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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-172

Medical Review(s)

MEDICAL OFFICER REVIEW

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

APPLICATION #:	*#21172*	APPLICATION TYPE:	*Resubmission*
SPONSOR:	*NovoNordisk*	PROPRIETARY NAME:	*NovoLog 70-30 Mix*
CATEGORY OF DRUG:	*Diabetes, Insulin analogue*	USAN / Established Name:	*Insulin aspart 70-30 mix X-14 70-30 mix*
		ROUTE:	*Subcutaneous injection*
MEDICAL REVIEWER:	*E. A. Koller, M.D.*	REVIEW DATE:	*9/20/01 safety update 10/15/01*

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
4/30/01	5/1/01	AZ, BM	Complete response

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
2/9/01	NDA 21172 BZ	Resubmission response
3/15/01	NDA #21172 BM	Diskettes with non-merged data sets
3/22/01	NDA #21172 BM, IN	SAS data sets
4/10/01	NDA #21172 BM	Diskette with alk phos data
7/1/01	NDA #21172 BM	Antibody assay information
7/19/01	NDA #21172 BM	Antibody information
7/23/01	NDA #21172 BL	Antibody information
7/25/01	NDA #21172 BL	Labeling
7/26/01	NDA #21172 BM	Labeling
8/6/01	NDA #21172 BM	Antibody information
8/16/01	NDA #21172 C	Antibody information
8/30/01	NDA #21172 BM	Antibody information
9/18/01	NDA#21172 BM	Trade name proposal
9/14/01	IND [redacted]	[redacted]
10/12/01	NDA #21172 BM	Safety update

Overview of Application/Review:

The sponsor has sought approval for an insulin analogue prepared by adding protamine to NovoLog. The addition of the protamine delays the absorption of the insulin analogue. Human insulin mixes composed of 50-50 and 70-30 NPH and regular insulin have been marketed. Manufacturers of such mixtures historically have been asked to demonstrate 20% or greater pharmacokinetic (PK)-pharmacodynamic (PD) differences from the mix or single component insulins that bracket the insulin mix under request for approval. For insulin analogues, manufacturers are also asked to demonstrate long-term safety. No superiority claims are permitted because the profile of an insulin mix should be matched to a particular patient's needs. Furthermore, fixed ratio insulins cannot provide the flexibility required by most patients, especially those with IDDM, to provide optimal glycemic control.

The sponsor had previously shown that the pharmacokinetic and pharmacodynamic profiles of NovoLog Mix 70-30 were

distinct from those of human insulin mix 70-30. (This comparison was permitted [redacted] In this submission, the sponsor demonstrated that the PK profile of NovoLog Mix 70-30 differed from that of NovovLog Mix 50-50. The differences in the PD profile were limited to approximately 10%. In a limited clinical trial, the sponsor demonstrated that moderate glycemic control could be obtained with BID dosing. Higher daily doses of NovoLog Mix 70-30 are required to obtain glycemic control equivalent to that achieved with human insulin mix 70-30. (This phenomenon has been observed with NovoLog, HumaLog, and the Humalog mixes.) Cross-reacting anti-insulin antibodies increase more after treatment with NovoLog Mix 70-30 than with human insulin mix 70-30. (This phenomenon has been observed with NovoLog, HumaLog, and the Humalog mixes as well.) Although antibodies may decrease with time, a difference from human insulin persists after 24 months of treatment. The clinical significance of these antibodies is unknown. Increases do not appear to be directly related to the increased dosing needs.

Outstanding Issues:

1--The label needs to be rewritten. The label must include the information on the limited glucodynamic differences from NovoLog 50-50, the high doses of insulin required to show PK-PD differences, the increased daily insulin dose requirements, the limited glycemic control obtained with BID dosing, and the persistent increases in antibodies and alkaline phosphatase relative to those observed in patients treated with human insulin. A comparative chart showing the profiles of the insulins marketed by the sponsor should be included to permit clinicians to select the insulin/insulin mix most appropriate for the patient.

2--The proposed trade name needs to be approved. The packaging and name should be distinctive enough to reduce prescribing, dispensing, and administration errors that appear to be increasing with the proliferation of insulin products.

Recommended Regulatory Action: Approval for use in vials, cartridges, and cartridges in one of the disposable pre-filled syringes contingent on changes in the label and successful completion of inspections

New Clinical Studies: _____ **Clinical Hold** _____ **Study May Proceed**

NDAs:

Efficacy / Label Supp.: **X** **Approvable** _____ **Not Approvable**

Signed: Medical Reviewer: Eliabeth Koller **Date:** 9/20/01

Medical Team Leader: _____ **Date:** _____

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1.—Medical Officer Review
1.1.—Administrative Summary
1.1.1.--NDA: *#21172*
1.1.2.--Review: *#2*
1.1.3.—Submissions
1.1.3.1.-- Paper submission: *2/9/01*
1.1.3.2.--EXCEL spreadsheet submission sufficient for review: *4/30/01*
1.1.3.4.--Major amendment: *None*
1.1.3.--Review completed: *9/20/01* Safety update reviewed: *10/15/01*
1.2.--Drug name
1.2.1.--Generic: *X-14 70-30 Mix, Insulin Aspart 70-30 Mix*
30% insulin aspart with 70% insulin aspart with protamine
1.2.2.--Proposed trade names: *Novolog Mix 70-30* [redacted] *70-30*
1.3.—Sponsor: NovoNordisk
1.4.--Pharmacologic category: *diabetic, insulin analogue*
1.5.--Proposed indications: *patients with diabetes*
(A pediatric waiver was provided because fixed combination insulin therapy is suboptimal for children, in view of DCCT findings.)
1.6..--Dosage form and route of administration and regimen:
1.6.1.--Dosage form: *Vials and Cartridges for use in pens or pre-filled syringes*
1.6.2.--Route of Administration: *Subcutaneous injection*
1.6.3.--Dosing: *BID*
1.7.--NDA classification: *Standard resubmission*
1.8.--Important related drugs:
Insulin Lispro, Insulin Lispro [redacted] *Mix, Insulin Lispro 50-50 Mix, Human Insulin 70-30 Mix, Human Insulin 70-30 Mix, Neutral Protamine Lispro, NPH Insulin*
1.9.--Related reviews:
Insulin Aspart NDA #20986,
Lispro 50/50 Mix NDA # [redacted]
Lispro [redacted] *Mix #* [redacted]
1.10.--Materials reviewed:
2/9/01 BZ Resubmission response
3/15/01 BM Diskettes with non-merged data sets
3/22/01 BM, IN SAS datasets
4/10/01 BM Diskette including alk phos information
4/30/01 AZ,BM Diskette with pt identifiers, diabetes type, discontinuation time
7/1/01 BM Antibody assay information
7/19/01 BM Antibody assay information
7/23/01 BL Labeling
7/25/01 BL Labeling
7/26/01 BM Antibody assay information
8/6/01 BM Antibody assay information
8/14/01 C
8/16/01 BM Antibody assay information
8/30/01 C Trade name proposal
9/18/01 BM Allergic reaction information
10/12/01BM Safety update
IND # [redacted] *N-030 S2 9/14/01 Adverse event*

2.--Executive Summary

NovoLog Mix 70-30 (insulin aspart 70-30; X-14 70-30) is an insulin analogue prepared by adding protamine to NovoLog. The addition of the protamine delays the absorption of the insulin analogue. Human insulin mixes composed of 50-50 and 70-30 NPH and regular insulin have been marketed. Historically, manufacturers of such mixtures have been asked to demonstrate 20% or greater pharmacokinetic-pharmacodynamic differences from the mix or single component insulins that bracket the insulin mix under request for approval. For insulin analogues, manufacturers are also asked to demonstrate long-term safety. No superiority claims are permitted because the profile of an insulin mix should be matched to a particular patient's needs. Furthermore, fixed ratio insulins cannot provide the flexibility required by most patients, especially those with IDDM (insulin dependent diabetes mellitus, Type 1 diabetes), to provide optimal glycemic control.

The sponsor had previously shown that the pharmacokinetic (PK) and pharmacodynamic (PD) profiles were distinct from those of human insulin mix 70-30. [ ] In the current submission, the sponsor demonstrated that the PK profile of X-14 mix 70-30 differed from that of X-14 mix 50-50 by approximately 20%. The comparative differences in the PD profile were limited to approximately 10%. It should be noted that the high doses used to provide sufficient insulin for pharmacokinetic sampling of basal-type insulins may introduce artifact. Early glucose lowering may be more prominent than that observed in a clinical setting.

In a single, small clinical trial with IDDM and NIDDM patients, the sponsor demonstrated that modest glycemic control could be obtained with BID dosing. Higher daily doses of X-14 mix 70-30 are required to obtain glycemic control equivalent to that achieved with human insulin 70-30. (This phenomenon has been observed with X-14, lispro insulin analogue, and the lispro mixes.) In addition, cross-reacting anti-insulin antibodies increase more after treatment with X-14 mix 70-30 than with human insulin 70-30. (This phenomenon has been observed with X-14, lispro, and the lispro mixes as well.) Although antibodies may decrease with time, a difference from human insulin persists after 24 months of treatment. The clinical significance of these antibodies remains uncertain. The increases in cross-reacting antibodies do not appear to be directly related to the increased dosing needs. Curiously, small, but persistent, differences in alkaline phosphatase levels were observed in patients treated with X-14 70-30 versus human insulin 70-30. (This phenomenon was observed with X-14 too.) The source of the alkaline phosphatase, bone versus liver, is unknown. Concomitant increases in other hepatic enzymes were not observed in the prior studies with X-14. (See the NDA review.)

The proliferation of insulin products increases the potential for errors in prescribing, dispensing, and administration. The potential for error might be reduced with a distinctive name and package, in addition to an educational campaign. The label should include a comparative chart showing the profiles of the insulins marketed by the sponsor to permit clinicians to select the insulin/insulin mix most appropriate for the patient.

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clinicians will also recognize that different ratios of insulins from the human insulin family may yield similar profiles to insulin products from the X-14 insulin family.

Such insulin mixes are frequently used with cartridges in reusable or disposable pen injectors. Reports of needlestick injuries to ancillary healthcare personnel administering the insulin have appeared in conjunction with increasing use of another insulin mix-pen. This problem should be addressed in the label and the patient insert. Pens that permit reuse without recapping are optimal and required in the hospital setting.

RECOMMENDATION: APPROVABLE FOR USE IN VIALS AND CARTRIDGES (in NovoPen 3 and 3-ml pre-filled syringe) WITH CHANGES IN THE LABEL AND SATISFACTORY COMPLETION OF THE INSPECTIONS.

