

VII. Integrated Review of Safety

In clinical trials, *insulin glulisine* was well tolerated and had a safety profile similar to insulin lispro (Homolog) and regular insulin. The frequency and overall pattern of TEAEs in pooled Type 1, Type 2, and pooled Type 1 plus Type 2 subject populations were generally similar and without noteworthy differences between *insulin glulisine* and comparator short-acting insulin preparations. The risk of severe hypoglycemic episodes or their sequelae (including seizures, unconsciousness, or trauma-related events) was comparable for *insulin glulisine* and comparator short-acting insulin preparations in individual trials or in the pooled analysis of trials. There was no evidence to suggest increased immunogenic potential or a risk of systemic hypersensitivity with *insulin glulisine* compared with comparator short-acting insulin preparations based on the reporting of possible systemic hypersensitivity reactions or the formation of antibodies to insulin or *E. coli* constituents. Additionally, *insulin glulisine* demonstrated a comparable frequency of injection site reactions compared with short-acting insulin comparators. Therefore, comparing *insulin glulisine* with short-acting insulin preparations did not demonstrate a difference in the frequency of adverse events commonly associated with human insulin therapy.

The frequency and type of all and serious cardiac TEAEs were similar in *insulin glulisine* and comparator groups in an analysis of pooled subjects with Type 1 and Type 2 Diabetes over all Phase III trials.

There were no overall discrepancies between *insulin glulisine* and short-acting insulin comparators in deaths due to cardiac causes, or in acute ischemic events or ventricular arrhythmias. No serious cardiac TEAE was considered by the investigator to be related to trial medication or was due to hypoglycemia. In subjects with Type 1 Diabetes, cardiac TEAEs were more commonly observed in *insulin glulisine* than comparator subjects. Trial 3001 was a major contributor to this imbalance: in this trial, *insulin glulisine* subjects had more cardiac risk factors than comparator subjects, including a higher incidence of ongoing hypertension, a higher use of cardiac medications at randomization, and a longer duration of diabetes than insulin lispro (Homolog) subjects. All subjects with Type 1 Diabetes who reported a serious ischemia-related cardiac TEAE had cardiac symptoms that predated entry into the trial or long-standing coronary artery disease demonstrated by cardiac catheterization during the trial. Therefore, in the overall pooled analysis of all Phase III trials, *insulin glulisine* demonstrated a similar cardiac safety profile to other short-acting insulin preparations.

Numbers of subjects exposed to study treatment

The numbers of subjects exposed to trial treatments are summarized below.

Table 2 – Numbers of adult subjects who received one or more doses of study treatment (Phase III studies)

	No. studies	No. subjects treated		
		Total	Glulisine	Comparators
Subjects with type 1 diabetes	3 (+ 1 extension)	1591	950	641
Study 3001/3011	-	672	339	333
(Study 3011) ^a		(589)	(302)	(287)
Study 3004	-	860	582	278
Study 3006	-	59	29	30
Subjects with type 2 diabetes	2 (+ 1 extension)	1766	883	883
Study 3002/3012	-	876	435	441
(Study 3012) ^a		(709)	(357)	(352)
Study 3005	-	890	448	442
Total exposed Phase III	5 (+ 2 extensions)	3357	1833	1524
Total exposed Phase I + III ^b	18 (+ 2 extensions)	3585	2045	1717

^a Subjects enrolled in the 3011 or 3012 extension study were previously treated in Study 3001 or 3002, respectively, and are therefore not counted in the sums of subjects treated.

^b Includes 228 adult subjects (212 who received glulisine and 193 who received one or more comparator) treated in 13 clinical pharmacology studies. Subjects who participated in more than one clinical pharmacology study of glulisine or who received more than one comparator in these studies are included only once. For more details, see the Summary of Clinical Safety, Section 1.2.1.

Dosing and duration of exposure

An overview of the numbers of subjects by duration of treatment is provided below.

Table 3 – Duration of exposure to glulisine (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006)

Treatment duration:	No. subjects treated with glulisine			
	≥1 day	≥12 weeks	≥26 weeks	≥52 weeks
All adult subjects (Phase I + III) ^a	2045	1572	1054	436
All subjects (Phase III)	1833	1572	1054	436
Subjects with type 1 diabetes	950	728	318	209
Subjects with type 2 diabetes	883	844	736	227

^a Includes 212 adult glulisine subjects treated in one or more 13 clinical pharmacology studies. Subjects who participated in more than one study of glulisine are counted only once.

In this clinical program, 436 subjects received *insulin glulisine* treatment for at least 52 weeks (1 year). The predefined titration targets were standardized across trials and were based on clinical practices acceptable for use in multinational trials.

Adverse Events

Deaths

During the *insulin glulisine* program as a whole, 10 deaths (5 in *insulin glulisine* and 5 in regular insulin subjects) were reported. One death occurred in Type 1 Diabetes and 9 deaths were in subjects with Type 2 Diabetes. None of the deaths was considered by the investigator to be related to trial treatment. A tabulated summary of all subjects who died is provided here.

Table 18 – Subject listing of all deaths

Study	Investigator/ Subject	Age/ Sex	Last day on study med./ Day of death	Primary cause of death ^a (Adverse event preferred term)	Related to study treatment
Treatment: glulisine					
3002	0214/20 ^b	77/M	27/28	Digestive hemorrhage shock (myocardial infarction, shock hemorrhagic)	No
3011	1303/06 ^c	50/M	338/340	Asystole (diabetic ketoacidosis, cardiac arrest)	No
3012	0143/24 ^c	70/M	191/195	Subdural hematoma (brain herniation, subdural hematoma, respiratory arrest)	No
3005	0351/03 ^c	87/M	84/85	Hemorrhagic intracerebral/ intraventricular accident (cerebral hemorrhage)	No
3005	0955/10	42/F	35/36	Bleeding of esophageal varices (esophageal varices hemorrhage)	No
Treatment: regular insulin					
3002	0308/07 ^b	59/F	55/56	Cardiac arrest (cardiac arrest)	No
3002	0309/02 ^b	67/M	43/44	Heart attack (cardiac arrest)	No
3012	0128/16 ^c	67/M	256/258	Massive pulmonary embolus (pulmonary embolism)	No
3012	0214/18	64/M	312/332	Gastric ulcer perforation (gastric ulcer perforation)	No
3005	2159/10 ^c	61/F	20/20	Aspiration (aspiration)	No

Subject age is on entry into the study.

^a Primary cause of death according to the investigator's assessment. The adverse event preferred terms shown are those with an outcome of death.

^b Previously reported in the original NDA submission, based on a final study database.

^c Previously reported in the original NDA submission, based on a preliminary study database or Pharmacovigilance reporting. Some information may have been updated in the current document.

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Common adverse events

In all trials, the investigator observed subjects for adverse events (local or systemic) and instructed subjects to report any events that occurred during the trial. All adverse events were recorded on the adverse event log page in the case report form (CRF). The period of observation for adverse events extended from the time a subject signed informed consent until the end of the specified observation period, which was one calendar day after the last injection of trial treatment. No alert terms for immediate reporting to the sponsor were specified in any trial.

Studies in Type 1 Diabetes

Over all trials in Type 1 Diabetes, 66.2% of *insulin glulisine* and 66.0% of pooled comparator subjects experienced 1 or more TEAE. In pooled trials in Type 1 Diabetes, the system organ classes most commonly affected by adverse events were infections and infestations, and nervous system disorders. Cardiac disorder adverse events occurred in 15 (1.6%) pooled *insulin glulisine* and 4 (0.6%) pooled comparator subjects.

Serious adverse events

In trials in Type 1 Diabetes, serious adverse events categorized as disabling were epilepsy NOS, vomiting NOS, and skin laceration (each in 1 *insulin glulisine* subject); there were none in comparator subjects. In trials in Type 2 Diabetes, serious adverse events categorized as disabling

were atrial fibrillation, suicide attempt, and upper limb fracture NOS (each in 1 *insulin glulisine* subject); hemoptysis and myocardial infarction (both in 1 regular insulin subject), and anaphylactic reaction, angina unstable, and depression (each in 1 regular insulin subject). Across all trials pooled, no individual non-hypoglycemia serious TEAE that was categorized as life threatening was reported in more than 1 subject in any treatment group.

Table 24 – Summary of all serious TEAEs by seriousness criterion (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006)

Seriousness criterion ^a	No. (%) subjects					
	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
Total no. ITT subjects	950 (100)	841 (100)	883 (100)	883 (100)	1833 (100)	1524 (100)
Total with serious TEAE	137 (14.4)	94 (14.7)	136 (15.4)	131 (14.8)	273 (14.9)	225 (14.8)
Death ^b	1 (0.1)	–	4 (0.5)	4 (0.5)	5 (0.3)	4 (0.3)
Life threatening	9 (0.9)	6 (0.9)	6 (0.7)	4 (0.5)	15 (0.8)	10 (0.7)
Hospitalization	40 (4.2)	28 (4.4)	105 (11.9)	101 (11.4)	145 (7.9)	129 (9.5)
Disabling	3 (0.3)	–	3 (0.3)	4 (0.5)	6 (0.3)	4 (0.3)
Congenital anomaly	–	–	–	–	–	–
All medically important:	111 (11.7)	74 (11.5)	50 (5.7)	41 (4.6)	161 (8.8)	115 (7.5)
Medically important—hypoglycemia	99 (10.4)	69 (10.8)	27 (3.1)	27 (3.1)	126 (6.9)	95 (6.3)
Medically important non-hypoglycemia-related	16 (1.7)	7 (1.1)	23 (2.6)	14 (1.5)	39 (2.1)	21 (1.4)

^a In this document, all severe symptomatic hypoglycemic episodes were programmatically assigned by the sponsor to the seriousness criterion of medically important. The investigator may have included these events under another category of seriousness. Such events may be shown more than once in the above table, but are counted once only in the total number of subjects with serious TEAEs.

