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APPLICATION NUMBER:

21-810

SUMMARY REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

DIVISION DIRECTOR'S MEMO

NDA:	21-809 and 21-810
Product name:	Novolog Mix 30/70 (30% insulin aspart protamine suspension and 70% insulin aspart injection) (NDA 21-809) Novolog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection) (NDA 21-810)
Sponsor:	Novo Nordisk
Date of Resubmission:	August 31, 2006 (letter date)
Reviewers:	Joanna Zawadzki, M.D. Xiaoxiong Wei, Ph.D.

BACKGROUND

These two NDAs were reviewed together as the original submission contained one pivotal PK/PD study in healthy volunteers, Study BIAsp 1086. This study was the primary focus of the clinical pharmacology and medical reviews and was the basis for not-approval of both applications. In Study BIAsp 1086, four different formulations of Novolog® (IAsp, BIAsp 70, BIAsp 50, and BIAsp 30) were studied in a healthy volunteer population. Using a euglycemic clamp procedure, the pharmacokinetics (pK) and pharmacodynamics (PD) of these different formulations, administered as a single 0.3 mg/kg subcutaneous injection, were assessed over a 24 hr period.

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Study 1746

As noted above, this study report was received on May 9, 2007, in response to lingering concerns regarding the approvability of BIAsp 50 and BIAsp 70. This study was reviewed by Dr. Jim Wei from the Office of Clinical Pharmacology. Please see his review dated June 15, 2007 for details of the trial design, conduct, and findings. Briefly, this was a double-blind, randomized, 4-period crossover study in type 1 diabetics with the primary objective of comparing the early PD (as GIR) of 0.4 U/kg of BIAsp 30, 0.4 U/kg BIAsp 50, 0.4 U/kg BIAsp 70, and 0.4 U/kg IAsp. Secondary objectives included comparison of PK across the different formulations.

As stated in Dr. Wei's review, the enrollment of type 1 diabetics over healthy volunteers might correct for any effect endogenous insulin production may have on the PK/PD assessments. This study did not measure insulin antibodies but the trial did not include any diabetic who had previously been treated with insulin aspart.

Pharmacodynamics

The PD parameter of interest identified by the applicant was the $AUC_{GIR,0\text{-}2hr}$ which would assess the early time points of insulin action. For the 4 products, greater bioavailability of insulin in the early period

should reflect the formulation with the most IAsp (IAsp>BIAsp70>BIAsp50>BIAsp30) which would translate into a higher glucose infusion rate (more glucose needed to counter the amount of insulin available to maintain euglycemia). The following tables from Dr. Wei's review summarizes the primary efficacy endpoint and comparison between two adjacent insulin products within the product line.

Table 1. Area under the GIR curve during the first 2 hours after s.c. injection of trial products ($AUC_{GIR,\ 0\text{-}2\ hr}$) in trial 1746 (from Table 14.2-8)

	IAsp	BIAsp 70	BIAsp 50	BIAsp 30
N	31	31	31	31
Mean (SD)	540	429	376	247

Table 2. ANOVA Comparison of ($AUC_{GIR,\ 0\text{-}2\ hr}$)

	IAsp vs BIAsp 70	BIAsp 70 vs BIAsp 50	BIAsp 50 vs BIAsp 30	BIAsp 70 vs BIAsp 30
Mean ratio	1.26	1.14	1.52	1.74
95% CI	1.08; 1.47	0.98; 1.33	1.31; 1.78	1.49; 2.03
P value	0.0038	0.0933	<0.001	<0.001

As expected, a higher GIR is observed in the first 2 hrs post injection for IAsp>BIAsp70>BIAsp50>BIAsp30. However, there was no statistically significant difference in the early PD assessment between the two formulations proposed for marketing, BIAsp70 and BIAsp50. These two products had a 14% difference in $AUC_{GIR,\ 0\text{-}2hr}$ that was not significant (p=0.09).

IAsp had a 45% greater $AUC_{GIR,\ 0\text{-}2hr}$ than BIAsp50. BIAsp50 had a 52% greater $AUC_{GIR,\ 0\text{-}2hr}$ than BIAsp30 that was significant (p<0.001).

$AUC_{GIR,\ 4\text{-}12hr}$ was also calculated to evaluate the intermediate time-action profile reflecting more the protaminated portion of the formulations. In this setting one would expect the converse of $AUC_{GIR,\ 0\text{-}2hr}$ with a higher GIR with BIAsp30>BIAsp50>BIAsp70>IAsp. From Table 3 in Dr. Wei's review there is evidence of this relationship and the following mean values and ratios are observed.