3.--Background

The sponsor resubmitted their application for approval of X14 70-30 insulin mix (30% very rapid acting component) on 4/30/01 in response to an approvable letter issued 11/7/00. The sponsor had previously provided data comparing X-14 70-30 insulin mix with human insulin 70-30 mix. The sponsor was asked to show that X-14 70-30 mix was distinct, by weight of evidence, from other insulin combinations that would be expected to be closest in pharmacokinetic and pharmacodynamic properties. A 20% difference in an insulin's profile as compared to comparators has been considered to support distinctiveness. The usual comparators would be X-14 50-50 mix

The sponsor also had previously stated that comparative studies with could not be done Because the sponsor had already shown X-14 70-30 was distinct from and more rapid in onset than human insulin 70-30 mix, it was presumed that X-14 70-30 would be distinct from and more rapid in onset than human NPH insulin. The sponsor was exempted from doing the direct comparison to NPH.

The sponsor had also previously provided results from a 3 month clinical trial comparing BID use of X-14 70-30 insulin mix with human insulin 70-30 mix in patients with insulin dependent diabetes mellitus (IDDM, Type 1) and non-insulin dependent diabetes mellitus (NIDDM, Type 2). Because long-term safety and efficacy are the most important issues for insulin analogue mix approval after the insulin analogue chemical entity has been approved and after a distinctive PK-PD profile has been delineated, sponsors are asked to provide long-term $HgbA1_c$ data in the context of the changes in anti-insulin antibody levels (which are typically higher with insulin analogues) and the doses required to maintain glycemic control. Sponsors are also asked to provide data on allergic reactions which could potentially increase because of the addition of protamine, which is known to be antigenic, to the insulin analogue, which itself is a foreign protein. Sponsors are also asked to provide long-term information on any findings that appeared during the development of the insulin analogue or its mix. In this case, the sponsor was asked to provide follow-up on alkaline phosphotase levels which was found to be unexpectedly

elevated during the clinical trials. Long-term data on these parameters were not provided with the initial submission, but were provided with the resubmission.

4.--Objectives
The sponsor has sought to remedy the deficiencies in the first submission of X-14 70-30 insulin analogue mix submitted 12/17/99:
a--by providing data to show that the pharmacokinetic and pharmacodynamic profiles of X-14 70-30 are distinct from those of X-14 50-50 mix.
b--by providing long-term safety data.

5.--CANDA
There was no CANDA submission. Additional data were provided on EXCEL spread sheets.

6.--Financial Disclosure
Dr. Anders Lindholm indicated in the first submission that there were no financial interests to disclose. He indicated in the 2/9/01 resubmission that there were no financial interests to disclose for the new PK-PD study 1086, in which X-14 70-30 was compared to X-14 50-50.

7.--Inspections and Data Validity
Inspections for the analytic assays, biopharmaceutical study, and clinical study are pending. (International travel has been delayed.)

Analysis of the clinical data was complicated by the randomization of 3 patients to 1 treatment and subsequent treatment with the other insulin. The data bases submitted did not clearly delineate these patients. There appear to be no other problems with the validity of the data.

8.--Pediatric Waiver
The sponsor was previously granted a pediatric waiver because most pediatric patients with diabetes, especially those who are prepubescent, are IDDM patients. Fixed ratio and BID dosing cannot provide the flexibility required to maintain the tight control that is essential for avoiding long-term diabetic complications. Even for post-pubertal adolescents with NIDDM linked to obesity, tight glycemic control is likely to be important because of the expected long-term duration of disease and the evidence from the United Kingdom Diabetes and Prevention Study suggesting attenuation of long-term complications with glycemic control. Furthermore, because there may be a mismatch between insulin and glucose levels with BID regimens and insulin prompts hunger, there is a risk of progressive obesity in these young NIDDM patients.

9.--Chemistry
See the first medical NDA #21172 review. See the first and second chemistry NDA #21172 reviews.

In the submitted label, the sponsor refers to vials, cartridges, and syringes. The 3 ml cartridge is to be used in the NovoPen 3. The 3 ml cartridge is to be also used in the 3 ml "pre-filled syringe". The device reportedly is similar to the Novolet device used in Europe. A similar pre-filled syringe was approved for use with Novolin products in 2000. There have been small cosmetic changes in the device submitted for review. Some confusion may arise because of the different duration of use instructions given for vials and cartridges. In the interests of safety, cartridges and vials should be discarded 2 weeks after opening. Additional confusion may arise because the mixing instructions given for cartridges in the pre-filled syringe differ from the mixing instructions given for the cartridges in the NovoPen. 3. In the interests of safety, both products should have the same instructions.

The sponsor also wants post hoc approval for the Flex pens, which use the 3 ml cartridges. The approval request was not submitted in the original NDA. As such, the Flex pens cannot be approved in this submission. The Flex pens should be submitted as a separate supplement for review.

10.--Pharmacology-Toxicology
See the first medical NDA #21172 review. See the first pharmacology-toxicology NDA #21172 review.

11.--Biopharmaceutics
The sponsor provided data from a 4-way cross-over, single-dose, euglycemic clamp study done using 0.30 U/kg of X-14 100% (no protamine), X-14 70-30, X-14 50-50, and X-14 30-70. The mixes are prepared, [redacted] protamine to attenuate absorption and vary the PK-PD profile. X-14 70-30 is the equivalent of mixing 30% X-14 (0% protamine) and 70% X-14 mixed with protamine. The time to reach the various area-under-the-curve (AUC) levels for insulin and glucose was delineated for the various insulin products. Ratios of these AUC levels and calculations of the time to reach AUC levels using X-14 values as fixed parameters permitted comparisons between the insulin products. The data support an approximate 20% difference in the pharmacokinetic profiles of X-14 70-30 and X-14 50-50 insulin mixes. Pharmacodynamic profiles were less distinct. The data suggest an approximate 10% difference in the pharmacokinetic profiles of X-14 70-30 and X-14 50-50 insulin mixes.

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Table 1. Pharmacokinetic Comparisons for Healthy Volunteers (n~34):

Time to Fraction of AUC-insulin	Pharmacokinetic Values (Hours)			Pharmacokinetic Ratios	
	X14 70-30	X14 50-50	X14 100%	X14 70-30 /X14 50/50	X14 70-30 /X14 100%
25%	1.43	1.23	1.07	1.17	1.34
50%	2.62	2.18	1.73	1.20	1.51
75%	4.95	4.13	2.62	1.20	1.89
100%	16.67	8.97	5.95	1.86	2.80

Table 2. Pharmacokinetic Comparisons for Healthy Volunteers (n-34):
Time for Compounds to Reach the Fractional AUC-insulin Levels of X-14 70-30 Mix

Time to Fraction of AUC-insulin of X14 70-30 Mix	Pharmacokinetic Values (Hours)		
	X14 70-30 Mix	X14 50-50 Mix	X14 100%
25%	1.43	1.10	0.84
50%	2.62	1.89	1.27
75%	4.95	3.65	1.66
100%	16.67	9.90	2.27

Table 3. Pharmacodynamic Comparisons for Healthy Volunteers (n~34):

Time to Fraction of AUC-glucose	Pharmacodynamic Values (Hours)			Pharmacodynamic Ratios	
	X14 70-30	X14 50-50	X14 100%	X14 70-30 /X14 50-50	X14 70-30 /X14 100%
25%	2.63	2.47	1.90	1.07	1.39
50%	5.02	4.68	3.17	1.07	1.58
75%	10.10	9.18	4.77	1.10	2.12
100%	24.00	19.17	9.00	1.25	2.67

Table 4. Pharmacodynamic Comparisons for Healthy Volunteers (n-34):
Time for Compounds to Reach the Fractional AUC-insulin Levels of X-14 70-30 Mix

Time to Fraction of AUC-glucose of X14 70-30 Mix	Pharmacodynamic Values (Hours)		
	X14 70-30 Mix	X14 50-50 Mix	X14 100%
25%	2.63	2.35	2.12
50%	5.02	4.50	3.60
75%	10.10	9.12	8.10
100%	24.00	23.00	---

12.--Clinical Data

12.1--Study Design

Clinical data from a 3-month, open-label, active control trial (Study 038) and its 21-month extension (Study 067) were provided. Both patients with IDDM and NIDDM were treated with BID dosing (pre-breakfast and pre-supper) with X-14 70-30 or human insulin 70-30. An active control was maintained during the extension phase. (See the first NDA review.)

Table 5. Disposition of Patients

Numbers (Percent) of Patients*			
Human Insulin Mix	Randomized	With HgbA1c-3 Months	With HgbA1c-24 Months
IDDM	49	47 (96%)	28 (57%)
NIDDM	102	96 (95%)	54 (53%)
X-14 Insulin Mix			
IDDM	55	49 (89%)	32 (58%)
NIDDM	85	82 (96%)	40 (47%)

*The patient numbers at 3 and 24 months exclude the 3 patients who received the incorrect treatment after randomization.

12.2--Patient Disposition

Data from the main study and its extension trial indicate that drop-out rates were not excessive during the main trial (5%), but that only 56% of completers of the main study entered the extension trial and had values at 24 months (Table 5). Drop-out rates were somewhat greater for patients with NIDDM who were treated with X-14 insulin mix.

12.3.--Results

12.3.1.--Efficacy

Data from the both the main study and its extension suggest that glycemic control was not optimal ($HgbA1_c$ <7%) in either treatment group. Glycemic control was somewhat better in patients with NIDDM than in those with IDDM (Table 6). Patients who dropped out before 24 months were more likely to have had a higher $HgbA1_c$ or a smaller change in $HgbA1_c$ from baseline at the end of the main study (3 months) (Tables 6 and 7).

$HgbA1_c$ values at 24 months were 0.25 units higher in patients with IDDM who were treated with X-14 insulin mix than in those treated with human insulin mix-although these differences were not statistically significant when assessed by t-test. Similarly, $HgbA1_c$ values at 24 months were 0.18 units higher in patients with NIDDM who were treated with X-14 insulin mix than in those treated with human insulin mix-although these differences were not statistically significant when assessed by t-test (Table 6). The median for the absolute levels of $HgbA1_c$ of IDDM patients treated with human insulin 70-30 did not differ appreciably from the mean whereas the median for $HgbA1_c$ values for IDDM patients treated with X-14 70-30 differed from the group mean. A similar picture was observed in the patients with NIDDM.