^b One additional death in a regular insulin subject was associated with a non-treatment-emergent adverse event and is not included in this table (Section 2.1.3).

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3006 (comparator aspart); Type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).
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Other serious adverse events

The incidence of hypoglycemia serious TEAEs was balanced between treatments in pooled trials in Type 1 or Type 2 Diabetes. In subjects with Type 1 Diabetes, serious TEAEs were reported in 137 (14.4%) *insulin glulisine* subjects and 94 (14.7%) pooled comparator subjects. Irrespective of treatment, the most commonly reported serious TEAEs in subjects with Type 1 Diabetes were associated with hypoglycemia (in 10.4% of *insulin glulisine* and 10.8% of pooled comparator subjects). In subjects with Type 2 Diabetes, serious TEAEs were reported in 136 (15.4%) *insulin glulisine* subjects and 131 (14.8%) pooled comparator subjects. Unlike trials in Type 1 Diabetes, the most commonly reported serious TEAEs in subjects with Type 2 Diabetes were not related to hypoglycemia, and the reporting of serious non-hypoglycemia TEAEs was similar in *insulin glulisine* and comparator subjects (12.8% of *insulin glulisine* and 12.1% of regular insulin subjects). In pooled trials in Type 2 Diabetes, serious hypoglycemia occurred in 3.1% of subjects in each treatment group.

Table 19 – Overview of serious hypoglycemia and serious non-hypoglycemia TEAEs (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006)

Type of event	No. (%) subjects					
	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
Total no. ITT subjects	950 (100)	641 (100)	883 (100)	883 (100)	1833 (100)	1524 (100)
All serious TEAEs	137 (14.4)	94 (14.7)	136 (15.4)	131 (14.8)	273 (14.9)	225 (14.8)
Hypoglycemia reported as a serious TEAE ^a	99 (10.4)	69 (10.8)	27 (3.1)	27 (3.1)	126 (6.9)	96 (6.3)
Serious non-hypoglycemia TEAEs ^b	45 (4.7)	29 (4.5)	113 (12.8)	107 (12.1)	158 (8.6)	136 (8.9)
Possibly related serious non-hypoglycemia TEAEs	3 (0.3)	-	-	-	3 (0.2)	-

^a All hypoglycemic episodes were considered possibly related to study insulin preparations.

^b For serious non-hypoglycemia TEAEs, the frequencies are arithmetically higher for glulisine compared with comparator subjects in type 1 studies pooled or type 2 studies pooled. However, in the overall type 1 plus type 2 population (All studies), the percent is lower in the glulisine versus comparator group (8.6% versus 8.9%). This is because most serious non-hypoglycemia TEAEs in the All studies grouping were derived from type 2 subjects, whereas the denominator in the pooled glulisine group includes notably more type 1 subjects than the denominator in the pooled comparator group.

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3006 (comparator aspart); Type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).

In pooled trials in Type 1 Diabetes and Type 2 Diabetes, the system organ classes most commonly affected by serious non-hypoglycemia TEAEs in *insulin glulisine* subjects were cardiac disorders and infections and infestations. In the overall population of Type 1 plus Type 2 trials pooled, the system organ class most commonly affected by serious non-hypoglycemia TEAEs in both treatment groups was cardiac disorders (in 2.1% of pooled *insulin glulisine* and 2.4% of pooled comparator subjects), and the most common serious nonhypoglycemia preferred term was myocardial infarction (in 0.5% of pooled *insulin glulisine* and 0.4% of pooled comparator subjects). Most cardiac disorder serious TEAEs occurred in subjects with Type 2 Diabetes.

Cardiac Adverse Events

The incidence of cardiac disorder TEAEs in the pooled analysis of trials in Type 1 plus Type 2 Diabetes was comparable between treatments (2.7% of *insulin glulisine* and 3.0% of pooled comparator subjects); There were no differences between *insulin glulisine* and short-acting insulin comparators in the incidence of deaths due to cardiac causes, acute ischemic events, ventricular arrhythmias, or any specific type of cardiac TEAE. No cardiac TEAE was associated with or ascribed to a severe hypoglycemic episode; No serious cardiac TEAE was considered by the investigator to be related to trial treatment. In subjects with Type 2 Diabetes, the incidence of cardiac TEAEs was comparable between treatments (5.5% of *insulin glulisine* and 6.6% of regular insulin subjects). In the pooled analysis of all Phase III trials in Type 1 Diabetes, the incidence of cardiac disorder TEAEs was greater in *insulin glulisine* than comparator subjects (1.5% of *insulin glulisine* and 0.5% of pooled comparator subjects). The greatest contributor to this imbalance was Trial 3001, in which 2.7% of *insulin glulisine* and 0.3% of comparator subjects reported cardiac TEAEs: In Trial 3001, risk factors for cardiac disease at trial entry differed between treatments: *insulin glulisine* subjects had durations of diabetes and insulin treatment that were approximately 2 years longer than in insulin lispro (Homolog) subjects. At

trial entry, ongoing hypertension was reported in 20.6% of *insulin glulisine* and 16.8% of insulin lispro (Homolog) subjects. At randomization, 32.7% of *insulin glulisine* subjects and 23.1% of insulin lispro (Homolog) subjects were receiving cardiac medications; In subjects with Type 1 Diabetes, all subjects reporting a serious cardiac TEAE related to coronary artery disease had known pre-existing coronary disease or symptoms at baseline or cardiac catheterization findings during the trial indicating long-standing atherosclerotic coronary artery disease.

In trials in Type 2 Diabetes and pooled trials in Type 1 plus Type 2 Diabetes, there were no noteworthy differences between treatments in the incidence of serious TEAEs by system organ class or by individual preferred term. Because of the reported imbalance in Trial 3001, trials in Type 1 Diabetes overall, 8 (0.8%) *insulin glulisine* and 1 (0.2%) comparator subjects reported a cardiac disorder serious TEAE.

Table 20 – Summary of all serious TEAEs in ≥0.5% of subjects in any pooled treatment group (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006)

System organ class/ Preferred term	No. (%) subjects					
	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
Total no. ITT subjects	950 (100)	641 (100)	883 (100)	883 (100)	1833 (100)	1524 (100)
Total with serious TEAEs	137 (14.4)	94 (14.7)	136 (15.4)	131 (14.8)	273 (14.9)	225 (14.8)
Cardiac disorders	8 (0.8)	1 (0.2)	30 (3.4)	36 (4.1)	38 (2.1)	37 (2.4)
Myocardial infarction	1 (0.1)	–	8 (0.9)	6 (0.7)	9 (0.5)	6 (0.4)
Coronary artery disease NOS	3 (0.3)	–	5 (0.6)	4 (0.5)	8 (0.4)	4 (0.3)
Angina pectoris	1 (0.1)	–	5 (0.6)	7 (0.8)	6 (0.3)	7 (0.5)
Angina unstable	–	–	3 (0.3)	6 (0.7)	3 (0.2)	6 (0.4)
Atrial fibrillation	–	–	1 (0.1)	4 (0.5)	1 (0.1)	4 (0.3)
General disorders and administration site conditions	1 (0.1)	2 (0.3)	7 (0.8)	3 (0.3)	8 (0.4)	5 (0.3)
Chest pain	1 (0.1)	1 (0.2)	5 (0.6)	1 (0.1)	6 (0.3)	2 (0.1)
Infections and infestations	8 (0.8)	4 (0.6)	23 (2.6)	16 (1.8)	31 (1.7)	20 (1.3)
Cellulitis	1 (0.1)	–	5 (0.6)	2 (0.2)	6 (0.3)	2 (0.1)
Pneumonia NOS	–	1 (0.2)	5 (0.6)	4 (0.5)	5 (0.3)	5 (0.3)
Urinary tract infection NOS	–	1 (0.2)	4 (0.5)	–	4 (0.2)	1 (0.1)
Metabolism and nutrition disorders	81 (8.5)	56 (8.7)	24 (2.7)	19 (2.2)	105 (5.7)	75 (4.9)
Hypoglycemia NOS	64 (6.7)	43 (6.7)	18 (2.0)	14 (1.6)	82 (4.5)	57 (3.7)
Hypoglycemic seizure	15 (1.6)	13 (2.0)	1 (0.1)	3 (0.3)	18 (0.9)	16 (1.0)
Diabetic ketoacidosis	5 (0.5)	2 (0.3)	–	1 (0.1)	5 (0.3)	3 (0.2)
Nervous system disorders	41 (4.3)	24 (3.7)	16 (1.8)	17 (1.9)	57 (3.1)	41 (2.7)
Hypoglycemic coma/unconsciousness	40 (4.2)	21 (3.3)	9 (1.0)	11 (1.2)	49 (2.7)	32 (2.1)

Table includes preferred terms in ≥0.5% of subjects in any pooled treatment group (type 1 diabetes, type 2 diabetes, or all studies). Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3006 (comparator aspart); Type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin). 11ae207t 12ae007t p3ac007t

Possibly related serious adverse events

During the *insulin glulisine* program as a whole, serious non-hypoglycemia TEAEs considered by the investigator to be possibly related to trial treatment were reported in 3 *insulin glulisine* and no comparator subjects. All of these events were in subjects with Type 1 Diabetes: one limb abscess (Trial 3004) and two overdose NOS (Trial 3001; Trial 3011).

Hypoglycemia reported as a serious adverse event

In spite of the baseline imbalance between treatments in the duration of diabetes and the duration of insulin therapy in Trial 3001*, overall trials in Type 1 Diabetes showed that serious hypoglycemia was reported in 99 (10.4%) *insulin glulisine* and 69 (10.8%) pooled comparator subjects. * The *insulin glulisine* group having an approximately 2-year longer duration of diabetes and duration of insulin therapy. Duration of diabetes is known to be a risk factor for severe hypoglycemia, and the baseline imbalance may have influenced the reporting of severe symptomatic hypoglycemic episodes.

