynamic and pharmacodynamic results in healthy subjects ($n = 16$) during a euglycemic clamp study (following administration of 0.3 U/kg of either glulisine, lispro or RHI). Adapted from Becker et al *P*-values were not recorded.[44]

	Insulin glulisine 0.3 U/kg	Insulin lispro 0.3 U/kg	RHI 0.3 U/kg
$INS\text{-}AUC_{0\text{-clamp end}}$ (μIU.min/mL)	29302	22116	21673
T_{max} (min)	56	50	84
MRT (min)	105	117	182
$GIR\text{-}AUC_{0–2}$ (mg/kg)	1026	976.3	674.8
$GIR\text{-}AUC_{0\text{-clamp end}}$ (mg/kg)	2839.6	2942.6	3234.7

Table 4. Pharmacodynamic comparisons of lispro versus glulisine in subjects without DM ($n = 80$), adapted from Heise et al.[45]

Variable	Insulin glulisine 0.2 U/kg	Insulin lispro 0.2 U/kg	Insulin glulisine 0.4 U/kg	Insulin lispro 4 U/kg
GIR-$AUC_{0–10h}$ (mg/kg)	1569 ± 521	1554 ± 521	1554 ± 512	2564 ± 811
GIR-$AUC_{0–1h}$	102 ± 75*	93 ± 73	158 ± 100*	112 ± 71
INS-$AUC_{0–1h}$	70 ± 24†	47 ± 22	135 ± 56†	84 ± 34

*$P < 0.05$, †$P < 0.001$ vs. corresponding lispro group.

Pharmacodynamic Studies Comparing Glulisine to RHI, Lispro and Aspart

Subjects without diabetes

Glulisine versus RHI

A randomised cross-over, euglycemic clamp study of sixteen healthy male subjects who received either 0.3 U/kg of glulisine, lispro or RHI demonstrated comparable pharmacokinetic and pharmacodynamic properties between glulisine and lispro. Both rapid acting analogues had a greater early glucose disposal (GIR-$AUC_{0–2}$) with similar overall glucose disposal (GIR-$AUC_{0\text{-clamp end}}$) and they reached maximal concentrations in approximately half the time (T_{max}) when compared with RHI. The median residence time (the average time that molecules of a drug reside in the body) was also approximately half. The total systemic availability of insulin was similar between the rapid acting analogues and RHI (INS-$AUC_{0\text{-clamp end}}$)[44] See Table 3.

Glulisine versus lispro

Eighty subjects without diabetes were stratified into four body mass index classes and were randomised to receive single injections of glulisine or lispro (0.2 or 0.4 U/kg), under euglycemic clamp conditions.[45] Although glulisine and lispro demonstrated comparable total glucose disposals as demonstrated by similar GIR-$AUC_{0–10}$, glulisine demonstrated earlier glucose disposal in both lean and obese subjects at both 0.2 U/kg or 0.4 U/kg doses. Furthermore, insulin gluslisine demonstrated significantly faster absorption as demonstrated by a more rapid INS-$t_{10\%}$ (time to reach 10% of maximal insulin concentration), than lispro. While the difference was only 5–6 minutes, Heise et al suggested that this was also clinically significant as it afforded a 25%–30% greater glucose disposal in the first hour[45] (See Table 4).

Subjects with type 1 diabetes mellitus

Glulisine versus RHI

In crossover studies of subjects with type 1 diabetes comparing pre- and post-prandial glulisine with RHI, glulisine had half the mean residence time (MRT) and achieved twice the peak concentration of insulin (INS-C_{max}) in half the time (INS-t_{max}) in comparison to RHI[46,47] There was also lower within-subject variability of INS-t_{max}.[46]

Early exposure to insulin (INS-$AUC_{0–2}$) was greater with glulisine as compared with RHI when administered immediately pre-meal.[46] Although a more rapid onset of action than regular human insulin, the total systemic availability did not differ[46,47] (See Table 5).

Table 5. Comparisons between pharmacokinetic parameters of glulisine and regular human insulin in a study of 20 patients with type 1 diabetes mellitus.[46]

Variable	Insulin glulisine Immediately pre-meal	Insulin glulisine 15 minute post meal	RHI 30 mins premeal	RHI immediately premeal
INS-$AUC_{0–2h}$ (μIU.min/mL)	7278	5959	4258	4091
INS-$AUC_{0–6h}$ (μIU.min/mL)	11,912	11,897	11500	11531
INS-t_{max}	55	57	82	97
INS-MRT	98	99	161	168