For patients with IDDM, the mean difference between treatment groups for the change in $HgbA1_c$ from baseline to 24 months was 0.32% and favored those treated with human insulin mix-although these differences were not statistically significant when assessed by t-test (Table 7). Similarly, for patients with NIDDM, the difference between treatment groups for the change in $HgbA1_c$ from baseline to 24 months was 0.20% and favored those treated with human insulin mix-although these differences were not statistically significant when assessed by t-test (Table 7). There was a disparity between medians and means of the changes in $HgbA1_c$ for NIDDM patients treated with human insulin mix, and both IDDM and NIDDM patients treated with NovoLog mix. This mean-median disparity was most profound in the IDDM patients treated with NovoLog mix.

These data suggest that a) there is a large degree of overlap in $HgbA1_c$ and change in $HgbA1_c$ values for the two treatments and b) the change in $HgbA1_c$ values are skewed in several patients groups-especially those treated with X-14 70-30 mix. Small sample size may contribute to the skewing.

Table 6. $HgbA1_c$ Levels by Treatment Cohort and Time

HgbA1c (%)				
Treatment Group	3 Months	At 3 Months-but DC prior to 24 Months	At 3 Months-but no DC prior to 24 Months	24 Months
Human Insulin Mix IDDM	8.26	8.30	8.24	**8.32 (median 8.20)**
X-14 Insulin Mix IDDM	8.44	8.59	8.33	**8.57 (median 8.20)**
P=	N.S.	N.S.	N.S.	0.41
Human Insulin Mix NIDDM	8.08	8.15	8.04	**8.13 (median 8.00)**
X-14 Insulin Mix NIDDM	7.92	7.96	7.88	**8.31 (median 7.95)**
P=	N.S.	N.S.	0.02	0.47

DC=discontinuation

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Table 7. Change in $HgbA1_c$ Levels from Baseline by Treatment Cohort and Time

Change in HgbA1c (%)				
Treatment Group	3 Months	At 3 Months-but DC prior to 24 Months	At 3 Months-but no DC prior to 24 Months	24 Months
Human Insulin Mix IDDM	-0.20	-0.12	-0.25	**-0.17 (median -0.15)**
X-14 Insulin Mix IDDM	0.01	0.08	-0.03	**0.21 (median 0.05)**
P=	0.20	N.S.	N.S.	**0.15**
Human Insulin Mix NIDDM	-0.10	-0.06	-0.14	**-0.04 (median 0.05)**
X-14 Insulin Mix NIDDM	-0.18	-0.09	-0.28	**0.16 (median 0.25)**
P=	N.S.	N.S.	N.S.	**0.30**

DC=discontinuation

12.3.2.--Integrated Efficacy and Safety Results

12.3.2.1.--General

To understand $HgbA1_c$ and changes in $HgbA1_c$ in the context of other potentially related parameters, patients with values for $HgbA1_c$, cross-reacting antibodies (specific binding), insulin dose, weight, and alkaline phosphatase at baseline and exit were assessed by the time of exit from the extension study (t=3 months in the main study (038) is the same as t=0 in the extension study {067]). Both means and correlation coefficients were calculated. Substantial numbers of patients were lacking all data points. Of the patients with IDDM treated with human insulin mix, only 80% had all values at exit. Only 59% had such values beyond 3 months. Similarly, of the patients with IDDM treated with X-14 insulin mix, only 73% had all values at exit. Only 60% had such values beyond 3 months.

Of the patients with NIDDM treated with human insulin mix, 86% had all values at exit, but only 60% had such values beyond 3 months. Similarly, of the patients with IDDM treated with X-14 insulin mix, 87% had all values at exit, but only 60% had such values beyond 3 months.

12.3.2.2.--Integrated Efficacy and Safety for Patients with IDDM

When changes in $HgbA1_c$ were assessed this way, values tended to be better for patients with IDDM treated with human insulin 70-30 despite the fact that patients treated with X-14 70-30 who discontinued early had more deterioration in glycemic control than those treated with human insulin 70-30 (Tables 8 and 9). Consistent with these changes in $HgbA1_c$ were the changes in weight: being greater in those treated with human insulin 70-30. Weight gain is typically seen with improvement in glycemic control when insulin is used.

Although improvement in glycemic control was less in the patients with IDDM treated with X-14 70-30, the increase in the total daily insulin dose was greater than that for those with IDDM treated with human insulin 70-30. The increase in insulin dose was most notable for those patients who completed the main trial, but who discontinued before the 24-month endpoint.

Cross-reacting antibody levels (specific binding % over total) increased more in the patients who used X-14 70-30 mix (Figures 1-4). Most patients with IDDM who were treated with human insulin 70/30 had low binding levels that remained low over time (Figure 4). Those few who had higher levels did not have much serial change in antibody levels. A greater proportion of patients treated with X-14 70-30 had higher binding levels (Figure 3). Some patients had higher levels at baseline. Others experienced a marked increase in the first 6 months on the insulin analogue mix. Sometimes these values decreased over time. There was no major trend for further increases in antibody binding with extended use (Table 8). Although there were increases in these cross-reacting antibodies, the clinical significance of these antibodies remains uncertain. They do not appear to directly affect changes in the daily insulin dose or glycemic control (Tables 8, 9, and 10).

12.3.2.3.--Integrated Efficacy and Safety for Patients with NIDDM
When changes in $HgbA1_c$ were assessed this way for patients with NIDDM, the two treatment groups were statistically comparable. To achieve this comparability, higher doses of X-14 insulin mix were utilized (Tables 8 and 9). In addition, there was a higher drop-out rate in those who were treated with X-14 insulin mix. Consistent with these changes in $HgbA1_c$ were the modest changes in weight: being comparable between the 2 treatment groups. Weight change is typically inversely related to changes in glycemic control.

Cross-reacting antibody levels (specific binding % over total) increased more in the patients who used X-14 70-30 mix (Figures 1, 2, 5, and 6). Most patients with NIDDM who were treated with human insulin 70-30 had low binding levels that remained low over time (Figure 6). As with the patients with IDDM, those few NIDDM patients treated with human insulin 70-30 who had higher levels did not have much serial change in antibody level. As with patients with IDDM, a greater proportion of NIDDM patients treated with X-14 70-30 had higher binding levels (Figure 5). Some patients had higher levels at baseline. Others experienced a marked increase in the first 6 months on the insulin analogue mix. Sometimes these values decreased over time. There was no major trend for an increase in antibody binding with extended use-although patients with NIDDM who discontinued early had greater increases in antibody binding if they were treated with X-14 70-30 mix (Table 8, Figure 2). The clinical significance of these cross-reacting antibodies remains uncertain. They do not appear to directly affect changes in the daily insulin dose or glycemic control (Tables 8, 9, and 10).

Table 8. Safety and Efficacy Parameters in Patients with All Parameters at the Given Timepoint: Change from Baseline and Correlation between Parameters that Could Affect Efficacy

Treatment Cohort by Drop-out Time		Change from Baseline					Correlation of Parameter Delta		
		$HgA1_c$ (%)	Antibodies (% binding)	Dose (U/kg)	Wt (kg)	Alk Phos (U/L)	$HgbA1_c$ vs Antibodies	$HgbA1_c$ vs Dose	Dose vs Antibodies
3 mo	HR IDDM (n=10)	0.00	-1.53	0.01	0.1	1.2	0.02	-0.31	-0.15
	X14 IDDM (n=7)	0.01	9.67	0.11	-1.1	-4.1	-0.84	-0.57	0.80
	P=	0.97	0.13	0.14	0.42	0.11			
6-18+ mo	HR IDDM (n=8)	0.09	-0.78	-0.01	1.0 (n=5)	-1.2	0.22	0.07	0.68
	X14 IDDM (n=9)	1.04	0.99	0.24	-4.1 (n=8)	-2.3	-0.55	0.49	-0.58
	P=	0.18	0.66	6 E04	0.07	0.88			
24 mo	HR IDDM (n=24)	-0.18	1.15	0.01	1.6	4.3	0.49	-0.06	0.31
	X14 IDDM (n=26)	0.14	11.24	0.13	1.0 (n=25)	8.6	-0.10	-0.07	0.10
	P=	0.20	0.002	0.006	0.57	0.14			
3 mo	HR NIDDM (n=27)	-0.10	0.28	0.05	-0.3	-2.4	-0.11	0.11	0.31
	X14 NIDDM (n=23)	-0.20	10.95	0.05	0.9	-1.51	-0.38	-0.44	0.20
	P=	0.64	0.02	0.92	0.26	0.84			
6-18+ mo	HR NIDDM (n=14)	0.03	2.10	0.04	3.1 (n=11)	-3.0	-0.29	-0.21	0.35
	X14 NIDDM (n=15)	-0.02	1.90	0.08	-2.5 (n=12)	1.1	0.62	-0.21	0.18
	P=	0.90	0.96	0.36	0.10	0.38			
24 mo	HR NIDDM (n=50)	-0.05	1.01	0.02	1.6	0.9	-0.07	-0.12	0.00
	X14 NIDDM (n=39)	0.14	4.77	0.12	1.3	5.4	-0.17	-0.16	0.29
	P=	0.38	0.16	0.002	0.70	0.11			

Antibodies=%binding bound/total with non-specific binding excluded

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Table 9. Safety and Efficacy Parameters in Patients: Change from Baseline and Correlation between Parameters that Could Affect Efficacy

Treatment Cohort At Last Timepoint with All Values	Change from Baseline					Correlation of Parameter Delta		
	$HgA1_c$ (%)	Antibodies (% binding)	Dose (U/kg)	Wt (kg)	Alk Phos (U/L)	$HgbA1_c$ vs Antibodies	$HgbA1_c$ vs Dose	Dose vs Antibodies
HI-IDDM (n=42)	-0.08	0.11	0.01	0.9	2.6	-0.03	-0.03	0.38
X14-IDDM (n=45)	0.29	9.00	0.14	-0.6	5.0	-0.34	0.14	0.08
P=	0.08	0.0002	7 E06	0.07	0.26			
HI-NIDDM (n=90)	-0.01	0.94	0.03	1.1	-0.3	-0.09	-0.05	0.03
X14-NIDDM (n=77)	0.00	6.50	0.10	0.3	2.6	-0.05	-0.14	0.19
P=	0.92	0.007	0.002	0.28	0.14			

Antibodies=% binding bound/total with non-specific binding excluded
HI=Human insulin

Table 10. Change in Parameters from Baseline vs the Tertile for Changes in Cross-reacting Anti-insulin Antibodies