In pooled trials in Type 2 Diabetes, serious hypoglycemia was reported in 27 (3.1%) subjects in each treatment group. This again was in spite of the baseline imbalance between treatments in the duration of diabetes, the duration of insulin therapy, and the duration of OHA use in Trial 3002 favoring the comparator arm. , there was an, with the *insulin glulisine* group having longer durations in all of these measures. These baseline imbalances may have influenced the reporting of severe symptomatic hypoglycemic episodes. The monthly rate of severe symptomatic hypoglycemia over the entire treatment phase of each trial is tabulated here.

Table 21 – Rate of severe symptomatic hypoglycemia per patient month over the entire treatment phase (Studies 3001, 3001/3011, 3002, 3002/3012, 3004, 3005, and 3006 by study) (ITT population)

Study	Premeal glulisine			Postmeal glulisine			Comparator		
	N	No. episodes	Mean rate (SD)	N	No. episodes	Mean rate (SD)	N	No. episodes	Mean rate (SD)
Type 1 diabetes									
3001/3011	339	90	0.0277 (0.1145)	–	–	–	333	65	0.0193 (0.0973)
3004	296	37	0.0474 (0.2378)	296	39	0.0543 (0.2299)	278	39	0.1254 (0.5682)
3006	29	2	0.0248 (0.0929)	–	–	–	30	2	0.0235 (0.0893)
Type 2 diabetes									
3002/3012	436	31	0.0080 (0.0449)	–	–	–	441	13	0.0177 (0.2813)
3005	448	9	0.0041 (0.0434)	–	–	–	442	16	0.0058 (0.0341)

Note: N = number of subjects evaluable.

The rate was calculated as (365.25/12 x number of hypoglycemia episodes)/(number of days exposed in the time window).

Data for Studies 3001, 3004, 3006, and 3002 were previously presented in the Summary of Clinical Efficacy of the 3006 study report (Section 8.7.1, 3011 CSR, Table T - 73, 3011 CSR, Table T - 82, 3012 CSR, Table T - 80, 3012 CSR, Table T - 89, 3005, Table T - 103, 3005, Table T - 107).

Hypoglycemia unawareness

A loss of awareness of hypoglycemia may result in more hypoglycemic episodes. Across all trials, 2 (0.1%) *insulin glulisine* and 10 (0.7%) pooled comparator subjects reported a TEAE of hypoglycemic unawareness. Hypoglycemic unawareness was considered to be possibly related with trial treatment in 1 (0.1%) *insulin glulisine* and 6 (0.4%) pooled comparator subjects. All occurrences of hypoglycemic unawareness were in subjects with Type 1 Diabetes.

Sequelae of serious hypoglycemia

The overall reporting of serious TEAEs of hypoglycemia was similar in each treatment group. Moreover, similar percents of subjects in each treatment group reported acute complications of hypoglycemia such as unconsciousness, seizure, or trauma. The most common preferred term for serious TEAEs of hypoglycemia in subjects with Type 1 Diabetes was hypoglycemia NOS (in 64

[6.7%] *insulin glulisine* and 43 [6.7%] pooled comparator subjects). Hypoglycemic coma-unconsciousness was reported in 40 (4.2%) *insulin glulisine* and 21 (3.3%) pooled comparator subjects. The most common preferred term for hypoglycemia in subjects with Type 2 Diabetes was also hypoglycemia NOS (in 18 [2.0%] *insulin glulisine* and 14 [1.6%] comparator subjects).

**Table 22 – Summary of hypoglycemia reported as a serious TEAE
(Studies 3001/3011, 3002/3012, 3004, 3005, and 3006)**

Category/ Preferred term name	No. (%) subjects					
	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
Total no. ITT subjects	950 (100)	641 (100)	883 (100)	883 (100)	1833 (100)	1524 (100)
Total with hypoglycemia reported as a serious TEAE	99 (10.4)	69 (10.8)	27 (3.1)	27 (3.1)	126 (6.9)	96 (6.3)
Hypoglycemia NOS ^a	64 (6.7)	43 (6.7)	18 (2.0)	14 (1.6)	82 (4.5)	57 (3.7)
Hypoglycemic coma/unconsciousness	40 (4.2)	21 (3.3)	9 (1.0)	11 (1.2)	49 (2.7)	32 (2.1)
Hypoglycemic seizure	15 (1.6)	13 (2.0)	1 (0.1)	3 (0.3)	16 (0.9)	16 (1.0)
Hypoglycemia assessed by investigator under seriousness criterion other than medically important ^b	13 (1.4)	11 (1.7)	1 (0.1)	5 (0.6)	14 (0.8)	16 (1.0)

^a Excludes 1 premeal glulisine subject in Study 3004 (Subject 4126/20) who reported 2 TEAEs of hypoglycemia NOS that were not categorized as serious TEAEs. These events followed an overdose of study medication and were described in detail in Section 5.5 of the Summary of Clinical Safety in the original NDA submission.

^b In this document, all severe symptomatic hypoglycemic episodes were programmatically assigned by the sponsor to the seriousness criterion of *medically important*. The investigator may have included such an event under another category of seriousness.

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3005 (comparator aspart); type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).

TEAEs in columns are not additive because an episode of hypoglycemia may have been reported in more than 1 category.

Only 6 *insulin glulisine* and 11 comparator subjects with serious hypoglycemia required hospitalization. In the majority of subjects reporting hypoglycemia NOS, no change was made to the trial medication. Only 3 occurrences of hypoglycemia resulted in discontinuation from the trial: 2 regular insulin subjects discontinued for a TEAE of hypoglycemia NOS, and 1 *insulin glulisine* and 1 regular insulin subject discontinued for a TEAE of hypoglycemic seizure. No serious TEAEs of hypoglycemia were categorized as permanently or significantly disabling.

Rate of severe nocturnal symptomatic hypoglycemia

The rate of severe nocturnal symptomatic hypoglycemia over the entire treatment phase of each trial was low and was as follows:

Table 23 – Rate of severe nocturnal symptomatic hypoglycemia per patient month over the entire treatment phase (Studies 3001, 3011, 3002, 3012, 3004, 3005, 3006 by study) (ITT population)

Study	Premeal glulisine			Postmeal glulisine			Comparator		
	N	No. episodes	Mean rate (SD)	N	No. episodes	Mean rate (SD)	N	No. episodes	Mean rate (SD)
Type 1 diabetes									
3001/3011	339	36	0.0106 (0.0435)	-	-	-	333	23	0.0067 (0.0366)
3004	286	22	0.0271 (0.1082)	296	27	0.0330 (0.1585)	278	15	0.0192 (0.0913)
3006	29	2	0.0248 (0.0929)	-	-	-	30	0	0.0000 (0.0000)
Type 2 diabetes									
3002/3012	435	13	0.0032 (0.0247)	-	-	-	441	7	0.0163 (0.2911)
3005	448	3	0.0017 (0.0228)	-	-	-	442	6	0.0022 (0.0221)

Note: N = number of subjects evaluable.

The rate was calculated as (365.25/12 x number of hypoglycemia episodes)/(number of days exposed in the time window).

Data for Studies 3001, 3004, 3006, and 3002 were previously presented in the Summary of Clinical Efficacy of the 3006 study report/Section 8.7.1. 3011 CSR, Table T - 70, 3011 CSR, Table T - 84, 3012 CSR, Table T - 80, 3012 CSR, Table T - 91, 3005, Table T - 103, 3005, Table T - 111.

Trauma-related Adverse events and serious hypoglycemia

Over all Phase III trials, there were 5 reports of trauma-related TEAEs in conjunction with a serious hypoglycemic episode (in 3 *insulin glulisine* subjects and 2 insulin lispro (Homolog) subjects). One subject on postmeal *insulin glulisine*-Trial 3004 reported a mild laceration concomitantly with hypoglycemic coma/unconsciousness. The 2nd subject on *insulin glulisine*-Trial 3001/3011 reported a moderate traumatic hematoma concomitantly with hypoglycemic coma/unconsciousness. The third subject in *insulin glulisine* arm-Trial 3002/3012 reported a severe fall resulting in mild bruising of the hand concomitantly with hypoglycemia NOS. One subject on insulin lispro-Trial 3001/3011 reported a moderate fall resulting in a moderate wrist sprain concomitantly with hypoglycemia NOS, and a moderate fractured rib and mild shoulder fracture concomitantly with hypoglycemic seizure. The 2nd subject on insulin lispro-Trial 3001/3011 reported a moderate head injury concomitantly with hypoglycemic coma-unconsciousness.

Potential systemic hypersensitivity reactions

Across all trials, 79 (4.3%) *Insulin glulisine* and 58 (3.8%) comparator subjects experienced potential systemic hypersensitivity reaction TEAEs. The most common potential systemic hypersensitivity reaction TEAE in *Insulin glulisine* subjects with Type 1 Diabetes was pruritus. The most common potential systemic hypersensitivity reaction TEAE in trials in Type 2 Diabetes and over all trials was dyspnea NOS. There were no noteworthy differences between treatments.