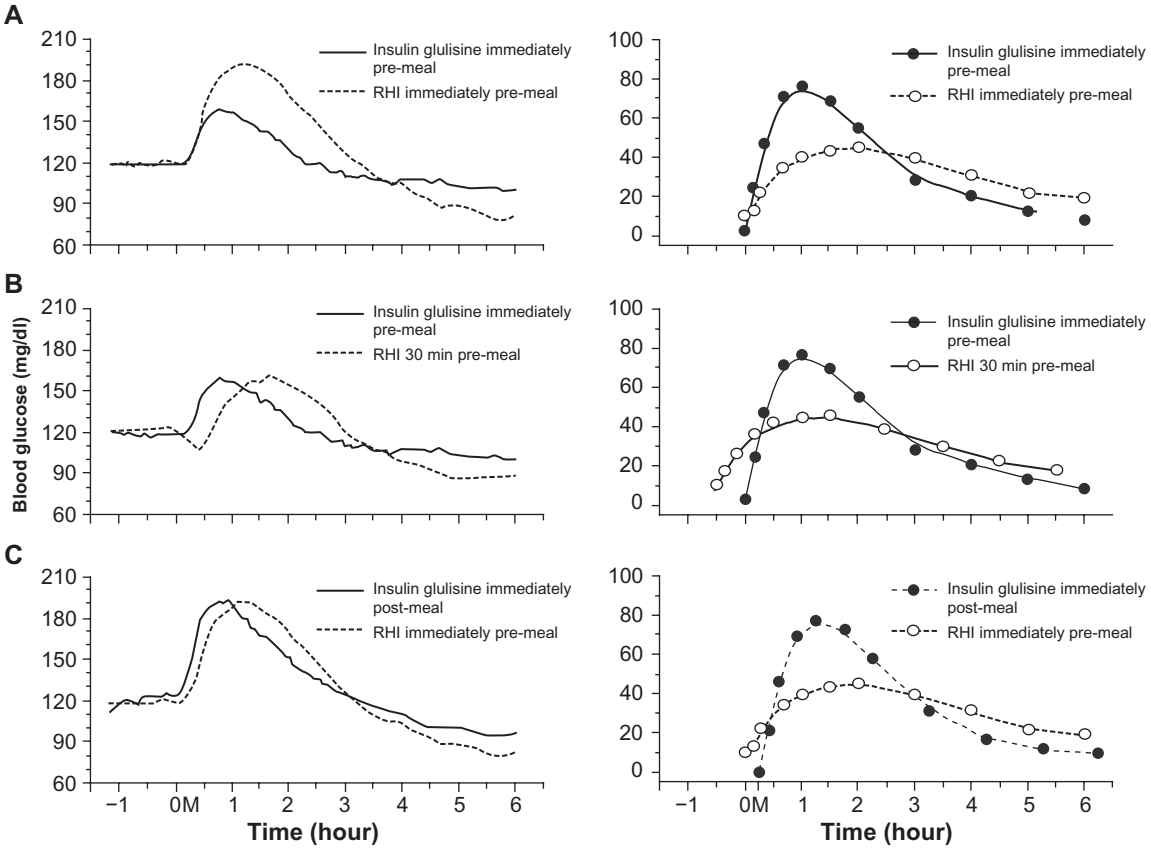

Figure 5. A comparison of blood glucose in mg/dL (left) and insulin concentrations μU/ml (right) following injection of either RHI or glulisine.[46] Copyright 2006 American Diabetes Association From Diabetes Care. 2006;29:1812–7. Reprinted with permission from The American Diabetes Association.

Glulisine provided tighter blood glucose control than RHI when both were administered immediately pre-meal. Blood glucose exposure during the first 2 hours following a standardised meal was significantly lower with glulisine than with RHI ($BG\text{-}AUC_{0-2}$ 180 vs. 209 mg.h/dL), while total blood glucose exposure after six hours ($BG\text{-}AUC_{0-6}$) was similar for the two treatment groups. Furthermore, post-meal glulisine and RHI given immediately pre-meal produced similar effects on post-prandial blood glucose exposure ($BG\text{-}AUC_{0-2}$ 337 vs. 334 mg.h/dL, $BG\text{-}AUC_{0-6}$ 777 vs. 770 mg.h/dL) and excursion (ΔBG_{max} 85 vs. 89 mg/dL)[46] (See Fig. 5).

Glulisine versus Lispro

A randomised, double-blind, cross over euglycemic clamp study of 24 subjects with type 1 DM compared the phamacodynamic and pharmacokinetic properties of 0.2 U/kg of glulisine versus lispro and RHI administered subcutaneously.[10] Glulisine and lispro had similar early and total insulin exposure along with early and total glucose disposal. However glulisine had a shorter median residence time compared with lispro (glulisine 96 mins vs. lispro 131 mins, see Table 6).

This study corroborated the greater early insulin exposure, greater early glucose disposal and shorter time to maximal concentration compared with RHI.[10]

Subjects with type 2 diabetes mellitus

Glulisine versus RHI

A euglycemic clamp study of 24 subjects with type 2 DM demonstrated higher early insulin exposure ($INS\text{-}AUC_{0-2}$) and higher maximal insulin exposure ($INS\text{-}C_{max}$) with both glulisine and lispro compared with RHI. Glulisine and lispro had faster pharmacodynamic action, with shorter times to 10% of maximal glucose infusion rate ($GIR\text{-}t_{10\%}$) compared with RHI.[48]

Table 6. Pharmacokinetic and pharmacodynamic properties of glulisine versus lispro and RHI in 24 subjects with type 1 diabetes mellitus. (Adapted from Burger et al).[10]

	Mean			Point estimate	
	Insulin glulisine 0.2 U/kg	**Insulin lispro 0.2 U/kg**	**RHI 0.2 U/kg**	**GLU/IL (95% CI)**	**GLU/RHI (95% CI)**
INS-$AUC_{0–2}$ (μIU.min/mL)	10625	8721	5412	117% (90;232)	153% (117;199)
INS-$AUC_{0\text{-clamp end}}$ (μIU.min/mL)	16120	16837	16610	97% (80;118)	95% (78;116)
T_{max} (min)	51	58	82	–9 min (–30;6)	–24 min (–40;–5)
MRT (min)	96	131	185	79% (65;97)	70% (57;86)
GIR-$AUC_{0–2}$ (mg/kg)	625	556	348	98% (71;126)	148% (108;188)
GIR-$AUC_{0\text{-clamp end}}$ (mg/kg)	1547	1495	1473	98% (74;121)	96% (73;119)

Glulisine versus Lispro

A euglycemic clamp study of 24 subjects with type 2 DM randomised to receive 0.2 U/kg of either glulisine, lispro or RHI demonstrated superimposable time-action profiles of glulisine and lispro.[48]

In randomised crossover studies of glulisine and lispro immediately prior to a standardised meal, there was overall no statistically significant difference in maximal glucose levels (GLU_{max}), time to GLU_{max}[49] or total glucose disposal ($GLU\text{-}AUC_{total}$).[50] However, glulisine demonstrated lower glucose excursions compared with lispro with a 12% lower pre-prandial subtracted maximal glucose concentration (ΔGLU_{max} glulisine:lispro 0.88, $P < 0.01$)[49] See Table 7.

Glulisine versus aspart

A cross over study of 37 obese subjects with type 2 DM randomised to receive either 0.2 U/kg of either glulisine or aspart immediately prior to a meal, demonstrated lower glucose excursion ($AUC_{0–1}$) during the first hour after a test meal and lower maximal glucose concentration (Glucose Max) with insulin glulisine.[51] Maximal insulin concentrations (C_{max}), insulin concentrations during the first hour (INS-$AUC_{0–1}$) and insulin concentrations throughout the entire study study (INS-$AUC_{0–6}$) were significantly higher following the administration of glulisine (See Table 8).

Clinical Studies Efficacy

Adult patients with type 1 DM

Glulisine vs. RHI

An open-label, randomised, controlled, parallel-group study compared the efficacy of glulisine with RHI over a 12 week study period (see Table 9a).[13] The primary analysis assessed non-inferiority for the difference in the adjusted mean change in HbA1c from baseline

Table 7. Pharmacodynamic results in 18 obese subjects with type 2 DM after treatment with 0.15 U/kg of either glulisine or lispro.[49]

Variable	**Glulisine**	**Lispro**	**Ratio (glulisine:lispro)**	**90% CI**	***P*-value**
GLU_{max} (mmol/L)	10.00	10.25	0.98	(0.94;1.01)	0.27
GLU_{min} (mmol/L)	4.61	4.53	1.02	(0.96; 1.07)	0.60
ΔGLU_{max} Overall (mmol/L)	3.55	4.06	0.88	(0.81; 0.95)	<0.01

Table 8. A pharmacokinetic/pharmacodynamic comparison of glulisine and aspart in 37 obese subjects with type 2 DM, administered prior to a standard meal.[51]

Variable	Glulisine	Aspart	*P*-value	Estimate for difference in means (90% CI) GLU/ASP
AUC 0–1h (mg.h/dL)	149	158	0.0455	94 (90;99)
Glucose Max (mg/dL)	170	181	0.0337	94 (95; 99)
C_{max} (pmol/L)	534	363	$P < 0.0001$	147 (133;163)
INS-AUC-$_{0–1h}$ (pmol.h/L)	272	138	$P < 0.0001$	197 (157;248)
INS-AUC-$_{0–6h}$ (pmol.h/L)	2002	1289	$P < 0.0001$	147 (133;163)

to endpoint. 860 adult patients with Type 1 DM were randomised to receive glulisine 0–15 minutes before meals ($n = 286$), glulisine immediately after meals ($n = 296$) or RHI 30–45 minutes before meals ($n = 278$). Patients had similar baseline characteristics in the three study arms. Insulin glargine was administered once-daily as basal insulin.