Treatment Group	Tertile	N	Mean Values of the Changes from Baseline				
			Antibody Binding (%)	HgbA1c (%)	Dose (U/kg)	Weight (kg)	Alk Phos (U/L)
HI 70-30 IDDM	High	14	4.36	-0.04	0.03	2.5	2.1
	Mid	14	-0.14	-0.09	0.04	0.6	3.0
	Low	14	-3.86	-0.11	-0.05	-0.6	2.6
X-14 70-30 IDDM	High	15	26.13	-0.21	0.16	1.1	2.9
	Mid	15	3.79	0.55	0.14	-0.2	4.5
	Low	15	-2.92	0.54	0.12	-2.6	7.8
HI 70-30 NIDDM	High	30	7.16	-0.12	0.04	1.7	-1,00
	Mid	30	0.01	0.03	0.06	1.3	-0.27
	Low	30	-4.36	0.04	0.00	0.1	0.40
X-14 70-30 NIDDM	High	26	23.95	0.03	0.14	1.0	3.65
	Mid	26	0.74	0.11	0.08	0.9	2.22
	Low	25	-5.65	-0.15	0.05	-1.0	2.76

Antibodies=% binding bound/total with non-specific binding excluded
HI=Human insulin

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Figure 1. Levels of Cross-reacting Antibodies by Discontinuation Cohort and Treatment Group

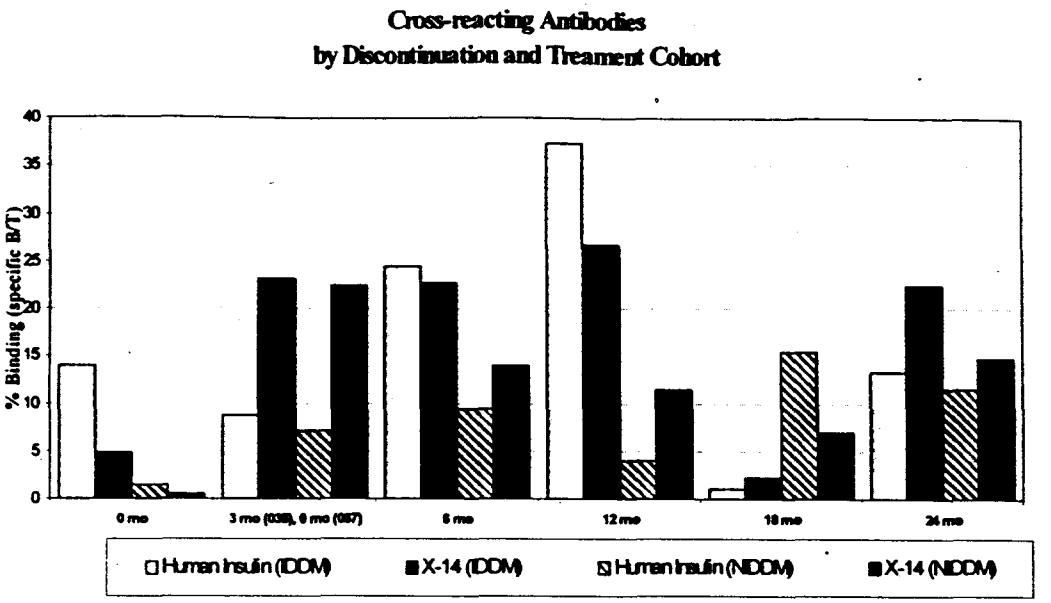


Figure 2. Change in the Levels of Cross-reacting Antibodies by Discontinuation Cohort and Treatment Group

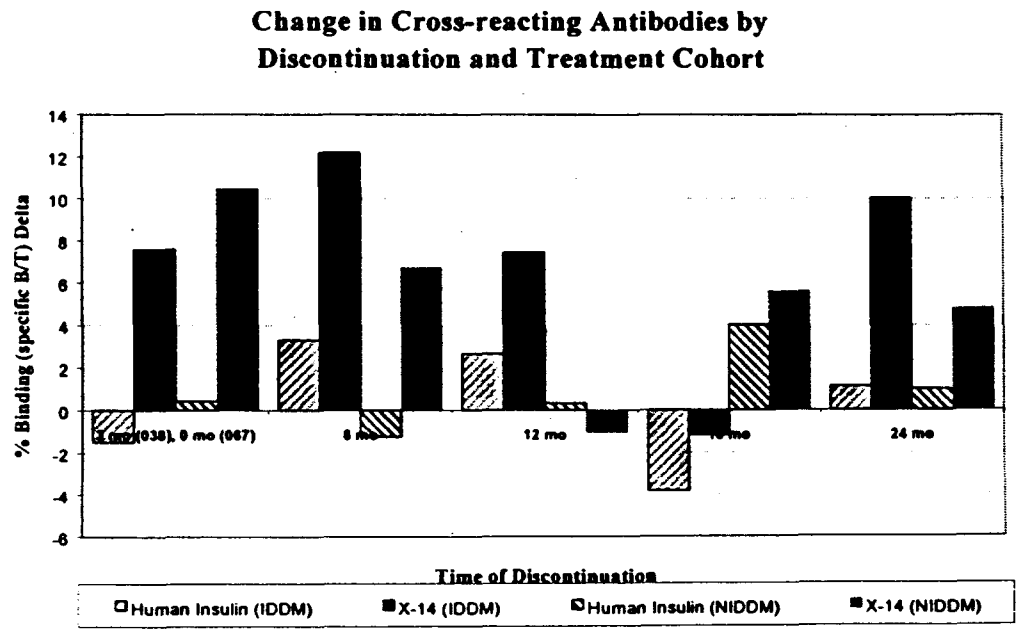


Figure 3. Serial Change in Cross-reacting Antibodies for Individual Patients with IDDM who were Treated with X-14 70-30 Mix

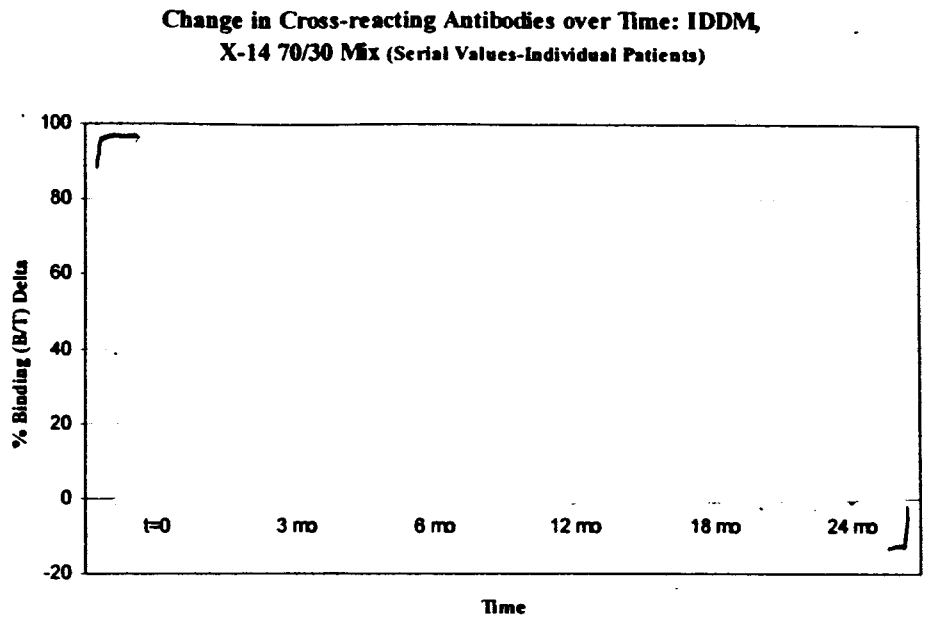


Figure 4. Serial Change in Cross-reacting Antibodies for Individual Patients with IDDM who were Treated with Human Insulin 70-30 Mix

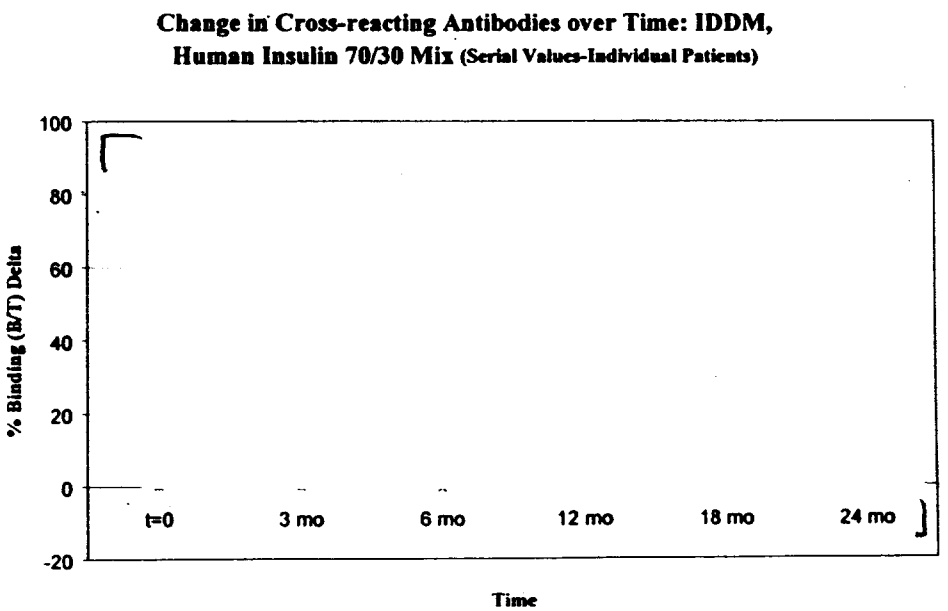


Figure 5. Serial Change in Cross-reacting Antibodies for Individual Patients with NIDDM who were Treated with X-14 70-30 Mix