Table 29 – Summary of all TEAEs meeting the criteria for potential systemic hypersensitivity reactions (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006)

Preferred term name	No. (%) subjects					
	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
Total no. ITT subjects	950 (100)	641 (100)	883 (100)	883 (100)	1833 (100)	1524 (100)
Total with 1 or more potential systemic hypersensitivity reaction TEAEs	20 (2.1)	11 (1.7)	58 (6.7)	47 (5.3)	79 (4.3)	58 (3.8)
Dyspnea NOS	-	2 (0.3)	16 (1.8)	16 (1.8)	16 (0.9)	18 (1.2)
Pulse absent	1 (0.1)	-	8 (0.9)	2 (0.2)	9 (0.5)	2 (0.1)
Pruritus	4 (0.4)	-	4 (0.5)	4 (0.5)	8 (0.4)	4 (0.3)
Urticaria NOS	3 (0.3)	2 (0.3)	4 (0.5)	5 (0.6)	7 (0.4)	7 (0.5)
Chest tightness	2 (0.2)	-	5 (0.6)	2 (0.2)	7 (0.4)	2 (0.1)
Asthma aggravated	-	2 (0.3)	6 (0.7)	4 (0.5)	6 (0.3)	6 (0.4)
Asthma NOS	2 (0.2)	2 (0.3)	3 (0.3)	3 (0.3)	5 (0.3)	5 (0.3)
Hypersensitivity NOS	2 (0.2)	-	3 (0.3)	7 (0.8)	5 (0.3)	7 (0.5)
Hypotension NOS	2 (0.2)	-	2 (0.2)	1 (0.1)	4 (0.2)	1 (0.1)
Dermatitis allergic	1 (0.1)	1 (0.2)	2 (0.2)	-	3 (0.2)	1 (0.1)
Drug hypersensitivity	1 (0.1)	2 (0.3)	1 (0.1)	-	2 (0.1)	2 (0.1)
Rash pruritic	1 (0.1)	-	1 (0.1)	2 (0.2)	2 (0.1)	2 (0.1)
Bronchospasm NOS	-	-	2 (0.2)	1 (0.1)	2 (0.1)	1 (0.1)
Obstructive airways disorder NOS	-	-	2 (0.2)	1 (0.1)	2 (0.1)	1 (0.1)
Angioneurotic edema	-	-	2 (0.2)	-	2 (0.1)	-
Eyelid edema	1 (0.1)	-	-	-	1 (0.1)	-
Laryngeal edema	-	-	1 (0.1)	-	1 (0.1)	-
Periorbital edema	-	-	1 (0.1)	-	1 (0.1)	-
Shock	-	-	1 (0.1)	-	1 (0.1)	-
Anaphylactic reaction	-	-	-	1 (0.1)	-	1 (0.1)

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator ispre); Study 3004 (comparator regular insulin); Study 3005 (comparator aspart); Type 2 diabetes: Study 3002/3012 (comparator regular insulin); Study 3005 (comparator regular insulin).
11ae213t, 12ae013t, p3ae013t

Two *insulin glulisine* subjects in Trial 3002 reported angioneurotic edema which was not considered by the investigator to be related to trial treatment, and the events resolved while the subjects remained on *insulin glulisine*. Both of these subjects were receiving an angiotensin-converting enzyme (ACE) inhibitor, which may explain the event.

Three *insulin glulisine* subjects reported localized edema according to the investigator's term (one case of periorbital edema in Trial 3002; one case of swelling left lower eyelid in Trial 3004; and one case of left vocal cord swelling in Trial 3005). Two of these events were mild in intensity and one was moderate in intensity, none were not associated with a change in trial medication, and there were no reported sequelae or countermeasures.

Six *insulin glulisine* experienced potential systemic hypersensitivity reaction TEAEs: urticaria (Trial 3001), chest tightness with body aches (Trial 3004), and urticaria (Trial 3002), dyspnea NOS (Trial 3005), allergic dermatitis (Trial 3005), and pruritus with upper respiratory tract infection NOS (Trial 3005). On the other hand, two comparator (regular insulin) subjects experienced similar systemic hypersensitivity reaction TEAEs: dyspnea NOS (breathlessness) (Trial 3005) and urticaria NOS on the abdominal skin (Trial 3005). All of these TEAEs were mild or moderate in intensity and resolved without sequelae. Only one *insulin glulisine* subject with allergic dermatitis discontinued from Trial 3005 due to this TEAE.

There was only one occurrence of dyspnea NOS in Subjects in the upper 95% quintile of increase in crossreactive insulin antibodies in Trials 3001/3011 and 3002/3012. There were no noteworthy differences between treatments in the reporting of potential systemic hypersensitivity

reactions for subjects with the largest increase from baseline to endpoint in crossreactive insulin antibody levels, and no indication that these occurrences increased with long-term *insulin glulisine* treatment.

Injection site reactions

In trials in Type 1 Diabetes, 40 (4.2%) *insulin glulisine* and 32 (5.0%) comparator subjects experienced injection site abnormality TEAEs. In trials in Type 2 Diabetes, 23 (2.6%) subjects in each treatment group experienced injection site abnormality TEAEs. None of these TEAEs were clinically noteworthy in nature, most were mild in intensity, and none resulted in discontinuation of trial treatment. There were no noteworthy differences between treatments in the incidence of any individual preferred term. The overall incidence of injection site abnormality TEAEs is tabulated here.

Table 31 – Summary of all TEAEs meeting the criteria for injection site abnormalities (Studies 3001/3011, 3002/3012, 3004, 3005, and 3008)

Preferred term name	No. (%) subjects					
	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
Total no. ITT subjects	952 (100)	641 (100)	883 (100)	883 (100)	1833 (100)	1524 (100)
Total with 1 or more injection site reaction TEAEs	43 (4.2)	32 (5.0)	23 (2.6)	23 (2.6)	53 (3.4)	55 (3.6)
Injection site bruising	8 (0.8)	8 (1.2)	10 (1.1)	12 (1.4)	18 (1.0)	20 (1.3)
Injection site hypertrophy	7 (0.7)	10 (1.6)	3 (0.3)	1 (0.1)	10 (0.5)	11 (0.7)
Injection site reaction NCS	5 (0.5)	1 (0.2)	3 (0.3)	–	8 (0.4)	1 (0.1)
Injection site pain	3 (0.3)	3 (0.5)	2 (0.2)	1 (0.1)	5 (0.3)	4 (0.3)
Injection site burning	5 (0.5)	1 (0.2)	–	2 (0.2)	5 (0.3)	3 (0.2)
Injection site hemorrhage	2 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	3 (0.2)	2 (0.1)
Injection site stinging	1 (0.1)	1 (0.2)	2 (0.2)	–	3 (0.2)	1 (0.1)
Injection site mass	1 (0.1)	–	1 (0.1)	2 (0.2)	2 (0.1)	2 (0.1)
Injection site induration	1 (0.1)	–	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)
Injection site tenderness	1 (0.1)	–	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)
Injection site atrophy	1 (0.1)	5 (0.8)	–	–	1 (0.1)	5 (0.3)
Injection site inflammation	1 (0.1)	1 (0.2)	–	1 (0.1)	1 (0.1)	2 (0.1)
Injection site pruritus	1 (0.1)	–	–	1 (0.1)	1 (0.1)	1 (0.1)
Injection site erythema	1 (0.1)	1 (0.2)	–	–	1 (0.1)	1 (0.1)
Injection site pigmentation changes	1 (0.1)	–	–	–	1 (0.1)	–
Injection site rash	1 (0.1)	–	–	–	1 (0.1)	–
Injection site swelling	–	–	1 (0.1)	–	1 (0.1)	–
Injection site discomfort	1 (0.1)	–	–	–	1 (0.1)	–
Injection site nodule	1 (0.1)	–	–	–	1 (0.1)	–
Injection site abscess	–	1 (0.2)	–	–	–	1 (0.1)
Injection site sclerosis	–	–	–	1 (0.1)	–	1 (0.1)
Injection site infection	–	1 (0.2)	–	–	–	1 (0.1)

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator ispro), Study 3004 (comparator regular insulin), Study 3005 (comparator espart); type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).
11ae235f, 12ae035f, p3ae035f

A total of 31 (1.7%) *insulin glulisine* and 20 (1.3%) comparator subjects experienced injection site abnormality TEAEs considered by the investigator to be possibly related to trial treatment. The most common possibly related injection site abnormality TEAE was injection site hypertrophy, which occurred in 9 (0.5%) of all *insulin glulisine* and 7 (0.5%) of all comparator subjects.

Diabetic ketoacidosis

In trials in Type 1 Diabetes, 5 (0.5%) *insulin glulisine* and 3 (0.5%) comparator subjects experienced ketoacidosis TEAEs. In trials in Type 2 Diabetes, only 1 regular insulin subject reported a TEAE of ketoacidosis. There were no noteworthy differences between treatments. The incidence of ketoacidosis TEAEs is summarized in the next table.

Table 32 – Summary of all TEAEs meeting the criteria for ketoacidosis
(Studies 3001/3011, 3002/3012, 3004, 3005, and 3006)

Preferred term name	No. (%) subjects					
	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
Total no. ITT subjects	950 (100)	641 (100)	883 (100)	893 (100)	1833 (100)	1524 (100)
Total with 1 or more ketoacidosis TEAEs	5 (0.5)	3 (0.5)	-	1 (0.1)	5 (0.3)	4 (0.3)
Diabetic ketoacidosis	5 (0.5)	2 (0.3)	-	1 (0.1)	5 (0.3)	3 (0.2)
Ketoacidosis	1 (0.1)	-	-	-	1 (0.1)	-
Ketosis	-	1 (0.2)	-	-	-	1 (0.1)

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3005 (comparator aspart); Type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).
11ae236t 12ae036t p.3ae036t

TEAEs meeting the criteria for diabetic ketoacidosis were categorized as serious TEAEs, but none was considered by the investigator to be related to trial treatment.

Antibodies to insulin and insulin analogs

Four types of antibodies were determined at a centralized laboratory using radiolabeled insulin binding assay methodology: crossreactive to human insulin and insulin analog (all subjects), *insulin glulisine*-specific (in *insulin glulisine* treated subjects), insulin lispro-specific (in insulin lispro-treated subjects), and human insulin-specific (in insulin lispro- and *insulin glulisine*-treated subjects) antibodies. In Trials 3001/3011 and 3002/3012, insulin antibody evaluations were performed using serum obtained at the baseline of Trials 3001 and 3002, at weeks 12, 26, 36, 52, and/or at the subject's last evaluation (endpoint). All subjects treated in these trials were to be included in the evaluations. Insulin antibody evaluations were not performed in any other Phase III trial. All tests were carried out at a single central laboratory. Antibody values were calculated by subtracting B/T in the presence of an excess of unlabeled insulin from B/T in the absence of added unlabeled insulin. In line with published literature, the sponsor reported 4 to 5 times higher crossreactive antibody levels in Type 1 Diabetes subjects compared with Type 2 Diabetes.