Pre-meal glulisine resulted in a significantly greater reduction in HbA1c compared with RHI 30–45 minutes premeal (–0.26% vs. –0.13%; $P = 0.02$). In addition, pre-prandial glulisine was associated with a significantly greater HbA1c reduction than post-prandial glulisine (–0.26% vs. –0.11%; $P = 0.006$). There was no significant difference in change in HbA1c between post-meal glulisine versus the pre-prandial RHI. Post-prandial glulisine was deemed non-inferior to pre-prandial glulisine and RHI in terms of mean baseline to endpoint change in HbA1c as determined by the pre-defined non-inferiority margin.

2-hour post-breakfast and 2-hour post- dinner measurements were significantly lower in the pre-meal glulisine group compared with post-meal glulisine (7.83 vs. 8.57 mmol/L, $P = 0.0017$ and 8.12 vs. 8.77 mmol/L, $P = 0.0137$, respectively) and pre-meal RHI (7.83 vs. 9.10 mmol/L, $P = 0.0001$ and 8.12 vs. 9.23 mmol/L, $P = 0.0001$, respectively). There was no significant difference in the 2-hour post-lunch blood glucose values between the three groups.

Glulisine versus lispro

In adult patients with Type 1 DM, the efficacy of glulisine compared with lispro has been assessed in 2 trials[14,17] both of which demonstrated that glulisine was non-inferior to lispro as determined by baseline to endpoint change in HbA1c. Both trials used glargine as the basal insulin (see Table 9a).

In the study by Dreyer et al[17] 672 patients were randomised to receive glulisine ($n = 339$) or lispro ($n = 333$) 0–15 minutes prior to meals over a 26 week treatment period. There was a similar reduction in mean HbA1c in both groups (adjusted mean change from baseline –0.14% in both groups). Pre-prandial, post-prandial, bedtime and nocturnal self-monitored blood glucose profiles were similar in each group.

A subsequent study by Kawamori et al[14] was performed in a Japanese population. Subjects were randomised to glulisine ($n = 132$) or lispro ($n = 135$) over a 28 week treatment period. Adjusted mean change in HbA1c was +0.10% in the glulisine group vs. +0.04% in the lispro group (95% CI –0.09 to 0.21; no *P*-value). There was no significant difference in adjusted mean 2-hour post-prandial blood glucose between glulisine and lispro (9.06 vs. 8.13 mmol/L; $P = 0.0647$) at endpoint.

Alternative regimens—continuous subcutaneous insulin infusions

In adult patients with Type 1 DM there are limited data on glulisine administered using CSII. A multicenter, controlled open label study[11] compared glulisine with aspart in 59 Type 1 DM subjects using CSII. The primary endpoint was to evaluate the compatibility of glulisine with pump use compared with aspart. The secondary end point evaluated changes in HbA1c levels. During the 12-week treatment period, participants received a basal rate of insulin with either aspart or glulisine as a bolus dose immediately before meals. The target blood glucose level for adjusting insulin was a fasting BGL of 5.0–6.7 mmol/L and post-prandial BGL of

Table 9a. Total insulin requirements and HbA1c changes at endpoint in type 1 diabetics.

Diabetes type	Author (yr study published, duration of treatment)	Treatment regimen	Total Insulin dose (Units/day)		HbA1c			
Adult type 1 diabetics			**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**Change**	***P*¥-value**
cw RHI	Garg et al[1] (2005, 12 wks)	Basal GLA + Post GLU	57.9 ± 1.53	58 ± 1.65	7.7	NR	–0.26	NR *P* = 0.014
		Basal GLA + Post GLU	57 ± 1.47	56.9 ±1.57	7.7	NR	–0.11	NR
		Basal GLA + RHI	55.3 ± 1.61	57.6 ± 1.78	7.6	NR	–0.13	
cw IL	Dreyer et al[1] (2005, 26 wks)	GLA + GLU	NR	NR	7.6	7.46	–0.14	
		GLA + LIS	NR	NR	7.58	7.45	–0.14	
	Kawamori R et al[2] (2008, 28 wks)	GLA + GLU	NR	NR	7.44	NR	+0.1	
		GLA + LIS	NR	NR	7.5	NR	+0.04	
Paediatric								
cw IL	Philotheou et al[2] (2008, 26 wks)	Basal NPH/ Glargine + GLU	NR	NR	8.2	8.31	0.1	
		Basal NPH/ Glargine + IL	NR	NR	8.17	8.37	0.16	

[1]Open Labelled Multicentre Randomised Parallel Group.
[2]MultiCentre, Open, Randomised, Parallel Group non inferiority trial.
¥*P*-value refers to HbA1c from baseline to endpoint.

6.7–8.9 mmol/L. After 12 weeks the recorded HbA1c was 7% (baseline 6.8%) in the glulisine group vs. 7.2% (baseline 7.1%) in the aspart group. The frequency of infusion site reactions, hypoglycemia and the time between catheter changes were similar for both insulin types (See Table 10).

Pediatric patients with type 1 diabetes

Glulisine versus RHI

There are no published trials comparing glulisine with RHI in pediatric patients with type 1 DM.

Glulisine versus Lispro

Glulisine was found to be non-inferior to lispro in a pediatric study.[16] 572 children, 4–17 years of age with type 1 DM , were randomised to receive treatment with either glulisine (n = 277) or lispro (n = 295) 0–15 minutes pre-meal and either once daily glargine or twice-daily NPH as a basal insulin over 26-weeks (NPH: 30.3% in the glulisine group vs. 27.1% in the lispro group; glargine: 69.7% in the glulisine group vs. 72.9% in the lispro group). The adjusted mean change in HbA1c was + 0.10% and + 0.16% respectively = NS). Glulisine was deemed non-inferior to lispro (–0.06% difference in HbA1c with glulisine-lispro; [95% CI: –0.24 to 0.12%]; prespecified non-inferiority margin 0.4%). Significantly more patients in the glulisine group reached ADA age-specific HbA1c targets at endpoint compared with the lispro group (38.4% vs. 32.0%; P = 0.0386) and this difference was most marked in the 13–17 year-old age-group with 31.1% of glulisine patients versus 21.1% of lispro patients reaching ADA age-specific HbA1c target of <7.5% at endpoint (P = 0.0251). There was no significant difference between treatment groups in the post-prandial blood glucose 2 hours after the start of the main meal (glulisine 9.20 mmol/L vs. lispro 9.04 mmol/L; P = NS).