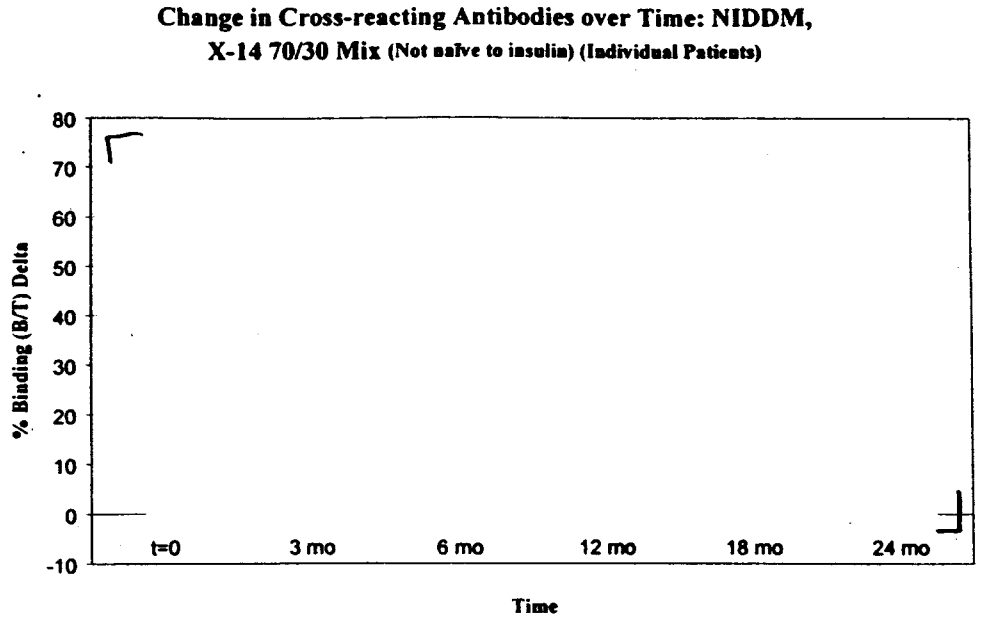
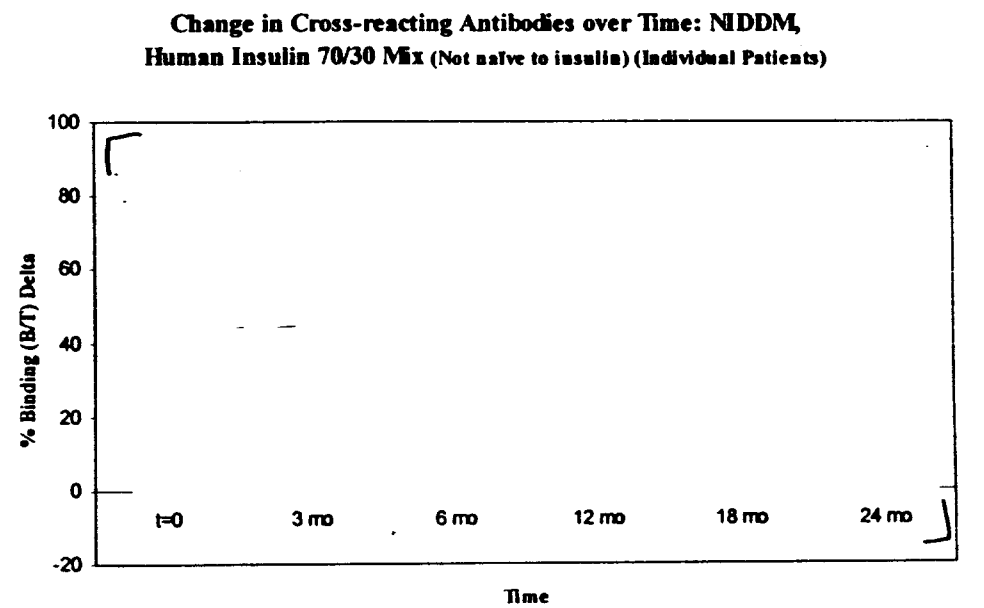


Figure 6. Serial Change in Cross-reacting Antibodies for Individual Patients with NIDDM who were Treated with Human Insulin 70-30 Mix



12.3.3.--Other Safety:

12.3.3.1.--Alkaline Phosphatase

Alkaline phosphatase levels have tended to be modestly higher in patients, especially IDDM patients, treated with X-14 analogue compared to those treated with human insulin. These relative differences were initially observed in the controlled clinical trials for X-14 (Insulin aspart; NovoLog) and, later, in the main study for X-14 70-30 mix. This unexpected finding has persisted in the extension study for X-14 70/30 mix (Table 8 and 9). No fractionation of the enzyme was done so it is not known whether the source is bone or liver. Concomitant increases in hepatic enzymes have not been observed.

12.3.3.2.--Allergic Reactions

There was 1 significant allergic-type reaction during the extension study. A male patient (0123) treated with Novolin 70-30 for almost 2 years was hospitalized for a rash. One of the provocative tests induced the reaction. Studies for underlying connective disorders were negative. The reaction did not appear to be related to insulin therapy. In the safety update, preliminary information was provided on a systemic allergic type reaction in a patient using X-14 70-30 in another ongoing clinical trial in Europe.

Local skin reactions were not routinely recorded so no comments can be made. Local injection site reactions have been recorded with another insulin analogue, especially with pump infusion.

13.--Reviewer's Commentary

a) U.S. insulin manufacturers have known since the late 1980s that they must show a 20% difference in the PK-PD profiles from neighboring insulins within an insulin family to be permitted to market their product.

The sponsor previously showed that, with very select time intervals that maximize differences, X-14 70-30 mix differed from human insulin 70-30 mix. [redacted] the sponsor was exempted from directly showing differences from such a basal insulin. Because human insulin 70-30 has been shown to have a more rapid profile than NPH, it was inferred that X-14 70-30 would have a more rapid profile than NPH.

[redacted]

In this submission the sponsor has provided data that suggest that the pharmacokinetic profile of X-14 70-30 mix differs from that of X-14 50-50 by ~20% (albeit by the use of very high doses that permit measurement of insulin levels, but may introduce artifact in the magnitude of the glucodynamic reponse). The differences in the pharmacodynamic profile of X-14 70-30 mix, however, is only about 10% different from the profile of X-14 50-50 mix. Furthermore, it is not clear as to whether the PK-PD profile differs from that of human insulin 50-50 mix. The range of X-14 content permitted in the X-14 "70-30" mixture may vary by as much as —% from batch to batch. This batch to batch variation may further obscure the distinctiveness of a fixed insulin product. Extremes in the variation may result in unexpected hyper or hypoglycemia clinically.

The sponsor should include a table that outlines the pharmacokinetic-glucodynamic profiles of various insulins available from NovoNordisk. Such a table will enable clinicians to better select the insulin that best meets the metabolic needs of a particular patient. NovoNordisk already has such a product reference guide in print.

b) Fixed ratio insulin mixtures cannot provide optimal glucose control because most patients do not have fixed dietary intake/metabolic demands and, as such, cannot predict the timing and relative dosing of insulin required for more than a single meal. Indeed the $HgbA1_c$ levels in both treatment arms of the main study and its extension show that glycemic control was mediocre. For select patients, the convenience of BID dosing may outweigh concerns for tight glycemic control. This convenience may be enhanced by immediate pre-meal (versus 30 minute pre-meal) dosing-although it is not clear that the similar profiles could not be achieved by human insulin 50-50 given immediately prior to meals.

c) In both the main study (038) and the extension trial (067), glycemic control appeared to be equivalent whether X-14 70-30 or human insulin 70-30 was employed. However, only limited conclusions about the equivalence of long-term glycemic control between X-14 70-30 and human insulin 70-30 can be made because of the mediocre control, the limited numbers of patients at 24 months, and the skewing of the $HgbA1_c$ data in patients treated with X-14 70-30 insulin analogue.

d) Increased insulin doses appear to be required to achieve comparable glycemic control when X-14 70-30 mix is utilized versus human insulin 70-30 mix. Similar insulin dose needs were observed with X-14 in the original NDA (#20986) and in the main study for X-14 70-30 mix (038). Approximately 1-5 U additional units of insulin per day were needed by a 70 kg person.

e) Increases in cross-reacting antibodies are more common in patients treated with X-14 70-30 mix versus human insulin 70-30 mix. The findings were observed in the main study (038) and the extension study (067) as well as with X-14 versus human regular insulin in the original NDA (#20986). The increases appear to be most prominent during the first 6 months of therapy. Antibody binding levels do not appear to substantially increase further over time-although differences between the X-14 70-30 and human insulin 70-30 mixes persist at 24 months. The changes in antibodies do not appear to be directly related to either changes in insulin dose or glycemic control.

f) Protamine is antigenic. The changes in the molecular structure of insulin analogues may render them more antigenic. (See original NDA for X-14, #20986.) Allergic reactions were noted with NovoLog. In the main study, there were 5 patients treated with NovoLog mix who developed allergic-type reactions; there was 1 such patient treated with human insulin mix. (See first review for NDA #21172.) There were no discontinuations from the main study (038) for allergic-type reactions. In the extension study (067), there were no serious allergic reactions or discontinuations for allergy with NovoLog Mix 70-30. Because the exposed population was small in the main study and even smaller in the extension study, the occurrence of such reactions cannot be excluded, but appear to be relatively uncommon.

g) Relative increases in alkaline phosphatase are greater in patients, especially those with IDDM, treated with X-14. These findings were present in the main (038) and extension (067) studies for X-14 70-30 as well as in the original NDA for X-14 (#20986).

h) The addition of new mixtures to the widening array of insulin products increases the potential for errors in prescribing, dispensing, and self-administration. The development of a self-explanatory label, distinctive packaging, and an education program for healthcare professionals could reduce these problems.

14.--Regulatory Conclusions

The sponsor has demonstrated that the X-14 70-30 has a pharmacokinetic profile that differs from X-14 50-50 when a single batch is used. Differences may be smaller from batch to batch of insulin. The sponsor has not demonstrated that X-14 70-30 has a pharmacodynamic profile that is distinct from X-14 50-50.

The sponsor cannot state or imply that X-14 70-30 has a more rapid pharmacokinetic or pharmacodynamic profile than human insulin mixtures. The PK-PD profile is likely to be similar to that of human insulin 50-50. The sponsor cannot state or imply that X-14 70-30 provides superior post-prandial control.

[ ] Only limited conclusions about the equivalence of long-term glycemic control between X-14 70-30 and human insulin 70-30 can be made because of the mediocre control, the limited numbers of patients at 24 months, and the skewing of the $HgbA1_c$ data in patients treated with X-14 70-30 insulin analogue.

Because a pediatric waiver was provided on the grounds that fixed ratio insulins are not flexible enough to provide good glycemic control in patients without endogenous insulin and that children should receive optimal control to maximize lifespan without diabetic complications,

RECOMMENDATION: APPROVAL FOR USE IN VIALS AND CARTRIDGES (for NovoPen 3 and 3-ml pre-filled syringe) WITH CHANGES IN THE LABEL
(Contingent on satisfactory inspections.)

14.--Label Review

14.1.--General Comments

The labels should be pharmacokinetic-pharmacodynamic labels primarily. The label should include comparative and glucodynamic data for the X-14 family of insulin analogues and the family of human insulin products.

The label should concentrate on the attributes of this particular insulin and how it compares to other insulins. It should not be a guide for the management of diabetes. Nor should it be a guide for the properties of and general use of insulin.