Changes in crossreactive insulin antibodies

The median change in crossreactive insulin antibody values by visit in subjects with Type 1 or Type 2 Diabetes are tabulated here. In both treatment groups of Trial 3001/3011, there were reductions from baseline to most time points for median crossreactive insulin antibody levels. The median decrease from baseline to endpoint was -0.210 %B/T in the *insulin glulisine* group and -0.260 %B/T in the insulin lispro (Homolog) group. In both treatment groups of Trial 3002/3012, there were small increases from baseline to most time points for median crossreactive insulin antibody levels. The median increase from baseline to endpoint was +0.030 %B/T in the *insulin glulisine* group and +0.060% B/T in the regular insulin group.

Table 36 – Crossreactive insulin antibody levels (expressed as %B/T difference) (Studies 3001/3011 and 3002/3012) (ITT population)

Timepoint	Glulisine				Comparators			
	N	Median	Min	Max	N	Median	Min	Max
Study 3001/3011								
Baseline	333	0.700	—	—	325	0.880	—	—
Change from baseline at:								
Week 12	297	0.050	—	—	290	-0.115	—	—
Week 26	281	-0.010	—	—	273	-0.180	—	—
Week 36	263	-0.130	—	—	244	-0.230	—	—
Week 52	258	-0.220	—	—	246	-0.290	—	—
Endpoint	333	-0.210	—	—	325	-0.260	—	—
Study 3002/3012								
Baseline	411	0.130	—	—	407	0.200	—	—
Change from baseline at:								
Week 12	374	-0.005	—	—	367	0.020	—	—
Week 26	366	0.010	—	—	354	0.020	—	—
Week 36	296	0.050	—	—	303	0.060	—	—
Week 52	298	0.040	—	—	313	0.060	—	—
Endpoint	411	0.030	—	—	407	0.060	—	—

Comparator: Lispro (Study 3001/3011), regular insulin (Study 3002/3012).

B/T = bound/free.

31os0011 32os0011

There were no correlations between crossreactive antibody levels and changes in GHb levels, basal or short-acting insulin doses, or all symptomatic and severe symptomatic hypoglycemia.

Changes in other insulin antibodies over time

Insulin-specific and *insulin glulisine*-specific antibodies were measured in the *insulin glulisine* group of Trial 3002/3012 and in Trial 3002/3012.

Table 37 – Human insulin-specific antibody levels (expressed as %B/T difference) (Studies 3001/3011 and 3002/3012) (ITT population)

Timepoint	Glulisine				Lispro			
	N	Median	Min	Max	N	Median	Min	Max
Study 3001/3011								
Baseline	333	0.250	—	—	325	0.110	—	—
Change from baseline at:								
Week 12	297	-0.040	—	—	290	-0.010	—	—
Week 26	281	-0.070	—	—	273	-0.010	—	—
Week 36	263	-0.060	—	—	244	-0.080	—	—
Week 52	258	-0.100	—	—	246	-0.080	—	—
Endpoint	333	-0.100	—	—	325	-0.060	—	—
Study 3002/3012								
Baseline	411	0.140	—	—	407	NA	—	—
Change from baseline at:								
Week 12	374	0.000	—	—	367	NA	—	—
Week 26	366	-0.010	—	—	354	NA	—	—
Week 36	296	-0.040	—	—	303	NA	—	—
Week 52	298	-0.040	—	—	313	NA	—	—
Endpoint	411	-0.040	—	—	407	NA	—	—

NA: not applicable. Due to the human nature of regular insulin used in this study, human insulin-specific antibody levels were not measured for the comparator group in Study 3002/3012.

31os0061 32os0071

In Trial 3001/3011, there were increases from baseline to all time points in the levels of *insulin glulisine*-specific antibodies in subjects treated with *insulin glulisine*. Such increases might be expected with initial exposure to a novel antigen (*insulin glulisine*). However, these increases were mostly stable after the first 26 weeks of treatment. In Trial 3002/3012, the median levels of *insulin glulisine*-specific antibodies remained near the baseline levels throughout the treatment phase in subjects treated with *insulin glulisine*.

On entry into Trial 3001, approximately 60% of subjects were receiving insulin lispro, and unadjusted median insulin lispro-specific antibody levels at baseline (0.270 %B/T) were higher than *insulin glulisine*-specific antibody levels at baseline (0.080 %B/T). There were essentially no changes in the levels of insulin lispro-specific antibodies in subjects treated with insulin lispro. At endpoint, the median absolute level of insulin lispro-specific antibodies (0.260 %B/T) in subjects treated with insulin lispro (Homolog) was higher than the absolute level of *insulin glulisine*-specific antibodies (0.110 %B/T) in subjects treated with *insulin glulisine*. There were small reductions from baseline in each treatment group for median human insulin-specific antibody levels.

Body weight

There were small increases in mean body weight in most completed Phase III trials, and no noteworthy differences between *insulin glulisine* and comparators in most trials. Increases in body weight are considered to be consistent with the significant within-group improvements in glycemic control observed in each trial. In Trial 3004 only, there were significant between-treatments differences in adjusted mean changes from baseline to endpoint: between the postmeal *insulin glulisine* (-0.3 kg) and regular insulin groups (0.3 kg), and between the postmeal *insulin glulisine* (-0.3 kg) and premeal *insulin glulisine* groups (0.3 kg).

Drug interactions

No focused drug interaction trials were performed in the *insulin glulisine* development program.

Overdose

Overall, 14 cases of overdoses were documented. Of these, 5 cases of overdose occurred without an adverse event, and 9 were reported as an adverse event (8 subjects receiving *insulin glulisine* and 1 subject receiving insulin lispro). Many of these cases involved inadvertent dosing errors, but some occurred when the usual dose of insulin was administered. There were 2 documented incidences of overdose associated with a pen confusion: in a *insulin glulisine* subject who injected *insulin glulisine* instead of glargine, and in a insulin lispro (Homolog) subject who injected insulin lispro (Homolog) instead of glargine.

Subgroup analyses

There were no unexpected or noteworthy differences between subgroups in the overall incidences of TEAEs or serious TEAEs of hypoglycemia across subgroups defined by age, BMI, sex, race, Hispanic ethnicity, or autonomic neuropathy at baseline. Any imbalances between subgroups in the incidences of TEAEs (e.g., a slightly higher incidence of TEAEs in older versus younger subjects) were considered to reflect the expected differences between these subpopulations, and were not attributable to *insulin glulisine*.

Overall Conclusions on Safety

- Compared with other short-acting insulin comparators, *insulin glulisine* was well tolerated.
- Ten deaths (5 *insulin glulisine* and 5 comparator subjects) occurred in completed trials in the *insulin glulisine* clinical development program. None of the deaths was related to the trial treatment.
- In the pooled analysis of all Phase III trials, the overall incidence of serious treatment emergent adverse events (TEAEs) was comparable in pooled *insulin glulisine* and pooled comparator groups.
- In the pooled analysis of Phase III trials, there were no clinically noteworthy differences between *insulin glulisine* and comparator short-acting insulin preparations in the overall incidences of TEAEs by system organ class, individual TEAEs, or possibly related TEAEs, and there were no consistent trends in these findings.
- The incidence of safety events specific to the administration of a recombinant derived insulin analog was comparable between treatments, and there were no noteworthy differences for the following parameters in individual trials:
 - The overall incidence of serious hypoglycemic events
 - The sequelae of hypoglycemic events, including seizure, coma/unconsciousness, TEAEs occurring at the time of—and causally related to—hypoglycemia, or TEAEs classified by the investigator as serious by a criterion other than medically important;
 - The incidence of eye TEAEs potentially related to diabetic retinopathy
 - The incidence of diabetic ketoacidosis
 - The incidence of injection site reactions
 - The incidence of potential systemic hypersensitivity reactions
 - The formation of cross-reacting insulin antibodies, human insulin-specific antibodies, or *insulin glulisine*-specific antibodies;
 - The formation of antibodies to *E. coli*.
- Due to the general concern about the possible effects of autonomic neuropathy on the occurrence of hypoglycemia, the subgroup of subjects with autonomic neuropathy at trial entry was assessed for TEAEs. The incidence of all TEAEs or severe hypoglycemic events in subjects with autonomic neuropathy was comparable between pooled *insulin glulisine* and comparator groups;
- In subpopulations defined by age, body mass index (BMI), sex, race, or Hispanic ethnicity, the incidence of TEAEs or serious hypoglycemia was comparable between pooled *insulin glulisine* and comparator groups.
- *Insulin glulisine* was well tolerated compared with insulin aspart (Novolog) when administered by continuous subcutaneous insulin infusion (CSII) using an external insulin pump, as evidenced by a comparable overall incidence in *insulin glulisine* and Insulin aspart (Novolog) groups for all TEAEs and TEAEs associated with the use of a recombinant insulin, as well as events specifically associated with the use of an external pump (including catheter occlusions, unexplained hyperglycemia, and infusion site reactions).

VIII. Dosing, Regimen, and Administration Issues

Subcutaneous *insulin glulisine*: Based on data from Phase I trials, *insulin glulisine* was administered s.c. 0 to 15 minutes before the start of a meal. Additionally *insulin glulisine* was also administered immediately postmeal in one arm of Trial 3004.

Active comparator arms: All Phase III trials were active controlled because of a clinical requirement for insulin therapy in the target subject population. All of the approved short acting insulins were used as the active comparator at least once during phase III trials. Regular insulin was the comparator in Trials 3002 and 3004. Lispro was used as the comparator in Trial 3001. Aspart, which is approved in the USA and EU for administration by CSII, was used as the comparator in Trial 3006.