Adult patients with type 2 diabetes mellitus

Glulisine versus RHI

There are two published trials (randomised, controlled, open-label parallel studies of 26 weeks duration) comparing glulisine with RHI in patients with type 2 diabetes.[21,20] Subjects were randomised to receive NPH and glulisine or NPH and RHI for

Table 9b. Total insulin requirements and HbA1c changes at endpoint in type 2 diabetics.

	Author (yr study published, duration of treatment)	Treatment regimen	Total insulin dose (Units/day)		HbA1c	
Adult patients with type 2 Diabetes Mellitus			**Baseline**	**Endpoint**	**Baseline**	**Endpoint**
cw RHI	Dailey et al[1] (2004, 26 wks)	Basal NPH + GLU	91.6	100.9	7.58	7.11
		Basal NPH + RHI	88.6	99.7	7.52	7.22
	Rayman et al[1] (2007, 26 wks)	Basal NPH + GLU	NR	NR	7.57	7.25
		Basal NPH + RHI	NR	NR	7.51	7.19
cw OAD	Kawamori et al[4] (2008, 16 wks)	GLU + OAD	13.3[α]	22.5[α]	8.99	NR
		GLU	14.2[α]	38[α]	9.02	NR
		OAD	–	N-	9.04	NR
Pre meal and Postmeal GLU	Lankisch[1] et al [OPAL] (2008, 26 wks)	Basal GLA + OAD + Pre B GLU	4.6 ± 1.9	11.2 ± 6.4	7.35	7.05
		Basal GLA + OAD + Pre M GLU	5.3 ± 2.3	12 ± 7	7.29	6.94
	Wynne et al (2008, 52 wks)	Basal GLA + PreGLU	NR	NR	8.42	7.03
		Basal GLA + PostGLU	NR	NR	8.26	7.18
cw Premixed	Fritsche et al (2008, 52 wks)	Basal GLA + GLU	NR	98 ± 48.7	8.6	7.3
		Premixed Insulin[φ]	NR	91.3 ± 44.3	8.5	7.7

[1]Open Labelled Multicentre Randomised Parallel Group.
[2]MultiCentre, Open, Randomised, Parallel Group non inferiority trial.
[3]Open Labelled Multicentre, Multinational, Randomised Controlled (1:1:1) Parallel Group.
[4]Open Lablled Randomised Parallel Group (Korea and Japan only).
[φ]The type of pre-mixed insulin not specified [χ]Adjusted mean difference in HbA1c –0.5%, $P = 0.0001$.
[α]Mean Daily dose [β]GLU+OAD and GLU-only to OAD-only was shown by a difference in adjusted mean HbA1c change of –1.46% ($P < 0.0001$) and –0.64% ($P < 0.0001$), respectively.
[γ]Postmeal GLU compared with RHI.
[€]Premeal GLU compared with post meal GLU.

26 weeks. Glulisine was administered 0–15 minutes before breakfast and dinner, and RHI 30–45 minutes before breakfast and dinner. The primary efficacy variable was baseline to endpoint mean change in HbA1c. Self-monitored seven-point blood glucose measurements were also recorded.

In the first trial,[21] 876 patients with relatively well-controlled type 2 diabetes (mean baseline HbA1c of 7.55%) were randomized to glulisine/NPH ($n = 435$) or RHI/NPH ($n = 441$). More than 2 injections of the bolus insulin were permitted based on the clinical judgement of the investigator. Subjects were allowed to continue on pre-study oral hypoglycaemic agents (OHA) at the same dose (unless hypoglycaemia necessitated a change in dose). In the second trial,[20] subjects were randomized to glulisine/NPH ($n = 448$) or RHI/NPH ($n = 442$) and were allowed to continue stable doses of OHA.

At the end of the 26-week period, the baseline to endpoint change in HbA1c was greater in subjects receiving glulisine versus RHI in the first study (–0.46 vs. –0.30%, $P = 0.0029$)[21] and not significantly different in the second study. (–0.32 vs. –0.35%, $P = 0.5726$).[20] Hence, glulisine was either non-inferior[20] or superior in comparison to RHI[21] with regards to changes in HbA1c.

Post-breakfast blood glucose measurements were lower in the glulisine group compared with the RHI group (8.66 vs. 9.02 mmol/L; $P < 0.05$) as were the post-dinner values (8.54 vs. 9.05 mmol/L; $P < 0.05$).[21] In the second study,[20] the 2 hour post-breakfast blood glucose measurements were significantly lower with insulin glulsine compared with RHI (adjusted mean 8.85 vs. 9.47 mmol/L; $P < 0.001$), but similar at all other measured time points.

Glulisine versus Lispro

There are no published trials comparing glulisine with lispro in patients with type 2 DM.

Alternative regimens

A 52-week open-label, randomised clinical trial[18] compared glulisine and once-daily insulin glargine (n = 153) with twice daily injections of pre-mixed insulin (n = 157) in patients with type 2 diabetes with suboptimal glycemic control previously receiving a pre-mixed insulin regimen (see Table 9b).

Published in abstract form, this study demonstrated that a basal-bolus insulin regimen using glargine and glulisine resulted in a greater improvement in HbA1c compared with a regime of pre-mixed insulin. The adjusted mean difference in HbA1c between groups was –0.5% (P = 0.0001; 95% confidence interval –0.71% to –0.24%). The glargine-glulisine group had significantly lower mean daytime BGL (P = 0.0033) and post-prandial BGL ($P < 0.0001$) compared with the pre-mixed insulin group.[18]

A 16-week open-label, randomised, parallel group controlled trial[22] compared glulisine and OHA (n = 130), with glulisine alone (n = 127) and OHA alone (n = 130) in patients with type 2 diabetes with suboptimal glycemic control previously receiving OHA (sulfonylurea or sulfonylurea + biguanide).