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Draft

Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elizabeth Koller
10/29/01 07:12:20 PM
MEDICAL OFFICER
safety update reviewed; information for physician and patient labels p
rovided

David Orloff
10/30/01 07:59:18 PM
MEDICAL OFFICER

NDA #21172 NovoLog Mix
N000 BM Resubmission/Data Sets and N000 BM Archival Data Sets
Letter date: 3/15/01 Received: 3/16 and 19/01
Letter date: 3/22/01 Received: 3/23/01
Received and reviewed by physician: 3/25/01
Received and reviewed by physician: 3/27/01
Sponsor: NovoNordisk

The submitted data sets are not that which we requested. There is one data set with serial insulin doses and another data set with lots of unnecessary demographic data, serial antibody data, and serial Hgba1c data. They include all of the antibodies- insulin specific, cross-reacting, and ⌒ when only the cross-reacting levels are needed. They do not appear to have included alk phos data. These data sets cannot be easily merged and rotated.

What is needed:

Patient ID	Treatment V1 V2 etc	Weight V1 V2 etc	HgbA1c V1 V2 etc	Cross-reacting Antibodies V1 V2 etc	Alk Phos V1 V2 etc	Insulin Dose-Total V1 V2 etc
AAAAAA						
BBBBBBB						
CCCCCCC						
XXXXXX						
YYYYYY						
ZZZZZZZ						

(V=visit)

Action Items:
1--This will need to be conveyed to the sponsor in a telecom.

S

Elizabeth Koller, M.D.
CC: HFD 510 RheeJ/Koller

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/s/

Elizabeth Koller
4/3/01 09:32:11 AM
MEDICAL OFFICER
Need telecom.

Saul Malozowski
4/3/01 10:12:58 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

NDA #21172 Insulin X-14 70/30 Mixture
Clarification of items to be listed in letter to sponsor
Sponsor: NovoNordisk

Action Items: To be communicated to sponsor:
1--Additional studies to show the distinctiveness of NovoLog Mix 70/30 compared to other insulin products in the insulin aspart family must be done. [redacted]

[redacted] NPH may be used as one of the comparators for NovoLog Mix 70/30. Please see comments from Biopharm.
2--It may not be implied or stated that that X-14 70/30 has a more rapid onset of action than human insulin or human insulin mixtures. Its profile is likely to be similar to that of human insulin 50/50. A table comparing the PK-PD profiles of the insulin and analogue products would be helpful. Head-to-head comparisons would not be required. The product reference guide that was published in 1998 could be used as a template.
3--Even if distinctiveness of this insulin mixture is established, it cannot be inferred or stated that the insulin provides superior post-prandial glycemic control.
4--The methodology for determining the antibody levels in both the short-term and long-term studies should be delineated. How non-specific antibody binding is delineated from specific antibody binding and how total antibody levels are delineated from free antibody levels should be indicated.
5--Long-term safety data regarding the clinical significance of cross-reacting antibodies should be provided. Insulin dose and HgbA1c data should be included.

/S/ 10/2/03
Elizabeth Koller, M.D.
CC: HFD 510 DF/RheeJ/Koller

/S/ 10/2/03

APPEARS THIS WAY
ON ORIGINAL

EXECUTIVE SUMMARY: NDA #21172 Biphasic Insulin Aspart 70/30

Introduction

The sponsor has developed a fixed ratio insulin with an insulin aspart (X-14 or Novolog) component. Protamine was mixed with X-14 to prepare an insulin that would have a more rapid onset of action than 70/30 (70% NPH+30% human regular), one of the currently available fixed dose insulins. The sponsor indicates that such an insulin could be given immediately before meals (versus 30-45 minutes before meals).

Type of Data Submitted

The sponsor presented single-dose, cross-over, comparative pharmacokinetic-pharmcodynamic (PK-PD) data:

a—Studies 031 and 033—24 hour sampling of insulin in normal volunteers dosed with 70%IAP+30%X-14 versus 70%NPH+30%human regular insulin, and

b—Study 1086—Euglycemic clamp assessment of glucose utilization and insulin levels in normal volunteers dosed with 70%IAP+30%X-14 versus 100% X-14 in normal volunteers.

The sponsor presented some clinical data:

a—Study 038--Three month efficacy-safety data from a single, parallel-design trial (study 038) in patients with IDDM (n=102) or NIDDM (n=186) treated with 70%IAP+30%X-14 or 70%NPH+30%human regular.

Results

Biopharmaceutic Data

a--X-14 70/30 insulin mixture was pharmacokinetically distinct from human insulin 70/30 when an area-under-the-curve$(AUC)_{insulin\ (0\text{-}90\ min)}$ parameter was employed.

b--X-14 70/30 insulin mixture was pharmacodynamically distinct from human insulin 70/30 when an $AUC_{insulin\ (0\text{-}90\ min)}$ parameter was employed.

c--X-14 70/30 insulin mixture was pharmacokinetically distinct from X-14 when an $AUC_{insulin\ (0\text{-}90\ min)}$ parameter was employed.

d--X-14 70/30 insulin mixture was pharmacodynamically distinct from X-14 when an $AUC_{insulin\ (0\text{-}90\ min)}$ parameter was employed.

Comments

Biopharmaceutic Data

a--The PK-PD studies outlined above were done with formulations that differed from the to be marketed formulations. There were no bridging studies to ensure that the PK-PD profiles remained the same with all three formulations.

b--The range of X-14 permitted in the mixtures suggest that PK-PD profile may vary by as much as — from batch to batch.

c--The sponsor has carefully selected AUC time intervals that will highlight differences. The differences are less apparent when longer time intervals are used.

d—The sponsor has not shown that the PK-PD profile differs from that of human insulin 50/50.

e-- The sponsor has presented only select data, i.e., 2 arms, X-14 and X-14 70/30, from a 4-way cross-over study.

The 4-arm study did not include — or

NPH. Consequently, the sponsor has not shown that the X-14 70/30 mix is distinct from the most logical nearest comparators: [redacted] or X-14 50/50.

Results

Clinical Data-Glycemic Control

a--Glycemic control as measured by HgbA1c was less than optimal at baseline in the 3 month clinical study (Table 1). Mean values for both treatment groups exceeded 8%.

b--Glycemic control did not improve substantially during the clinical trial. The maximal decrease in HgbA1c was 0.2%.

c--There were no clinically significant differences between the treatment groups for HgbA1c at endpoint and the change in HgbA1c over the duration of the study whether an intent-to-treat or completer analysis was performed.

d--There were no gender differences for the change in HgbA1c over the duration of the study for patients with NIDDM. The same, however, cannot be said for patients with IDDM who were treated with X-14 70/30. The glucose control in the women deteriorated. The small size of this subgroup may contribute to this deviant observation.

e--The sponsor collected fasting and post-prandial glucose data. The latter included 90 minute post-prandial glucose levels, glucose excursions (the 90 minute post-prandial glucose minus the pre-prandial glucose level), the 90 minute post-prandial areas-under-the-curve (AUC) for glucose, and the mean glucose profiles (a composite of glucometer readings obtained before meals, 90 minutes after meals, at bedtime, and at 2 A.M). The meaning of these glucose parameters remains uncertain. No glucose measurements were made via a laboratory. They are all derived from glucometer readings collected by the patients in an unblinded fashion. Furthermore, the none of these glucose parameters correlated well with another well validated estimate of mean glucose exposure, HgbA1c.

Table 1

Mean Intent-to-treat Values for HgbA1c, Insulin Doses, and Cross-reacting Antibodies in Patients Who Had Values for All Parameters at Baseline and Study Exit*

Study 038 Treatment Group	HgbA1c (%)			Total Daily Dose (U/kg)			Cross-Reacting Antibodies+ (% Binding)		
	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta
X14-IDDM *n=48*	8.41	8.41	-0.002	0.638	**0.713**	**0.075**	11.71	**26.79**	**15.08**
HI-IDDM *n=45*	8.45	**8.28**	**-0.17**	0.619	0.628	0.009	12.26	12.66	0.40
	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=0.089	P=0.003	P=N.S.	P=0.001	P=5.4x10-6
X14-NIDDM *n=80*	8.08	**7.89**	**-0.20**	0.564	0.606	**0.042**	10.24	**18.98**	**8.74**
HI-NIDDM *n=95*	8.19	8.08	-0.11	0.578	**0.604**	0.026	9.28	9.69	0.41
	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=0.002	P=3.7x10-5

*Does not include the 3 patients who were treated with the wrong insulin: #26, 83, and 574. Analysis showed that exclusion of these patients did not substantively change the analysis.

+It is not known whether these values include non-specific antibodies.

X-14=X-14 70/30 HI=Human insulin 70/30

Comments

Clinical Data-Glycemic Control

a--The DCCT established that good glycemic control decreased the risk for long-term diabetic complications in patients with Type 1 diabetes mellitus. Intensive therapy with its multiple daily glucose assessments and pre-prandial and pre-bedtime adjustments of insulin via QID injections

or subcutaneous infusion has been associated with lower HgbA1c values and better clinical outcomes than conventional BID therapy. A similar improvement in diabetic complications was observed for patients with NIDDM and lower HgbA1c levels in the United Kingdom Prospective Diabetes Study. Some patients are unable or unwilling to use intensive therapy because of the number of insulin injections required, the complexities of pump use, and/or the number of glucose fingerstick checks. For convenience, these patients and their physicians may elect to pursue conventional therapy with BID dosing regimens with a rapid acting insulin is given in conjunction with a longer acting insulin e.g. NPH, lente, or ultralente at breakfast and with the evening meal in which the rapid acting insulin provides glycemic control for the meal immediately following and the longer acting insulin provides insulin coverage for the mid-day meal, the pre-bedtime snack, and the nocturnal interval. If patients mix their own insulin, the ratio of rapid acting insulin to longer acting insulin can be adjusted for anticipated meal size and physical activity although less precisely than with QID dosing or pump infusion. Pre-mixed insulins have a fixed ratio. This may be perceived as "easier" by patients, and it reduces potential contamination of the short acting insulin vial with protamine, a compound used to delay absorption. Fixed ratio insulins, however, are less flexible, particularly for patients with erratic schedules. They do not permit easy adjustment for the physiologic needs associated with two meal periods. Adjustment for one meal and exercise period frequently results in hyperglycemia/hypoglycemia with the other meal period. Most patients are unable to achieve tight glycemic control with BID insulin dosing, and this is accentuated in patients using fixed-ratio insulins. Indeed the HgbA1c data suggest that glycemic control was less than optimal—regardless of treatment mixture (Table 1). Although convenience may be further enhanced by immediate pre-meal (versus 30 minute pre-meal) dosing, it is not clear that these same results could not have been achieved by another insulin mixture already on the market human insulin 50/50.

b—Because the correlation coefficients for the various glucose parameters and HgbA1c values did not exceed 0.6., this suggests that these parameters lack clinical significance and/or that the self-collected glucose values were not accurate or representative of the true values for the parameters. difference for glucose exposure is relatively short. There may be insufficient time for pathologic glycosylation to occur-limiting the clinical significance of any rapid glucose lowering.

c--The sponsor cannot state or imply that the insulin will provide superior post-prandial glycemic control. Limited data suggest from 13 domiciled patients with NIDDM suggest that post-prandial glycemic control was actually better with human insulin 70/30 after lunch.