Dose adjustment: The dosage of short acting insulin was adjusted in an individualized manner to reach target 2-hour postprandial glucose values, which were uniformly applied across trials and based on generally accepted clinical practice guidelines. If the patient used a whole blood referenced glucometer, the target 2-hour postprandial glucose was 6.7 to 8.9 mmol/L (120 to 160 mg/dL). If a plasma referenced glucometer was used, the target 2-hour postprandial glucose was 7.1 to 9.6 mmol/L (128 to 172 mg/dL). After accounting for the different glucose values obtained using whole blood and plasma determinations, these BG targets were identical. All values were converted to whole-blood parameters for data presentation.

Basal insulin: Consistent with common clinical practice, the insulin regimens in Phase III trials included a short-acting insulin preparation together with along-acting insulin to provide basal insulin supply. The basal insulin was also given, together with the short acting comparator in the run-in phase of all trials. Basal insulin preparations were dosed according to their respective officially approved documentation. The basal insulin used in trials 3001, 3004, 3006 was glargine, whereas NPH was used in trials 3002 and 3005.

Mixing: The non-inferiority results of Trial 3002 took into account that two thirds of the patients mixed *insulin glulisine* or regular insulin with NPH immediately before injection. When *insulin glulisine* was mixed with NPH in Trial 3002, *insulin glulisine* was to be drawn into the syringe first (as recommended in the officially approved documentation for regular insulin and insulin lispro), and the solution was to be injected immediately after mixing. The results of a clinical pharmacology trial demonstrated that *insulin glulisine* mixed with NPH immediately before injection attenuated the peak concentration of *insulin glulisine*, but the time to peak and the total bioavailability of *insulin glulisine* were not affected (Trial 1012).

Coadministration of OHAs: Due to the widespread clinical use of combined OHA and insulin therapy in Type 2 Diabetes, the concomitant use of OHAs was permitted in Trial 3002.

Dose adjustment: The investigator was encouraged to adjust the short-acting insulin in an individualized manner to reach target 2-hour postprandial glucose values, which were uniformly applied across trials and based on generally accepted clinical practice guidelines. In all countries outside North America, self-monitored BG (SMBG) measurements were performed using a whole blood-referenced meter, and the target values were 6.7 to 8.9 mmol/L (120 to 160 mg/dL). In Canada and the USA, SMBG monitoring was performed using a plasma-referenced meter and the target BG values were 7.1 to 9.6 mmol/L (128 to 172 mg/dL). After accounting for the

different glucose values obtained using whole blood and plasma determinations, these BG targets were identical. All values were converted to whole-blood parameters for data presentation. Titration of basal insulin was carried out as needed to meet prespecified targets and to enable the effect of each short-acting insulin treatment to be more readily detected.

Site of injection: For *insulin glulisine* and other short-acting trial treatments, the recommended anatomical area for s.c. injection was the abdomen. More than 85% of subjects in the completed Phase III efficacy trials injected their short-acting insulin into the abdomen, and therefore no analyses were performed based on the anatomical area of administration. In a clinical pharmacology trial conducted in 16 nondiabetic men, the pharmacokinetic and pharmacodynamic properties of *insulin glulisine* were maintained irrespective of the anatomical area of s.c. administration (Trial 1004).

Postmeal administration of insulin glulisine:

Please see trial 3004 above (pages 24 and 29). The primary objectives of the trial were achieved: the noninferiority of postmeal *insulin glulisine* to regular insulin and to premeal *insulin glulisine* in the change from baseline to endpoint in GHb was demonstrated. Additionally, the noninferiority of premeal *insulin glulisine* to regular insulin was demonstrated. Based on the predefined noninferiority margin of 0.4%, the noninferiority of postmeal *insulin glulisine* to premeal *insulin glulisine* and to regular insulin, and the noninferiority of premeal *insulin glulisine* to regular insulin, was shown by the 98.33% CI values. Statistically significant reductions from baseline in GHb were observed in all three treatment groups. Postmeal *Insulin glulisine* was well tolerated. There were no noteworthy differences in the reporting of safety parameters between postmeal *insulin glulisine* and the premeal *insulin glulisine* or regular insulin groups, or in a pooled analyses of *insulin glulisine* subjects compared with regular insulin subjects. The main findings of trial 3004 are tabulated as follows:

Treatment (ITT evaluable subjects)	GHb (%)		Symptomatic hypoglycemia Mean rate/month ^b		Adjusted mean daily insulin dose (IU) Change from baseline at endpoint ^c		
	Baseline	Change at endpoint	All	Severe	Short- acting	Basal	Total
	Mean	Adjusted mean ^d					
ITT population							
Glulisine premeal (N=286)	7.73	-0.26	3.46	0.05	-0.88	0.93	0.04
Glulisine postmeal (N=296)	7.70	-0.11	3.71	0.05	-0.47	0.24	-0.22
Regular insulin (N=276)	7.64	-0.13	3.49	0.13	1.75	0.65	2.35
Postmeal glulisine-regular:	Change at endpoint: Difference: 0.02 98.33% CI (-0.11; 0.16) p= 0.6698 ^d		p=0.7462	p=0.2566	p=0.0012	p=0.3630	p=0.0014
Premeal glulisine-regular:	Difference: -0.13 98.33% CI (-0.26; 0.01) p= 0.0234 ^d		p=0.8079	p=0.2093	p=0.0001	p=0.4420	p=0.0042
Postmeal glulisine- premeal glulisine	Difference: 0.15 98.33% CI (0.02; 0.29) p= 0.0062 ^d		p=0.5662	p=0.0014	p=0.5451	p=0.0896	p=0.7414

Continuous Subcutaneous Insulin Infusion:

Please see trial 3006 above (pages 24 and 30). The trial compared the safety and compatibility of *insulin glulisine* and insulin aspart (Novolog) when used in external pumps in terms of catheter

occlusions, GHb assessment, insulin doses, blood glucose (BG) parameters, hypoglycemic episodes, unexplained hyperglycemia, adverse events, laboratory data, and vital signs. Both insulins were individually titrated and administered in a basal and bolus fashion by an external insulin pump. The majority of subjects in this trial were either using the Disetronic pump H-Tron plus V100 (66.1%) or MiniMed programmable pumps (30.5%). The models of the MiniMed pumps used were 506, 507, 507c, and 508. Only 2 subjects used the Disetronic pump D-Tron. Subjects were using MiniMed catheters (Sof-set Micro QR and Sof-set Ultimate QR, Quick-set) or Disetronic catheters (Rapid, Rapid C and D, and Tender), and glass and plastic reservoirs.

No imbalances between treatments in the number of subjects with infusion site reactions reported as TEAEs (3 *insulin glulisine*, 4 insulin aspart). No cases of diabetic ketoacidosis were reported in the trial. In addition, no relevant differences between treatment groups were noted in parameters of glycemic control, including insulin dose, GHb, FPG, 7-point BG profiles and hypoglycemic episodes, nor in TEAE reporting.

Overall Conclusion on Dosing and Administration

- A) *Insulin glulisine* is administered by subcutaneous injection as a short acting insulin to control postprandial glucose levels in diabetic patients receiving appropriate dosage of basal insulin. The efficacy of *insulin glulisine* is maintained relative to other short-acting insulin comparators when coadministered with different basal insulin preparations (glargine or NPH).
- B) *Insulin glulisine* is administered 0-15 minutes before the meals. Delaying the injection of *Insulin glulisine* for up to 20 minutes after starting the meal does not significantly reduce its safety or efficacy. *Insulin glulisine* administered immediately after ingesting a meal is noninferior to *insulin glulisine* administered 0 to 15 minutes before a meal, based on changes from baseline to endpoint in GHb. Both regimens are noninferior to regular insulin administered 30 to 45 minutes before a meal.
- C) To minimize the number of injections, *insulin glulisine* may be drawn into the syringe containing NPH insulin immediately (within 2 minutes) prior to injection. Observational data indicate that immediate (within 2 minutes of injection) syringe premixing of *insulin glulisine* with NPH does not alter the efficacy of *insulin glulisine*.
- D) The site of SC administration does not play an important role in the PK or PD of *Insulin glulisine*. The BMI of the patient does not significantly influence the PK or PD of *Insulin glulisine*.
- E) *Insulin glulisine* can be administered via a continuous subcutaneous insulin infusion (CSII) system (insulin pump). *Insulin glulisine* is noninferior to insulin lispro when administered by CSII pump for 12 weeks in patients with Type 1 Diabetes.

IX. Special Populations

Subgroup analyses performed in each efficacy trial demonstrated that the treatment effects of *insulin glulisine* were observed consistently across subpopulations based on demographics (age, sex, race), Hispanic ethnicity, BMI, baseline glycemic control, duration of diabetes, or pretrial use of glargine or a rapid-acting insulin analog.

Additional analyses in Trial 3002 demonstrated that the efficacy of *insulin glulisine* was maintained

- 1) after concomitant administration of OHAs or
- 2) immediate syringe premixing of *insulin glulisine* with NPH.

For some subgroup analyses (e.g., race other than white, and Hispanic ethnicity), interpretation of the findings was limited by the small number of subjects within certain subgroups.

In the few cases in Trial 3001, interactions with treatment were indicated but the clinical relevance of the findings was uncertain due to a small number of subjects in the subgroup, or the lack of similar findings in other trials. Furthermore, most interactions were observed for a single efficacy parameter within each trial:

- sex for the variable severe nocturnal symptomatic hypoglycemia;
- duration of diabetes for all symptomatic hypoglycemia and nocturnal symptomatic hypoglycemia

In a clinical pharmacology trial of 24 nondiabetic subjects with different degrees of renal function, the pharmacokinetic properties of *insulin glulisine* were generally maintained in subjects with decreased renal function covering a wide range of renal impairment. However, some trials have shown that sensitivity to rapid-acting insulin preparations increases as renal function declines. On this basis, careful glucose monitoring and dose adjustments of insulin preparations, including *insulin glulisine*, may be necessary in patients with renal dysfunction. In a clinical pharmacology trial of 18 nondiabetic obese subjects, the rapid-acting properties of s.c. administered *insulin glulisine* were maintained compared with regular insulin (Trial 1010).