All groups were noted to have a reduction in adjusted mean HbA1c at endpoint. There was a significant difference in adjusted mean change in HbA1c in the glulisine + OHA group as well as the glulisine monotherapy group compared with continuation of OHA alone (–1.46%, $P < 0.0001$ and –0.64%, $P < 0.0001$ respectively). Both glulisine groups had better 2-hour post-prandial BGL than the OHA-only group.[22]

A randomised open-label parallel-group study of 393 patients with suboptimally controlled type 2 DM on a glargine and OHA regimen demonstrated a significant improvement in HbA1c over a 24 week treatment period with a single-dose of glulisine either at breakfast or at main meal time. This improvement was equivalent and occurred regardless of whether administration occurred at breakfast (7.35% to 7.03%; $P < 0.0001$) or at the main meal time (7.29% to 6.94%; $P < 0.0001$).[19]

Safety

Hypoglycemia

Hypoglycemia is the most common adverse outcome associated with insulin treatment. Most studies demonstrated similar rates of hypoglycaemia with glulisine when compared with other rapid acting insulins in patients with type 1 or type 2 DM.[11,13,14,17,20,21]

As would be expected, hypoglycemia occurred more frequently with glulisine treatment than with OHA-only treatment.[22]

In the studies detailed below, symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from low BGLs.[13,14,17,21,20] Severe symptomatic hypoglycemia was defined as an episode requiring the assistance of another person[11,13,17,20,21,22] and was associated with a confirmed BGL < 1.9 mmol/L[13,22] or <2.0 mmol/L[11,13,20,21] or prompt recovery after administration of glucose or glucagon.[11,13,20,21,22] Nocturnal hypoglycemia was defined as an episode that occurred while the patient was asleep (between bedtime and prior to morning awakening).[13,17,20,21]

Adult patients with type 1 diabetes mellitus

In adult patients with type 1 diabetes, rates for hypoglycemia associated with glulisine were similar compared with lispro. In the 26 week study by Dreyer et al rates of symptomatic, severe and nocturnal hypoglycemia (number of events per patient month) in the glulisine and lispro groups were 3.64 vs. 3.48 (symptomatic), 0.03 vs. 0.02 (severe) and 0.55 vs. 0.53 (nocturnal); no P-values given.[17] In the Japanese study by Kawamori et al the mean monthly rate (events per patient-month) of all symptomatic hypoglycemia (glulisine 3.93 vs. lispro 3.86; P = 0.1642), severe symptomatic hypoglycemia (glulisine 0.02 vs. lispro, 0.02; P = 0.6583), and severe nocturnal symptomatic hypoglycemia (glulisine 0.00 vs. lispro, 0.01; P = 0.6637) events were similar for both treatment groups.[14]

Overall, no statistically significant differences were noted in the rate or incidence of patients reporting one or more episodes of all symptomatic or nocturnal hypoglycemia between immediately pre- and post-meal glulisine and RHI administered 30–45 minutes prior to meal. The incidence and rate of severe hypoglycemia were similar in the pre-meal glulisine (inci-

Table 10. Adapted from Sanofi-Aventis prescribing information.[52]

	Glulisine (n = 29)	Aspart (n = 30)	*P*-value
Pts with 1 or more catheter occlusion	13.8% (4/29)	26.7% (8/30)	NS
Infusion site reactions	10.3% (3/29)	13.3% (4/30)	NS
Catheter changes/month	14.1	14.8	NS
Mean time between catheter changes (days)	2.1 +/– 0.3	2.0 +/– 0.2	NS
Patients with ≥1 episode of unexplained hypoglycemia	20.7% (6/29)	40.0% (12/30)	NS

Abbreviation: NS, not significant.

dence: 24 patients [8.4%]; rate 0.05 ± 0.24 event per patient-month) and post-meal glulisine groups (incidence: 25 patients [8.4%]; rate 0.05 ± 0.23 event per patient-month). Severe hypoglycemia was insignificantly more frequent in the pre-meal RHI group (incidence: 28 patients [10.1%]; rate 0.13 ± 0.96 event per patient-month).[13]

In adult Type 1 patients receiving CSII the incidence of all symptomatic and nocturnal hypoglycemic events may have been more common in the glulisine group compared with patients receiving aspart but no P values were reported (all symptomatic: 89.7% vs. 80.0%; severe: 6.9% vs. 6.7%; nocturnal: 69.0% vs. 50.0%).[11]

Pediatric patients with type 1 diabetes mellitus

In pediatric patients with Type 1 diabetes, symptomatic and severe hypoglycemic monthly rates (events/patient-month) were similar in the glulisine group compared with the lispro group (Symptomatic: 3.10 vs. 2.91, P = NS; severe: 0.06 vs. 0.07, P = NS).[16]

Type 2 diabetes mellitus

More patients receiving treatment with glulisine reported at least one episode of symptomatic hypoglycemia compared with patients receiving OHA treatment only (64.6% glulisine + OHA group, 59.8% glulisine monotherapy group and 14.6% in the OHA-only group).[22]

Hypersensitivity and injection site reactions

In a 26 week study in 672 patients with Type 1 diabetes systemic hypersensitivity reactions occurred in six patients in the glulisine group (1.8%) vs. four patients in the lispro group (1.2%). The incidence of injection site reactions was low and similar between the groups (glulisine 3.2% vs. lispro 4.2%). In patients with type 2 diabetes, the incidence of systemic hypersensitivity and injection site reactions were similar with glulisine compared with the RHI (6.9% vs. 5.2% and 3.2% vs. 2.3%, respectively).[17]

Weight Gain

Adult patients with type 1 diabetes mellitus

There were no significant differences in body weight at baseline or endpoint in patients treated with glulisine compared with lispro[14,17] and aspart via CSII[11] in adult patients with type 1 diabetes. Post-meal glulisine had a clinically significant decrease in body weight of –0.3 kg in comparison with pre-meal RHI and glulisine (P = 0.03).[13] This may be attributable to patients being able to adjust insulin doses according to the meal consumed immediately prior to the insulin dose. The daily short-acting insulin dose was lower in the post-meal glulisine group compared with pre-meal RHI (P = 0.0012) but not with the pre-meal glulisine.[13]

Adult patients with type 2 diabetes mellitus

There was no significant difference in adjusted mean change in body weight with glulisine treatment compared with RHI treatment over 26 weeks in patients with type 2 diabetes (glulisine + 1.8 kg vs. RHI + 2.0 kg, P = 0.369).[21] Similar results were obtained in another study comparing post-meal glulisine with pre-meal glulisine (+5.77 kg weight gain in pre-meal glulisine group vs. +4.70 kg weight gain in post-meal glulisine group; P = 0.079).[23] Patients treated with glargine-glulisine showed significantly greater weight gain than patients treated with pre-mixed insulin (+3.6 vs.