Results

Clinical Data-Insulin Dosing

a--Insulin doses were increased for all treatment groups, but did not account for all of the changes in glycemic control (Table 1).

b--The dose increase was greater for patients in the X-14 70/30 arms. Increased insulin doses (~1-6 U/day) may be required to achieve comparable glycemic control when the X-14 mixture is utilized. Similar increased dose needs were observed with X-14 in the original NDA.

Results

Clinical Data-Hypoglycemia

a--Hypoglycemia rates also appear to be similar for X-14 70/30 and human insulin 70/30 mixtures. Curiously, the rates of hypoglycemia appear to exceed those predicted by the Diabetes Control and Complications Trial (DCCT).

b--The timing of hypoglycemic events appeared to be similar—regardless of whether an X-14 mixture or a comparable human insulin mixture was employed.

Comments

Clinical Data-Hypoglycemia

a--These higher rates may reflect the limitations of a BID dosing regimen with any fixed insulin combination or a higher degree of reporting in this study than in the DCCT.

Results

Clinical Data-Cross-reacting Antibodies and Antigenicity

a--Cross-reacting antibody levels appeared to be higher with the X-14 70/30 product than with human insulin 70/30 product (Table 1). These differences were apparent despite the parallel design that was employed. The antibody findings are consistent with that of the original NDA for X-14 insulin.

Comments

Clinical Data-Cross-reacting Antibodies and Antigenicity

a--It is known that cross-reacting antibody levels may increase over time and that protamine and insulin analogues are antigenic. The sponsor did not submit raw data from the extension study. They intend to submit data in 2001. This limits the kind of conclusions that can currently be made regarding long-term exposure.

b--The significance of cross-reacting insulin antibodies remains uncertain. In the controlled portion of the registration trial, most patients had low levels of cross-reacting antibodies. More patients treated with X-14 70/30 had higher levels of cross-reacting antibodies than patients treated with human insulin 70/30, but the number of patients with higher antibody levels was not limited to isolated outliers. Most importantly, patients with increases in antibody binding did not clearly have increased insulin needs to achieve comparable glycemic control.

Other Comments

a--Inferences about PK-PD activity likely will be made by clinicians who read the composition section of any label and or the drug name itself. The sponsor must have the data to support these inferences.

b--The label should include a table that outlines the PK-PD profiles of the various insulins available from NovoNordisk. This will enable clinicians to better select the appropriate insulin for their individual patients. NovoNordisk already has such a product reference guide in print.

c--The addition of new mixtures to the widening array of insulin products potentially increases the risk for errors in dispensing and self-administration. The development of a self-explanatory label, unique packaging, and an educational program for professionals and patients would reduce although not eliminate problems.

RECOMMENDATION: APPROVABLE WITH THE SATISFACTORY COMPLETION OF STUDIES TO SHOW THE DISTINCTIVENESS OF X-14 70/30 COMPARED TO OTHER INSULIN PRODUCTS AND WITH CHANGES IN THE LABEL AS WELL AS WITH THE SUBMISSION OF ADEQUATE LONG-TERM ANTIBODY DATA ACCOMPANIED BY HGBA1c AND INSULIN DOSE DATA.

1. Medical Officer Review
1.1. Administrative Summary
1.1.1. NDA: #21172
1.1.2. Review: #1
1.1.3. Submissions
1.1.3.1. Paper submission: 12/17/99
1.1.3.2. CANDA submission: none
1.1.3.3. Major amendment: none
1.1.3.4. Other submissions: 1/5/00 BI
1/24/00 BM
3/28/00 BM
4/7/00 BM
4/13/00 SU
5/12/00 BM
6/21/00 BM
7/6/00 BM
7/19/00 BC
8/4/00 BZ
8/27/00
8/29/00 SU+other major biopharm data (9/5/00 FAX)
1.1.3.5. Review completed: 8/28/00
1.2. Drug Name
1.2.1. Generic names: 30% Insulin Aspart and — % Insulin Aspart Protamine
1.2.2. Proposed trade names: [redacted] 70/30
1.3. Sponsor: NovoNordisk
1.4. Pharmacologic category: diabetic; insulin analogue
1.5. Proposed indications: Dosing BID
1.6. Dosage form and route of administration:
1.6.1. Dosage form: vials for injection, pre-filled syringes, and cartridges for use in specified pens.
1.6.2. Dosage: to be titrated
1.6.3. Route of administration: Subcutaneous
1.7. NDA drug classification: Standard
1.8. Important related drugs: human insulin (semi-synthetic and recombinant), animal insulins, insulin analogues, and insulin-like growth factor
1.9. Related reviews: #20986 original review
1.9. Materials reviewed:
Pre-IND package 3/10/00
IND # [redacted]
NDA #21172 1-3, 29, 32-34, 41-45
Safety update: 4/13/00
Submissions: 1/24/00
3/28/00
4/7/00
5/12/00
6/21/00
7/6/00
8/4/00
8/24/00

8/29/00 SU+other major biopharm data (9/5/00 FAX)

1.10. Table of contents

2.--Introduction

The Diabetes Control and Complications Trial (DCCT) established that good glycemic control decreased the risk for long-term diabetic complications in patients with Type 1 diabetes mellitus. Intensive therapy was associated with lower HgbA1c values and better clinical outcomes than conventional therapy. Typically, intensive therapy involves pre-prandial dosing with a more rapid acting insulin in conjunction with a longer acting insulin to provide a basal level of control throughout the day. Four or more injections are required daily. Alternatively, patients utilize subcutaneous insulin infusions delivered by pump. A basal rate is based on the anticipated activity level. Insulin boluses are given to cover food consumption. Additional insulin is given in the event of unexpected hyperglycemia. Conversely, insulin rates/injection doses are reduced in the event of hypoglycemia.

Intensive therapy requires frequent monitoring of blood glucose. Fingerstick sampling is typically performed between four and six times per day. Some patients are unable or unwilling to use intensive therapy because of the number of insulin injections required, the complexities of pump use, and/or the number of glucose fingerstick checks. Unfortunately, tight glycemic control is also associated with increased risk of hypoglycemia. These patients and their physicians may elect to pursue conventional therapy with BID dosing regimens instead. Typically a rapid acting insulin is given in conjunction with a longer acting insulin e.g. NPH, lente, or ultralente at breakfast and with the evening meal. In other words, the rapid acting insulin provides glycemic control for the meal immediately following. The longer acting insulin provides insulin coverage for the mid-day meal, the pre-bedtime snack, and the nocturnal interval. If patients mix their own insulin, the ratio of rapid acting insulin to longer acting insulin can be adjusted for anticipated meal size and physical activity. Pre-mixed insulins have a fixed ratio. This may be perceived as "easier" by patients, and it reduces potential contamination of the short acting insulin vial with protamine, a compound used to delay absorption. Fixed-ratio insulins, however, are less flexible, particularly for patients with erratic schedules. They do not permit easy adjustment for the physiologic needs associated with two meal periods. Adjustment for one meal and exercise period frequently results in hyperglycemia/hypoglycemia with the other meal period. Most patients are unable to achieve tight glycemic control with BID insulin dosing and this is accentuated in patients using fixed-ratio insulins.

The development of pre-mixed insulins incorporating the rapid acting insulin analogue, insulin aspart/X-14/Novolog,

[ ]

[redacted] Insulin Aspart Protamine (IAP). Protamine was mixed with X-14 to prepare a fixed ratio insulin that would have a more rapid onset of action than 70/30 (70% NPH+30% human regular), one of the currently available fixed dose insulins (although the rapidity of onset may be similar to that of 50% NPH+50% human regular). This insulin could be given immediately before meals (versus 30-45 minutes before meals). [redacted]

The sponsor has presented comparative PK-PD data from 70%IAP+30%X-14 vs 70%NPH+30%human regular insulin and 70%IAP+30%X-14 vs 100% X-14 as well as three month efficacy/safety data from a single trial, study 038, in patients with IDDM or NIDDM. The sponsor did not present comparative data with their other biphasic insulins, nor did they present comparative data distinguishing 70%IAP+30%X-14 from NPH or [redacted] or 50% human insulin NPH+50% regular insulin. Because protamine and insulin analogues are antigenic, sponsors have been encouraged to provide long-term data on the magnitude and clinical significance of such antigenicity. The sponsor provided antibody, insulin dose, glycemic control, and allergic reaction data for the three month trial. Limited interim data from the extension trial, study 067, were presented, but the raw data were not available for review.

3.--Prior Agreements

In lieu of extensive clinical testing, the sponsor was requested to provide:
a--pharmacokinetic and pharmacodynamic studies that would demonstrate that each mixture was distinct from the other X-14 mixtures and from X-14 as well as NPH (or [redacted],
b--labeling that would show the how the X-14 products compared to one another on a pharmacokinetic-pharmacodynamic (PK-PD) basis,
c--labeling that would show how the X-14 products compared to human insulin products on a PK-PD basis, (Head-to-head comparison studies would not be required.)
d—and multi-year studies to assess long-term changes in the levels of cross-reacting antibodies and the effect of these antibodies on the doses of insulin required to maintain comparable levels of glycemic control as measured by HgbA1c.

On 2/19/99 Ms. T. Marion and Dr. McElligott were contacted to discuss the importance of doing studies that would show the PK-PD profile of any X-14 insulin mixture with other insulins in the X-14 family and with its counterpart in the human insulin family. [redacted], was also discussed. The sponsor was requested to provide data showing the distinctiveness of X-14 70/30 from other X-14 products by May, 2000 for consideration in this review cycle. The sponsor submitted interim data from two arms of a four-arm study (1086). Reformatting of the data were requested. The CD-ROMs received were unreadable. Replacement data had not been received at the time of this review, but were added 9/8/00.

4.--Objectives

The sponsor has sought to show that:
a--the PK-PD profile of X-14 70/30 mix is distinct from human insulin 70/30 and
b--there were no major differences in glycemic control for patients treated with X-14 mixtures vs human insulin mixtures.

5.--CANDA

There was no CANDA submission. Additional data were provided on EXCEL spread sheets. (The data on the spread sheets were not corrected for incorrect treatment administration after randomization.)