Subgroup analyses performed in Phase III efficacy trials demonstrated that the effectiveness of *insulin glulisine* with respect to changes in GHb and the incidence of symptomatic hypoglycemia was maintained across subgroups of subjects with a BMI of ≤ 28 kg/m² or > 28 kg/m².

**APPEARS THIS WAY
ON ORIGINAL**

X. Conclusions and Recommendations

OVERALL CONCLUSIONS

1. Human studies support the specificity of *insulin glulisine*'s actions to insulin receptors, i.e. *insulin glulisine* does not seem to cause any adverse events in humans that are not known to be caused by insulin.
2. The secondary and tertiary structures of glulisine are not different from those of native sequence human insulin. Animal and in vitro studies support molar equipotency in binding and stimulation of insulin-receptor-mediated effects of glulisine and native sequence human insulin.
3. The clinical safety of *insulin glulisine* is acceptable compared with other insulin products, particularly in terms of death, serious adverse events, and immunogenicity.
4. Human data support the potency of *insulin glulisine* on insulin receptor sites, i.e. its ability to achieve adequate glycemic control, and the sustainability of its hypoglycemic effects.
5. The incidence of hypoglycemia in patients treated in trials with *insulin glulisine* was similar to the incidences observed with comparator insulins.
6. Like insulin lispro and insulin aspart, insulin glulisine does not appear to have immunogenic properties which limit its sustained administration to humans.

CLINICAL RECOMMENDATIONS

- A. **Recommendation on Approvability**
From the clinical perspective, Apidra (insulin glulisine) may be approved for the treatment of diabetes mellitus.
- B. **Recommendation on Phase IV Studies and/or Risk Management Steps**
No specific risk management steps are recommended. Trials in children will be required to support pediatric use.

K. Eddie Gabry, M.D., M.S., F.A.C.E.
Division of Metabolic and Endocrine Drug
Products, FDA CDER
Parklawn 14B-45, HFD-510
gabryk@cder.fda.gov

ABBREVIATIONS AND DEFINITIONS

AUC	Area under the curve
AUC _(0-end) or AUC _(0-clamp end)	Area under the curve between time zero and the end of sampling
BG	Blood glucose
BMI	Body mass index
C _{max}	Maximum concentration
CSII	Continuous subcutaneous insulin infusion
CTD	Common Technical Document
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
DTSQ	Diabetes Treatment Satisfaction Questionnaires
ECG	Electrocardiograms
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GHb	Total glycated hemoglobin
GIR	Glucose infusion rate
GIR _{max}	Maximum glucose infusion rate
Glargine	Insulin glargine (Lantus)
Glulisine	Insulin glulisine (Apidra)
HbA _{1c}	Glycated hemoglobin A _{1c} species
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention-to-treat
i.v.	Intravenous(IV)
Lispro	Insulin lispro (Humalog)
NOAEL	No-observed adverse effect level
NOS	Not otherwise specified
NPH	Neutral Protamine Hagedorn insulin
OHA	Oral hypoglycemic agents
PP	Per protocol
Regular insulin	Regular human insulin
RIA	Radioimmunoassay
s.c.	Subcutaneous
SMBG	Self-monitored blood glucose
td	Duration of action
T _{max}	Time to maximum concentration/maximum GIR

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this page is the manifestation of the electronic signature.**

/s/

Kamal Gabry
4/12/04 01:31:56 PM
MEDICAL OFFICER

All of your suggestions have been incorporated. Thank you.

David Orloff
4/13/04 10:11:16 AM
MEDICAL OFFICER
Concur with Dr. Gabry's recommendations. Summary memo by Dr.
Meyer. No DD memo to be written.

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: NDA 21629
(submitted electronically
6/18/03)
IND 61956
(submitted 5/2/01)

Application Type: New Molecular
Entity
10-month Review
USAN / Established Name: Glulisine
HMR 1964

Sponsor: Aventis Pharmaceuticals
Pharmaceutical: Insulin (3031500)
Category:

Proprietary Name: APIDRA
Route of Administration: Subcutaneous
injection

Indication: Treatment of adult Type 1
(DM1) and Type 2 (DM2)
diabetes mellitus

Dosage: U-100 (100 units/ml)

Reviewer: Joanna K. Zawadzki, M.D.

**Amendment to Filing
Review Completed:** 8/05/03

Chemistry Reviewer:

Xavier Ysern, Ph.D.

Pharmacology Reviewer:

Herman Rhee, Ph.D.

Biopharmaceutics Reviewer:

Jim Wei, Ph.D.

Statistical Reviewer:

Lee-Ping Pian, Ph.D.

Project Manager:

Julie Rhee

AMENDMENT TO FILING REVIEW SUMMARY (See filing review submitted to DFS 7/31/03):

On preliminary filing review of NDA 21629 (glulisine, Aventis), the submitted application was thought to be incomplete, as data from Study 3005, a 26-week open-label, randomized, controlled, parallel, multinational, ongoing study in 846 patients with Type 2 diabetes mellitus, was not included in the submission. The NDA submission was deemed fileable after the discussion with the sponsor that a complete written Integrated Summary of Safety report would be submitted with the 120-day safety update, integrating safety data from Study 3005 (as well as from the extension Studies 3011 and 3012) into the previously submitted safety database:

OUTSTANDING ISSUES: See above.

RECOMMENDED REGULATORY ACTION:
NDA submission may be filed.

N drive location:

SIGNATURES: Medical Reviewer: Joanna K. Zawadzki, M.D. Date: 8/05/03

Medical Team Leader: David G. Orloff, M.D. Date:
and Division Director

AMENDMENT TO FILING REVIEW SUMMARY (See filing review submitted to DFS 7/31/03):

On preliminary filing review of NDA 21629 (glulisine, Aventis), the submitted application was thought to be incomplete. Study 3005, a 26-week open-label, randomized, controlled, parallel, multinational, ongoing study in 846 patients with Type 2 diabetes mellitus, is a pivotal study for the requested indication: treatment of adult patients with Type 1 and Type 2 diabetes mellitus. During the pre-NDA meeting (11/25/02), there was agreement that all efficacy data would be submitted to the FDA at the time of the NDA submission. Data from Study 3005 are not included as a separate study report, nor are these data included in the Integrated Summaries of Efficacy and Safety.

When the FDA contacted the sponsor by telephone on 7/31/03, the sponsor confirmed that Study 3005 would not be completed until late August 2003. The sponsor then forwarded the following email:

“Study 3005 (type 2 patients) is still ongoing. As agreed at the pre-NDA meeting, when we submit the 120 day safety update we will include final data from the study but no report will be available at that time. Final study report is planned to be available second week of December. The 120 day safety update will include an updated Summary of Clinical Safety (SCS). This SCS will be updated with data coming from study 3005 (and also studies 3011 and 3012 for which final reports will be included).”

There was further discussion in the Division and also with the sponsor and the following comment was sent to the sponsor:

“The 120-day safety update should include electronic data and a text report summarizing the safety data from the initial NDA submission and an Integrated Summary of Safety (ISS) report of all the safety data, including the data from the previously submitted studies and Study 3005 and the two extension studies (Studies 3011 and 3012). The submission cannot be considered complete if the updated and revised data and text are not included in the Integrated Summary of Safety. In other words, what we want is essentially a rewritten ISS with all the data.”

Conclusion:

The NDA submission was deemed fileable after the discussion with the sponsor that a complete written Integrated Summary of Safety report would be submitted with the 120-day safety update, integrating the safety data from Study 3005 (as well as Studies 3011 and 3012) into the previously submitted safety data base.

Cc: Relevant Reviewers in HFD 510 and Co-locates:
Xavier Ysern, Ph.D., Herman Rhee, Ph.D., Jim Wei, Ph.D., Lee-Ping Pian, Ph.D., J. Todd Sahlroot, Ph.D., Hae-Young Ahn, Ph.D., Julie Rhee

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/s/

Joanna Zawadzki
8/6/03 09:34:39 AM
MEDICAL OFFICER

This review is an amendment to the filing review
dated 7/31/03.

David Orloff
9/3/03 06:14:00 PM
MEDICAL OFFICER

Mary Parks
9/4/03 01:54:47 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: NDA 21629
(submitted electronically
6/18/03)
IND 61956
(submitted 5/2/01)

Application Type: New Molecular
Entity
10-month Review
USAN / Established Name: Glulisine
HMR 1964

Sponsor: Aventis Pharmaceuticals
Pharmaceutical Insulin (3031500)
Category:

Proprietary Name: APIDRA
Route of Administration: Subcutaneous
injection

Indication: Treatment of adult Type 1
(DM1) and Type 2 (DM2)
diabetes mellitus

Dosage: U-100 (100 units/ml)

Reviewer: Joanna K. Zawadzki, M.D.

**Date Filing Review
Completed:** 7/31/03

Chemistry Reviewer:

Xavier Ysern, Ph.D.

Pharmacology Reviewer:

Herman Rhee, Ph.D.

Biopharmaceutics Reviewer:

Jim Wei, Ph.D.

Statistical Reviewer:

Lee-Ping Pian, Ph.D.

Project Manager:

Julie Rhee

FILING REVIEW SUMMARY: (see Fileability Review)

OUTSTANDING ISSUES: (see also Fileability Review)

The submitted application is not complete. Study 3005, a 26-week open-label, randomized, controlled, parallel, multinational, ongoing study in 846 patients with Type 2 diabetes mellitus, is a pivotal study for the requested indication: treatment of adult patients with Type 1 and Type 2 diabetes mellitus. During the pre-NDA meeting (11/25/02), there was agreement that all efficacy data would be submitted to the FDA at the time of the NDA submission. Data from Study 3005 are not included as a separate study report, nor are the data included in the Integrated Summaries of Efficacy and Safety.