+2.2 kg; $P = 0.0073$).[18] Similar weight increases were demonstrated over a 24-week treatment period with a single injection of glulisine regardless of whether the injection was administered at breakfast or at main meal time (+1.0 kg vs. +0.9 kg) in patients with type 2 DM on basal insulin glargine and OHA.[19] Patients with Type 2 diabetes who received glulisine treatment gained weight while patients who continued on OHA only did not over 16 weeks. Change in body weight from baseline to endpoint was +1.91 kg in the glulisine + OHA group; +1.39 kg in the glulisine monotherapy group and –0.47 kg in the OHA-only group; no *P*-values given.[22]

Treatment Emergent Adverse Events (TEAEs)

Adult patients with type 1 diabetes mellitus

Treatment with glulisine was not associated with a greater proportion of treatment adverse events compared with lispro or RHI in adult patients with type 1 DM. In the study by Dreyer et al[17] the proportional of patients who experienced TEAEs was comparable for both groups (64.6% in the glulisine group vs. 61.9% in the lispro group). A similar proportion of patients in each group experienced serious adverse events (16.2% in the glulisine group vs. 12.6% in the lispro group; no *P*-value given). Only one of the serious adverse events was considered possibly treatment-related (one patient in the glulisine group who had a glulisine overdose without hypoglycemia). In the study by Kawamori et al.[14] the incidence of TEAEs was similar in the two treatment groups, although slightly fewer patients in the lispro group experienced TEAEs possibly related to the study treatment (6.7% vs. 9.1%) or serious TEAEs (5.9% vs. 7.6%); no *P*-values given and details of adverse events not documented.

In a study comparing pre- and post-meal glulisine to RHI,[13] the number of patients reporting adverse events during the study was 174 (60.8%) in the pre-meal glulisine group 196 (66.2%) in the post-meal glulisine group and 174 (62.6%) in the RHI group. Serious adverse events were recorded by 29 patients (10.1%) in the pre-meal glulisine group 28 patients (9.5%) in the post-meal glulisine group and 35 patients (12.6%) in the RHI group demonstrating that the incidence of adverse events was similar between the groups.

Patients receiving glulisine via CSII did not suffer significantly more complications compared with patients receiving aspart in terms of catheter occlusions or the rate or frequency of catheter changes. Unexplained hypoglycemia occurred more frequently in the aspart group compared with the glulisine group (40% vs. 21%) but the difference was not significant. Injection site complications were similar between groups (see Table 8).[11]

Adult patients with type 2 diabetes mellitus

In type 2 DM, the number of patients reporting at least one TEAE was 58% in both the glulisine and RHI groups in the study by Rayman et al[20] and 82.3% in the glulisine group compared with 79.6% in the RHI group in the study by Dailey et al.[21] Serious TEAEs were reported in 9.6% of patients receiving glulisine compared with 11.8% receiving RHI,[20] and 12.6% of patients receiving glulisine compared with 11.6% in the RHI group[21] in the aforementioned studies respectively. Similar numbers of patients experienced TEAEs regardless of whether glulisine was administered at breakfast or main mealtime (44.4% vs. 46.7%).[19] Similar frequency of TEAEs were noted in patients receiving glulisine and OHA, glulisine monotherapy or OHA only. The proportion of patients with at least one TEAE was 61.5% in the glulisine + OHA group; 62.2% in the glulisine monotherapy group and 62.3% in the OHA-only group. However serious TEAEs were reported by more patients receiving combination therapy; 6.9% in the glulisine + OHA group 2.4% in the glulisine monotherapy group and 3.1% in the OHA-only group.[22]

From the above studies, it can be concluded that there is no evidence that glulisine is associated with more TEAEs than lispro, aspart or RHI.

Patient Preference

Glulisine is available as a pre-filled pen (Apidra Solostar™) as well as in vials. The pre-filled insulin pens allow for accurate dosing, are convenient and easy to use and therefore facilitate compliance.[53] However there are no published trials comparing the use of glulisine with other short-acting insulin analogues.

Place in Therapy

Insulin therapy is mandatory in the treatment of type I DM due to a state of absolute insulin deficiency,

generally in basal-bolus or continuous subcutaneous infusion regimens. These are intended to mimic the physiology of insulin secretion and have both been shown to be safe and effective in the establishment of glycemic control.

Type 2 DM is a disorder of relative insulin deficiency and insulin resistance where background and prandial insulin secretion continues to occur, but is insufficient to provide optimal glycemic control. OHAs are usually used first line to either reduce insulin resistance or to enhance endogenous insulin secretion. However, many patients also subsequently need exogenous insulin supplementation as the state of relative insulin deficency is progressive over time. Initially the usual requirement is to increase the background insulin levels (basal insulin) and later to increase mealtime increments (bolus insulin) to improve post-prandial glycemic control. A single dose of rapid-acting analogue can initially be added to cover the meal causing the greatest post-prandial excursion. Second and third doses may then be added for other meals.

Rapid acting insulins are available in pre-mixed preparations with longer-acting insulins, but a set ratio between the rapid and intermediate acting insulin can be problematic in attempting to mimic a physiological pattern of insulin secretion. A basal-plus regimen of insulin administration, utilising a rapid-acting analogue such as glulisine in addition to an intermediate or long acting insulin allows greater flexibility of insulin titration and provides a more physiological profile of insulin levels. At this stage, there does not appear to be sufficient data to compare the use of glulisine with other rapid-acting analogues in the treatment of diabetic ketoacidosis or hyperosmolar non-ketotic coma.

Conclusion

The newest rapid-acting insulin analogue, glulisine, owes its monomeric stability along with its rapid dissociation and absorption to the strategic substitution of the amino acid lysine for asparagine (position B3) and glutamic acid for lysine (position B29). It stands alongside the other rapid-acting insulin-analogue counterparts, lispro and aspart, as a safe and effective treatment of diabetes mellitus.

In comparison to RHI, glulisine displays a favourable pharmacodynamic and pharmacokinetic profile. Euglycemic-clamp studies in non-diabetic patients have demonstrated glulisine's quicker rate of absorption, greater early glucose disposal and shorter mean residence time as compared to RHI. Cross-over studies in type I diabetic patients comparing glulisine with RHI have also demonstrated shorter mean residence times and the achievement of significantly higher insulin concentrations in shorter periods of time in those on glulisine. In type 2 diabetic patients, glulisine displayed higher maximal insulin exposure rates and shorter times to 10% of maximal glucose infusion rates as compared to RHI. Furthermore, efficacy trials have demonstrated significantly greater reductions in HbA1c in both type I and type 2 diabetic patients.

In comparison to lispro, glulisine has a similar pharmacokinetic and pharmacodynamic profile. There is evidence from two separate euglycemic clamp studies (one involving healthy, non-diabetic subjects and another, patients with type I diabetes [published in abstract form only]) suggesting that glulisine has a shorter mean residence time, slightly faster absorption rate and therefore greater early glucose disposal rates as compared with lispro. The clinical significance of such findings is debatable with efficacy trials demonstrating similar reductions in post-prandial glucose and HbA1c in adult and pediatric type I diabetic patients. The safety profile of both is comparable with similar rates of hypersensitivity, hypoglycemia and weight gain.