Table 3. PD Assessment At Intermediate Time Point of 4-12 hrs

	Mean $AUC_{GIR,\ 4\text{-}122hr}$	IAsp/BIAsp70	BIAsp70/BIAsp50	BIAsp50/BIAsp30	BIAsp70/BIAsp30
IAsp	543				
BIAsp70	876	0.62			
BIAsp50	846		1.04		
BIAsp30	1029			0.82	0.85

There is a 38% difference in GIR at the intermediate time period between IAsp and BIAsp 70 and an 18% difference between BIAsp50 and BIAsp30. There is essentially no difference in the intermediate PD profile between the two formulations proposed for marketing, BIAsp70 and BIAsp50. Dr. Wei has commented on the paradoxical finding of a 15% PD difference between BIAsp70 and BIAsp30 versus an 18% PD difference between BIAsp50 and BIAsp30. I believe this finding more likely reflects the inability to demonstrate an adequate distinction between the BIAsp70 and BIAsp50 and that this 3% difference in the ratios may represent test variability more than product variability.

Not presented in Dr. Wei's table was the comparison of $AUC_{GIR, 4\text{-}12hrs}$ between IAsp and BIAsp50. The ratio of the mean would be 0.64, representing a 36% difference in GIR between the IAsp and BIAsp50 formulations at the intermediate time point.

In conclusion, the PD assessment failed to show a distinction in the early and intermediate time points between BIAsp70 and BIAsp50. However, a PD distinction in both time points (0-2 and 4-12hrs) was observed for the IAsp vs BIAsp50 vs BIAsp30. A similar statement can be made for the comparison of IAsp vs BIAsp70 vs BIAsp30; however, for additional concerns that I will discuss below, I do not believe that BIAsp70 should be approved.

Pharmacokinetics

Cmax of insulin Aspart was measured for each of the four formulations. For this parameter, all four formulations had distinct profiles as summarized in the following tables from Dr. Wei's review.

Table 4. Cmax for serum IAsp and BIAsp preparations (mU/L)

	IAsp	BIAsp 70	BIAsp 50	BIAsp 30
N	31	31	31	31
Mean	191	141	94	63

Table 5. ANOVA Comparison on Cmax

	IAsp / BIAsp 70	BIAsp 70 / BIAsp 50	BIAsp 50 / BIAsp 30	BIAsp 70 / BIAsp 30
Mean ratio	1.35	1.51	1.49	2.25
95% C.I.	1.22; 1.50	1.36; 1.67	1.34; 1.65	2.03; 2.49
P value	<0.001	<0.001	<0.001	<0.001

Similar to previous studies, Study 1746 demonstrated a decreased bioavailability of insulin aspart levels with increasing amounts of protamine. The PK differences at intermediate time points were also less as summarized in the following table.

Table 4. PK Assessment at Intermediate Time Point of 4 to 12 hrs

	AUC $IAsp_{4\text{-}12hr}$	IAsp/BIAsp70	BIAsp70/BIAsp50	BIAsp50/BIAsp30	BIAsp70/BIAsp30
IAsp	90				
BIAsp70	142	0.63			
BIAsp50	136		1.04		
BIAsp30	150			0.91	0.95

The PK difference between IAsp and BIAsp70 was 37% but decreased with comparison of BIAsp70 to BIAsp50 (4%), BIAsp50 to BIAsp30 (9%), and BIAsp70 to BIAsp30 (5%). The PK difference between IAsp and BIAsp50 was 34%.

In conclusion, this study demonstrated sufficient PK differences among the 4 different formulations for the early time point. At intermediate stages, the distinction was only evident between IAsp and BIAsp70. In considering approval of only BIAsp50 of the two products proposed in NDA 21-809 and 21-810, there is obvious distinction in PK profile between IAsp and BIAsp50. The difference between BIAsp50 and the next adjacent formulation, BIAsp30, within the product line is modest at 9% and may reflect the reduced bioavailability with higher protamine concentrations in the BIAsp30 formulation.