RECOMMENDED REGULATORY ACTION: N drive location:
Refuse to File (RTF)

SIGNATURES: Medical Reviewer: Joanna K. Zawadzki, M.D. Date: 7/31/03

Medical Team Leader: David G. Orloff, M.D. Date:
and Division Director

45 DAY MEETING CHECKLIST

NDA 21629 glulisine (APIDRA, Aventis)
IND 61956 (HMR 1964, glulisine)
Dates: 6/18/03 (submission date)
7/29/03 (filing meeting)
8/17/03 (filing date)
~2/15/04 (review in DFS)
4/18/04 (10-month PDUFA due date)

FILEABILITY REVIEW:

On initial overview of the NDA application:

CLINICAL:

- (1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? Yes
Note: The electronic NDA was submitted in a format that was not compatible with Acrobat version 5, the current FDA version. After extensive review of the repeat error message "illegal operation 're' inside a text object" in many of the submitted documents, the technical support staff (both FDA and sponsor) concluded that Acrobat version 4 needed to be used. This Acrobat version was loaded on this reviewer's computer 7/21/03 and in the preliminary review no further error messages have been noted.
- (2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? yes
- (3) On its face, is the clinical section of the NDA legible so that substantive review can begin? yes
- (4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? yes
- (5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? See response to #16 below
- (6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? Yes, with comment as follows: Final labeling is drafted after review. Discrepancies between study design and proposed draft labeling appear to be review issues
- (7) Are all data sets for pivotal efficacy studies complete for all indications requested?
No.

- (8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? *The data for the second pivotal study in DM2 (Study 3005) have not been submitted.*
- (9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division? *The applicant has submitted line listings for serious adverse events, but separate line listings for cardiac adverse events have not been noted in the preliminary review.*
- (10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the US population? *Not found on initial overview.*
- (11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? *It appears that the requisite case record forms have been submitted, but this cannot be fully ascertained at this time.*
- (12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? **Yes**
- (13) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? *No. See response to #16 below.*
- (14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package? **Yes**
- (15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? *No. See response to #16 below*
- (16) From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. *The NDA is not fileable. All the efficacy data discussed at the pre-NDA meeting have not been submitted. The efficacy data from the second study in patients with Type 2 diabetes mellitus (Study 3005) should be submitted in the NDA application, as discussed at the pre-NDA meeting. See Filing Comments.*

Filing Comments:

(1) The minutes from the pre-NDA meeting (11/25/02) state: "All efficacy data is to be included in the NDA at the time of NDA submission." The overview data for the submitted studies (Studies 3001, 3002, 3004, and 3006) are summarized in the sponsor's table below. (2.5clinicaloverview.pdf,pg 13)

Table 2 – Overview of completed controlled Phase III studies

	3001	3002	3004	3006
Population	Type 1 DM adults	Type 2 DM adults	Type 1 DM adults	Type 1 DM adults
Region	Europe, South Africa	N. America, Australia	N. America, Australia	Europe
No. treatment arms	2	2	3	2
Glulisine	0-15 min before meals	0-15 min before meals	0-15 min before meals OR immediately after meals ^a	CSII (external pump); bolus immediately before meals
Comparator	Lispro 0-15 min before meals	Regular insulin ^b 30- 45 min before meals	Regular insulin ^b 30-45 min before meals	Aspart immediately before meals
Frequency	At mealtimes	At least twice daily (before breakfast and dinner)	At mealtimes	At mealtimes
Route and device	s.c. injection using pen injection device ^c	s.c. injection using syringe	s.c. injection using syringe or pen injection device ^c	CSII using external insulin pump ^d
Basal insulin	Glargine once daily	NPH insulin twice daily	Glargine once daily	Glulisine or aspart as a continuous infusion
Duration of treatment	26 weeks	26 weeks	12 weeks	12 weeks
No. subjects treated	Glulisine: 339 Lispro: 333	Glulisine: 435 Regular insulin: 441	Premeal glulisine: 286 Postmeal glulisine: 296 Regular insulin: 278	Glulisine: 29 Aspart: 30

^a The earlier of the following times: immediately after completing a meal or 20 minutes after starting a meal.

^b Regular insulin: Humulin® R (Eli Lilly and Company).

^c Pen injection devices: Study 3001: NovoPen® 3 for glulisine
for lispro: Study 3004: NovoPen® 3 for glulisine

^d Study 3006: MiniMed programmable pump (models 507, 507c, and 508), Diabetic HI-Ton Plus V100, or D-Ton Catheters were Mini Med
(Set: set: Micro CR and Set: set: Ultra: CR, Quick set, or Disettes (Rapid, Rapid C and D, and For: set)

Approximately 95% of patients with DM1 and 80% of patients with DM2 completed the studies.

Study 3005, a 26-week multinational, multicenter, randomized, open-label, parallel study in subjects with type 2 DM (n=846 planned; 675 thus far), compares the efficacy (change in GHb from baseline to endpoint) and safety of glulisine with regular insulin. The data from this ongoing study are not included in the NDA submission. (2.5clinicaloverview.pdf, pg 17). The FDA project manager has confirmed that Study 3005 is ongoing and that it will be completed in late August 2003.

The largest market for rapid-acting recombinant human insulin is the population of patients with type 2 diabetes mellitus. About 90 to 95% of patients with diabetes mellitus have type 2 diabetes mellitus, and about half of the patients with type 2 diabetes mellitus are treated with insulin. Thus, the efficacy and safety data of the ongoing Study 3005 are essential for review of the proposed indication.

Studies 3100 and 3012 are extension studies for studies 3001 and 3002, and the sponsor states that study reports will be submitted during the review period,

(2) Study Population

The submitted NDA study exposure is smaller than that in the sponsor's filing proposal at the pre-NDA meeting.

Population Exposure		
	Proposed	Submitted (% of proposed)
Total # of subjects exposed to glulisine	>1500	1385 (~92%)
# of subjects exposed to glulisine > 6 months	>700	524 (~75%)
# of subjects exposed to insulin glulisine 1 yr	>100	176
120-day safety update	~700	

On preliminary review, there are no comments in the submitted NDA why a smaller population sample was submitted than discussed at the pre-NDA meeting. Safety populations in the NDA submissions for the approved rapid-acting recombinant human insulin analogs, lispro (Humalog, Lilly) and aspart (NovoLog, Novo Nordisk), comprised over 875 and 700 patient-years, respectively.

Preliminary Safety Comments: (preliminary signals)

(1) Cardiac Adverse Events

Though the actual numbers of cardiac adverse events are small, the rate of all cardiac events in the DM1 population treated with glulisine (14/950, 1.5%) is 3x the rate in those treated with a comparator (aspart, lispro, or regular Humulin insulin)(3/641, 0.3%); in Study 3001 the rate of cardiac events observed in the DM1 population treated with glulisine (9/339, 2.7%) is 9x the rate in those treated with lispro (1/333, 0.3%). The rate of all serious cardiac events (in the group of subjects with serious adverse events in \geq 0.5% of subjects) in patients with DM1 treated with glulisine (8/950, 0.8%) is 4x the rate compared to those treated with a comparator (aspart, lispro, or regular Humulin insulin) (1/641, 0.2%).

The rate of all cardiac events in the DM2 population treated with glulisine (24/435, 5.5%), is similar to the rate in those treated with regular insulin (29/441, 6.6%). The rate of all serious cardiac events (in the group of subjects with serious adverse events in \geq 0.5% of subjects) in the DM2 population treated with glulisine (12/435, 2.8%), is similar to the rate in those treated with regular insulin (16/441, 3.6%).

(2) Hypoglycemia

The incidence of severe hypoglycemia in patients with DM1 may be slightly greater in the group treated with glulisine. The incidence of serious hypoglycemia rated as severe in patients with DM2 treated with glulisine did not differ from those treated with regular insulin, but the total incidence of serious hypoglycemia appeared to be slightly greater (1.4x) in the glulisine-treated patients with DM2.

Review Considerations:

Study 3001 in patients with DM1 used a pen injection device, but the label proposes only insulin vial use.

Filing Meeting (7/29/03) Discussion (see Meeting Minutes):

The pharmacology and biopharmaceutical reviewers both found the application fileable. The chemistry reviewer agreed that the submission was fileable but requested additional information clarifying the use of different cartridges in the external insulin pump. The statistics reviewer and statistics team leader would prefer that the study report for Study 3005 (multinational study in patients with Type 2 diabetes mellitus) be available at filing, but consider the submission otherwise fileable. These comments, as well as the filing comments above, were discussed with Dr. Orloff.

Recommendations: (Comments to be conveyed to the Sponsor)

Refuse to File (RTF)

Data from the pivotal multinational study in patients with Type 2 diabetes mellitus (Study 3005) have not been submitted in this NDA application.

The minutes from the pre-NDA meeting (11/25/02) relate the following agreement between the sponsor and the FDA: "All efficacy data is to be included in the NDA at the time of NDA submission." We need all the safety and efficacy data for the trials the sponsor proposed (and we agreed) would support the application. Since this application is not complete, it can not be filed.

Joanna K. Zawadzki, M.D.
Reviewing Medical Officer

David G. Orloff, M.D.
Diabetes Team Leader
Director, Division of Metabolic and Endocrine Drug Products

Cc: Relevant Reviewers in HFD 510 and Co-locates:
Xavier Ysern, Ph.D., Herman Rhee, Ph.D., Jim Wei, Ph.D., Lee-Ping Pian, Ph.D., J.
Todd Sahlroot, Ph.D., Hae-Young Ahn, Ph.D., Julie Rhee

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/s/

Joanna Zawadzki
7/31/03 02:27:58 PM
MEDICAL OFFICER

David Orloff
8/3/03 04:14:49 PM
MEDICAL OFFICER