There are limited data comparing glulisine and aspart. Furthermore, the utility of glulisine in the management of gestational diabetes, diabetic ketoacidosis and hyperosmolar non-ketotic state requires further elucidation with limited data published in these areas. Similarly, the administration of glulisine via CSII has not been studied in detail.

In conclusion, glulisine is a safe and effective rapid-acting insulin analogue. The available data from this extensive review of the literature suggests there are only minimal pharmacokinetic and pharmacodynamic differences between glulisine, lispro and aspart and there are no data to indicate that these are clinically relevant. The choice of which analogue to prescribe may well therefore be determined by subjective factors such as personal preference or the insulin delivery device (e.g. the SoloStar pen).

Abbreviations

GIR, Glucose infusion rate; GIR-AUC, Glucose infusion rate (area under curve); GIR-AUCss, Glucose infusion rate (area under curve) at steady state; INS-AUC, Insulin concentration (area under curve); MRT, Mean residence time; C_{max}, Maximal insulin concentration; T_{max}, time to reach C_{max}; BG_{max}, maximal blood glucose excursion; BG-AUC, Blood glucose area under curve; ΔBG_{max}, maximal blood glucose concentration minus baseline glucose concentration.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. King H, Aubert R, Herman W. Global Burden of Diabetes 1995–2025. *Diabetes Care*. 1998;21(9):1414–31.
2. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. *NEJM*. 2005;353(25):2643–53.
3. The Diabetes Control and Complications Trial Research Group The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *NEJM*. 1993;329(14):977–86.
4. Mauer M, Zinman B, Gardiner R, et al. Renal and Retinal Effects of Enalapril, *NEJM*. 2009;361(1):40–51.
5. Heart Protection Study Collaborative Group MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo controlled. *Lancet*. 2002;360(1):7–22.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–53.
7. UK Prospective Diabetes Study (UKPDS) Group Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ*. 1998;317:703–13.
8. Becker R, Frick A, Nosek L, Heinemann L, Rave K. Dose-Response Relationship of Insulin Glulisine in Subjects With Type 1 Diabetes. *Diabetes Care*. 2007;30(10):2506–7.
9. Danne T, Becker R, Heise T, Bitner C, Frick A, Rave K. Pharmacokinetics, prandial glucose control and safety of Insulin Glulisine in Children and Adolescents with Type 1 Diabetes. *Diabetes Care*. 2005;28(9):2100–5.
10. Burger F, Scholz H, Frick A, et al. Pharmacodynamics and pharmacokinetics of insulin glulisine versus insulin lispro and regular human insulin in patients with type 1 diabetes. *Diabetes*. 2004;53 Suppl 2:(abstract no 2350-PO)A557.
11. Hoogma R, Schumicki D. Safety of insulin glulisine when given by subcutaneous infusion using an external pump in patients with Type 1 Diabetes. *Hormone and Metabolic Research.*2006;38:429–33.
12. Senstius J, Poulsen C, Hvass A. Comparison of in vitro stability for insulin aspart and insulin glulisine during simulated use in insulin pumps. *Diabetes technology and therapeutics*. 2007;9(6):517–21.
13. Garg SK, Rosenstock J, Ways K. Optimized Basal-Bolus Insulin Regimens in Type 1 Diabetes: Insulin Glulisine versus regular human in combination with basal insulin glargine. *Endocrine Practice*. 2005;11(1):11–7.
14. Kawamori R, Kadowaki T, Ishii H, et al. Efficacy and Safety of Insulin Glulisine in Japanese patients with Type 1 Diabetes mellitus. *Diabetes Obesity and Metabolism*. 2009;11:891–9.
15. Garg SK, Ellis SL, Ulrich H. Insulin glulisine: a new rapid-acting insulin analogue for the treatment of diabetes. *Expert Opin Pharmacother.* 2005;6(4):643–51.
16. Philotheou A, Arslanian S, Blatniczky L, et al. Efficacy and Safety of insulin Glulisine versus Insulin Lispro as part of a basal-bolus insulin regimen in children and adolescents with Type 1 diabetes mellitus. *Diabetologia*. 2008;51,Suppl. 1:Abstract No. 950.
17. Dreyer M, Prager R, Robinson A, et al. Efficacy and Safety of Insulin Glulisine in Patients with Type 1 Diabetes. *Hormone and Metabolic Research.*2005;37:702–7.
18. Fritsche A, Larbig M, Bohler S, et al. Superior Efficacy of a basal-bolus regimen with insulins glargine and glulisine vs. a two-injection pre-mixed insulin regimen in Type 2 diabetes patients: results of the GINGER study. *Diabetologia*. 2008;Abst 186.
19. Lankisch MR, Ferlinz KC, Leahy JL, Scherbaum WA and group., Orals Plus Apidra and LANTUS (OPAL) study. Introducing a Simplified approach to insulin therapy in Type 2 Diabetes: A comparison of two single dose regimens of insulin glulisine plus glargine and oral antidiabric drugs. *Diabetes Obesity and Metabolism*. 2008;10:1178–85.
20. Rayman, G, Profozic V, Middle M. Insulin Glulisine imparts effective glycaemic control in Patients with Type 2 Diabetes. *Diabetes Research and Clinical Practice*. 2006;76(2):304–12.
21. Dailey G, Moses RG, Rosenstock J, et al. Insulin Glulisine Provides Improved Glycaemic Control in patients with type 2 Diabetes. *Diabetes Care*. 2004;27(10):2363–8.
22. Kawamori R, Iwamoto Y, Kadowaki T, et al. Effects of Glulisine as mono- or add-on therapy in patients with Type 2 Diabetes mellitus. *Diabetes Obesity and Metabolism*. 2009;11:900–9.
23. Wynne AG, Nakhle S, Brusco A, et al. Influence of preprandial and postprandial insulin glulisine on A1c and body weight in patients with type 2 diabetes mellitus receiving basal insulin therapy: a multicenter, randomized, parallel, open label study. *Diabetes*. 2008:57, Suppl. 1: A 722, pp. abstract No. 2664-PO.
24. Aventis Pharmaceuticals Inc. Apidra TM. Insulin glulisine (rDNA origin) injection. [Online]. http://www.acessdata.fda.gov/drugsatfda_docs/label/2008/021629s015lbll.pdf.
25. Apidra PI. [Online]. Available from http://products.sanofi-aventis.us/apidra/apidra.pdf.
26. Humalog PI. [Online]. http://pi.lilly.com/us/humalog-pen-pi.pdf
27. Novolog PI. [Online]. http://www.novolog.com/NovoLog_Prescribing_Info.pdf
28. Heise T, Heinemann L. Rapid and long-acting insulin analogues as an approach to improve insulin therapy: an evidence-based medicine assessment. *Curr Pharm Des.* 2001;7(14):1303–25.
29. Brems DN, Alter LA. Beckage MJ, et al. Altering the association properties of insulin by aminio acid replacement. *Protein Eng.* 1992;5(6):527–33.
30. Poulsen C, Langkjaer L, Worsoe C. Precipitation of insulin aspart and insulin glulisine products used for continuous subcutaneous insulin infusion. *Diabetes Technol Ther*. 2005;7(1):142–50, 2005.
31. Sluzky V, Tamada JA, Klibanoc AM, et al. Kinetics of insulin aggregation in aqueous solutions upon agitation in the presence of hydrophobic surfaces. *Proc Natl Acad Sci U S A.* 1991;88(21):9377–81.
32. Brange J. *Galenics of Insulin: The Physico-chemical and Pharmaceutical Aspects of Insulin and Insulin Preparations.* 1987. Berlin, Germany: Springer-Verlag.
33. Richards JP, Stickelmeyer MP, Flora DB, Chance RE, Frank BH, DeFelippis MR. Self association properties of monomeric insulin analogs under formulation conditions. *Pharm Res.* 1998;15:1434–41.
34. Zoete V, Meuwly M, Karplus MP. Study of the insulin dimerization: binding free energy calculation and per-residue free energy decomposition. *Proteins.* 2005;61:79–93.