6.—Financial disclosure

Dr. Anders Lindholm has indicated that there are no financial interests to disclose. At the time of this review, such disclosure was not provided for the subsequently submitted cross-over study (#1086).

7.—Pediatric waiver

The sponsor was previously granted a pediatric waiver because most pediatric patients with diabetes, especially those who are prepubescent, are Type 1 patients. Fixed ratio and BID dosing cannot provide the tight control needed to avoid the long-term complications of diabetes. Even in post-pubertal patients with diabetes primarily linked to childhood obesity, tight control is likely to be important because of the expected long duration of disease. Such BID dosing regimens with fixed ratios are unlikely to provide tight control and minimize insulin-hunger that could foster progressive obesity.

8--Chemistry issues

Recombinant X-14 insulin analogue is produced in Saccharomyces cerevisiae using DNA technology is similar to that employed by the sponsor for the production of other insulin products. Insulin Aspart Protamine is produced by adding protamine (approximately 0.33 mg/ml) to an X-14 — insulin, not by [redacted] The specifications for the biphasic 70/30 mix permit the soluble component to range from [redacted] % at expiry. Mannitol was added to a final concentration of 36.4 mg/ml. Sodium chloride was added to a final concentration of 0.58 mg/ml. Zinc [redacted], was added to a final concentration of 32.7 ug/ml. Phenol and meta-cresol concentrations were 1.50 mg/ml and 1.72 mg/ml respectively. The suspension is then [redacted] to a final pH of 7.20 to 7.44. The pre-filled — (3 ml), cartridges (3 ml), and vials (10 ml) are filled with pre-mixed suspensions prepared in this way. The sponsor intends to eliminate [redacted] from its closures to reduce potential allergic responses. [redacted] Stability studies were not complete at the time of NDA submission.

The formulation was changed during development (Table 1). [redacted]

Table 1
Insulin Formulations Used in Studies

Ingredients	Composition 1 Phase I clinical trial: 031 (Formulation manufactured until [redacted]	Composition 2 Phase I clinical trial: 033 (Formulation manufactured until [redacted]	Composition 3 Phase I-III clinical trials: ?032, 038, 046, 1086 (Formulation manufactured until [redacted]
insulin aspart	[redacted] (100 U/ml)	[redacted] (100 U/ml)	[redacted] (100 U/ml)
[redacted]	[redacted]	[redacted]	[redacted]
Mannitol	[redacted]	[redacted]	[redacted] (36.4 mg/ml)
Phenol	[redacted] (1.50 mg/ml)	[redacted] (1.50 mg/ml)	[redacted] (1.50 mg/ml)
m-cresol	[redacted] (1.72 mg/ml)	[redacted] (1.72 mg/ml)	[redacted] (1.72 mg/ml)
zinc [redacted]	32.7 ug/ml	32.7 ug/ml	32.7 ug/ml
NaCl	[redacted]	[redacted] (0.58 mg/ml)	[redacted] (0.58 mg/ml)
disodium hydrogen phosphate, dihydrate	[redacted]	[redacted] (1.25 mg.ml)	[redacted] (1.25 mg.ml)
protamine sulphate	~0.33 mg/ml	~0.33 mg/ml	~0.33 mg/ml
PH	7.3	7.3	7.3

9.--Pre-clinical Issues
The sponsor conducted a single-dose, placebo controlled, toxicology study in 80 rats dosed with up to 2000 U/kg of aged and fresh X-14 70/30. Human insulin 70/30 was not used as a comparator. Reportedly there was decreased motor activity and piloerection in animals from the higher dose groups.

Local toxicity studies using the preparations used in the phase 3 studies were not conducted.

Immunogenicity studies conducted in rabbits suggest that X-14 and NPH are more antigenic than human insulin70/30 mixture (Table 2).

Table 2
Immunologic Responses in Rabbits Given Various Insulin Preparations

	X-14 70/30 (fresh)	X-14 70/30 (old)	human insulin 70/30 (fresh)	human insulin 70/30 (old)	NPH	ultralente
# w/o detectable immunogenic response	3	1	7	7	5	0*

#=number There were 5/group/sex
w/o=without
*There was one rabbit death in the study; it occurred in the ultralente group.

The sponsor conducted a single-dose, PK study in rats; n=36 male, n=36 female. The low doses of X-14 70/30 were 4.3 U/kg and 3.1 U/kg respectively in females and males. The

high doses were 8.3 U/kg and 6.1 U/kg in females and males respectively. The sponsor reported linear kinetics (p188).

The sponsor conducted a single-dose, cross-over, PK-PD study in fasted (until 6 hr post dosing), non-diabetic pigs using 0.15 U/kg of human regular insulin and X-14 70/30 pH 7.2 and X-14 70/30 pH 7.4, n=8. (Pig skin is relatively similar to human skin so pigs are good models to assess absorption profiles.) Reportedly the X-14 70/30 mixtures lowered insulin more promptly than human regular insulin, and the pH did not alter the PK results significantly for the two X-14 70/30 mixtures. The insulin t1/2 values were 174 minutes, 93 minutes, and 82 minutes for human insulin 70/30, X-14 70/30 (pH 7.4), and X-14 70/30 (pH 7.2) respectively. Reportedly the X-14 70/30 mixtures lowered glucose more promptly than human regular insulin, and the pH did not alter the PD results significantly for the two X-14 70/30 mixtures. Reportedly the glucose levels with the pH 7.2 version differed statistically from the glucose levels with regular insulin 20 to 105 minutes post dosing, and the glucose levels with the pH 7.4 preparation differed from regular insulin 50 to 90 minutes post dosing. The glucose profiles for the two X-14 compounds were not appreciably different. This was followed by another cross-over study in eight pigs using a single dose of 0.15 U/kg using two formulation of X-14 70/30, pH 7.2 vs 7.6. There were some differences. Cmax was higher (459 vs 251 pM), tmax shorter (30 vs 45 max), and t1/2 (91 vs 105 min) shorter for the formulation with the pH of 7.2 than the pH of 7.6. This was followed by yet another PD study in eight, non-diabetic pigs using 0.2 U/kg of human insulin 70/30 and X-14 70/30 pH 7.1 and X-14 70/30 pH 7.4. The mean glucose lowering 30 minutes post injection was -14 mg/dl, -26 mg/dl, and +4.5 mg/dl for X-14 70/30 pH 7.1 and X-14 70/30 pH 7.4 respectively. Although the interpretation of both the PK and PD data from these studies may be limited by the secretion of endogenous insulin, the sponsor concluded that the pH range for the insulin product should be limited to 7.2 to 7.4.

A 5-way cross-over PK-PD study was conducted in eight pigs dosed using 0.15 U/kg of X-14, X-14 30/70, X-14 50/50, X-14 70/30, and [redacted] The data suggest that there are glucodynamic differences between [redacted] and the X-14 mixtures, as well as X-14. The glucodynamic differences between the mixtures and the differences from X-14, however, are less clear (p187, Figure 1).

10.--Pharmacokinetic-Pharmacodynamic Issues

10.1. Formulation changes

The formulation was changed during development (Table 1). [redacted] PK-PD bridging studies comparing the various formulations were not conducted.

10.2. Protamine changes

Studies to assess the inter-changeability of protamine as long and thin crystals and protamine as short and broad crystals were done (Study 032). The study showed that the crystal forms are interchangeable.

10.3. Pre-mixing vs self-mixing

The sponsor did not do any studies to show that self-mixed combinations of X-14 70/30 was pharmacokinetically similar to the same insulin combination when given as a pre-mixture.

10.4. Comparative studies

10.4.1. X-14 70/30 vs human insulin 70/30

In a single-dose, crossover study in fasted, normal volunteers (031; n=23, formulation #1) dosed with X-14 70/30 and human insulin 70/30, the ratio of the respective AUC $_{\text{insulin (0-90 min)}}$ values was 1.86; $p<0.0001$, the ratio of the respective C_{max} values was 1.51; $p<0.001$, and the difference of the respective t_{max} values was –60.0; $p<0.001$. In a single-dose crossover clamp study in fasted normal volunteers (033; n=32, formulation #2) dosed with X-14 70/30 and human insulin 70/30, the ratio of the respective AUC $_{\text{insulin (0-90 min)}}$ values was 2.24; $p<0.0001$, the ratio of the respective C_{max} values was 2.02; $p<0.001$, and the difference of the respective t_{max} values was –95.0; $p<0.001$ (Tables 3-8). Between-product differences exceeded 20%--suggesting that the PK profiles of these two insulin preparations from different insulin families could be distinguished from one another when given as a single injection.

10.4.2. X-14 70/30 vs X-14

In a single-dose, 4-arm crossover clamp study in fasted normal volunteers (study 1086; 34 received X-14 70/30, 33 received X-14; formulation #3) dosed with X-14 70/30 and X-14, the ratio of the respective AUC $_{\text{insulin (0-120 min)}}$ values was 0.409 ($p<0.001$), the ratio of the respective C_{max} values was 0.454 ($p<0.001$), and the difference of the respective t_{max} values was 0.13 hours ($p=0.295$). Between-product differences exceeded 20% (Tables 3, 4, 9-12).

Table 3

Comparisons of Pharmacokinetic Parameter Ratios of Insulins Using Log Transformed Data (Data from Dr. Sun)

Pharmacokinetic Parameter	Study	Insulin Pair	Mean Ratio	90% Confidence Interval
AUC-insulin(0-t)	031	X-14 70/30 vs HI 70/30	1.048	0.968—1.135
	033	X-14 70/30 vs HI 70/30	1.158	1.08—1.24
	1086	X-14 70/30 vs X-14	0.58	0.546—0.630
	1086	X-14 70/30 vs X-14 50/50	NA	NA
	NA	X-14 70/30 vs —	NA	NA
AUC-insulin(0-6 hr)	031	X-14 70/30 vs HI 70/30	1.231	1.144—1.325
	033	X-14 70/30 vs HI 70/30	1.608	1.468—1.760
	1086	X-14 70/30 vs X-14	0.485	0.446—0.526
	1086	X-14 70/30 vs X-14 50/50	NA	NA
	NA	X-14 70/30 vs —	NA	NA
Cmax-insulin	031	X-14 70/30 vs HI 70/30	1.512	1.375—1.662
	033	X-14 70/30 vs HI 70/30	2.02	1.798—2.270
	1086	X-14 70/30 vs X-14	0.38	0.336—0.433
	1086	X-14 70/30 vs X-14 50/50	NA	NA
	NA	X-14 70/30 vs —	NA	NA

AUC=area-under-the-curve

HI=human insulin

NA=not available