35. Becker RH, Frick AD, Burger F, et al. A comparison of the steady state pharmacokinetics and pharmacodynamics of a novel rapid-acting insulin analog, insulin glulisine and regular human insulin in health volunteers using the euglycemic clamp technique. *Exp Clin Endocrinol Diabetes*. 2005;113(5):292–7.
36. Hennige AM Strack V, Metzinger E, et al. Effects of new insulin analogues HMR1964 (insulin glulisine) and HMR1423 on insulin receptors. *Diabetologia*. 2005;48:1891–7.
37. Frick A, Becker HA, Wessel D, et al. Pharmacokinetic and glucodynamic profiles of insulin glulisine following subcutaneous administration at various injection sites. *Diabetes*. 2003;53 Suppl 1 [Abstract 511-P], p. A119.
38. Apidra prescibing information. Bridgewater, NJ, USA, April 2007. Available from. [Online]. http://products.sanofi-aventis.us/apidra/apidra.html.
39. Duckworth WC, Bennett RG, Hamel FG. Insulin degradation: progress and potential. *Endocrine Reviews*. 1998;19(5):608–24.
40. Frick AD, Scholz H. Burger F, et al. Absorption of insulin glulisine when mixed with NPH insulin. *Diabetes*. 2004;Suppl 2 [abstract 1329-P], p. A321.
41. Frick AD, Burger F, Scholz H, et al. Time action profile of insulin glulisine (GLU) versus regular human insulin (RHI) and insulin lispro (IL) in obese patients. *Diabetes*. 2004;53 Suppl 2. [abstract 526-P].
42. Rave K, Nosek L, Heinemann L, et al. Insulin glulisine: pharmacokinetic (PK) and pharmacodynamic (PD) properties in comparison with insulin lispro and regular human insulin in Japanese and Caucasian volunteers. *Diabetes*. 2004;53 Suppl 2 [Abstract], p. A143.
43. Jaros M, Martinek V, Piechatzek R, et al. Pharmacokinetics of insulin glulisine in renally impaired patients without diabetes. *Diabetes*. 2004;53 Suppl 2. [abstract 1330-P], p. A321.
44. Becker RHA, Frick A, Wessels D. Pharmacodynamics and pharmacokinetics of a new, rapidly-acting insulin analog, insulin glulisine. *Diabetes*. 2003;52 Suppl 1[abstract no. 471-P].
45. Heise T, Nosek L, Spitzer H, et al. Insulin glulisine: as faster onset of action compared with insulin lispro. *Diabetes Obesity and Metabolism*. 2007;9(5):746–53.
46. Rave K, Klein O, Frick A, Becker RHA. Advantage of premeal-injected insulin glulisine compared with regular human insulin in subjects with type 1 diabetes. *Diabetes Care*. 2006;29(8).
47. Nosek L, Becker RHA, Frick AD, et al. Prandial blood glucose control with pre- and post-meal insulin glulisine versus regular human insulin. *Diabetes*. 2004;53 Suppl 2 [abstract no. 588-P]:A139–40.
48. Becker RHA, Frick AD, Kapitza CK, et al. Pharmacodynamics and pharmacokinetics of insulin glulisine compared with insulin lispro (IL) and regular human insulin (RHI) in patients with type 2 diabetes. *Diabetes*. 2004;53 Suppl 2.[abstract no 503-p]:A119.
49. Luzio S, Peter R, Dunseath GJ, et al. A comparison of preprandial insulin glulisine versus insulin lispro in people with type 2 diabetes over a 12 hour period. *Diabetes Res Clin Pract*. 2004;79(2):269–75.
50. Wernsting M, Atahi K and Larbig M. Effects of insulin glulisine on postpradial plasma glucose levels in subjects with type 2 diabetes after a standard meal in comparison to insulin lispro. *Diabetes*. 2008;57 Suppl 1 [abstract no. 200-OR] p6.
51. Bolli G, Luzio S, Porcellati, et al. Pharmacodynamic (PD) and pharmacokinetic (PK) effects of subcutaneous insulin glulisine (GLU) vs. insulin aspart (ASP) prior to a standard meal in obese subjects with type 2 diabetes (T2D). *ADA 69th Scientific Session*. 2009;Abstract 555-P.
52. Sanofi-Aventis Prescribing Information. [Online]. http://www.sanofi-aventis.us/live/us/en/layout.jsp?scat=8D52920D-5655–4CCB-A499-EE05C6172519.
53. Carter JN, Beilin J, Morton A, de Luice M. Usability, Participant Acceptance and Safety of a Pre-Filleds Insulin Injection Device in a 3-Month Observational Survey in Everyday Clinical Practice in Australia. *Journal of Diabetes Science and Technology*. 2009;3(6):1425–31
54. Rolla A. Pharmacokinetic and pharmacodynamic advantages of insulin analogues and premixed insulin analogues over human insulin: impact on efficacy and safety. *American journal of medicine*. 2008;121(6 Suppl 1): S1–19.
55. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analalogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database of systematic reviews. 2006. No. 2.
56. Robinson D, Wellington K. Insulin glulisine. *Drugs*. 2006;66(6):861–9.