Comments on Primary Medical Officer's Review

Dr. Zawadzki has recommended that this NDA not be approved. I do not concur with her recommendation and I have presented my argument throughout this memo that from a clinical perspective the BIAsp 50 formulation can be approved and labeling negotiations can proceed. During labeling negotiations with the firm, Dr. Zawadzki raised other objections to the approval of this supplement. One of these included a concern raised at a September 2007 meeting regarding reports of hypoglycemia and death in this NDA. Information was requested of the company regarding these reports to which they informed the FDA that these data were submitted with the original NDA. The company resubmitted these data and I noted that none of the hypoglycemic events occurred with the BIAsp50-treated patients. There were two deaths reported in this NDA. One death was due to B-cell lymphoma and one was a cardiac arrest. In review of the case report for the latter death I noted that paramedics reported the blood glucose level and that it was normal. Consequently, I do not believe these safety concerns are substantiated based on the data submitted and reviewed here.

DMETS/DSCRS Reviews

The Division of Medication Errors and Technical Support provided a review of carton and container labeling changes proposed submitted as part of an annual report. Their review (see DFS document dated February 2, 2008) outlined several deficiencies which were submitted to the company by email on February 22, 2008.

A. General Comments
1. Change the color of NovoLog Mix 50/50 to a more contrasting color to differentiate from the other NovoLog products (for both FlexPen and PenFill labels).
2. Increase the prominence of the differentiating color on PenFill labels to clearly distinguish from other NovoLog products.
3. We recommend "New Product Strength" appear on product labels and labeling for a period of time not to exceed six months.

B. FlexPen Container (Retail and Sample)
Revise the strength to include "(U-100)" [i.e. 100 units/mL (U-100)].

C. PenFill Carton (Retail and Sample)
Increase the prominence of the secondary expression of strength, "100 units/mL (U-100)".

On March 3, 2008, the company responded to these requests committing to make all the changes except A1. The company argued that the currently marketed NovoLog Mix 50/50 in Europe contains the same color scheme as proposed for the U.S. product and would have "global implications". The company also responded to request regarding postmarketing AEs from the European marketing experience. NovoLog Mix 50/50 has been marketed since May 1, 2007. From that time point until March 2008, the company reports no AEs related to medication errors with other NN insulin products.

I have read the DMETS review. I note that they make a valid argument regarding the similar shade of color (blue) between the two NovoLog mixtures. The marketing period in Europe is not of a sufficient duration to adequately argue no risk or minimal risk of medication errors. As this product is viewed more as a convenience product since patients can individually mix long-acting and short-acting insulins of the Novo Nordisk product line, I concur with DMETS that prior to U.S. approval, the color scheme for NovoLog Mix 50/50 should be changed to be more distinct from NovoLog mix 70/30.

CONCLUSIONS

The applicant is proposing for marketing two Novolog mixtures to complement the currently available products, Novolog and Novolog 70/30 mix. These two products contain insulin aspart with different proportions of protamine to produce one formulation that has predominantly short-acting activity (BIAsp70) and one that has equal proportions of short and long-acting activity (BIAsp50). In the original NDA for these products, b(4)

In the resubmission, the applicant provided two different studies, one evaluating PD and one evaluating PK differences between BIAsp70 and BIAsp30. Both these studies suggested a difference between the two formulations; however, there were no comparative data with BIAsp50.

Study 1746 was a euglycemic study in type 1 diabetics and included the full product line proposed for marketing. In this study, there was no PD distinction between the two new formulations, BIAsp50 and BIAsp70. However, satisfactory distinctions can be observed if the applicant were to propose marketing of either IAsp, BIAsp70, BIAsp30 **OR** IAsp, BIAsp50, BIAsp30. Given these two choices, I would argue that the availability of BIAsp70 and BIAsp30 may result in medication errors as pharmacist, clinicians, or patients may confuse between a 70/30 and 30/70 mixture, an error that can result in a serious clinical AE. Furthermore, the availability of a BIAsp50 product may be more relevant to clinical dosing as it is unusual to require more short-acting insulin than long-acting insulin afforded with the BIAsp70 formulation. However, it should be noted that the BIAsp50 formulation does have a modest PD difference at the intermediate time point of 18% and a PK difference of 9%, relative to the currently marketed Novolog 70/30 mix, which must be reflected in labeling. Table 5, below, also summarizes the PK/PD distinctiveness between the IAsp and BIAsp50 formulations at both the early and intermediate time points.

I believe that the availability of BIAsp50 can be safely labeled to provide, within this product line of insulin mixtures, a formulation for patients who might require more short-acting insulin than provided with the marketed BIAsp30. Since insulin regimens are highly individualized with factors such as diet, timing of meals, exercise, or episodes of hypo/hyperglycemia often dictating dosing, careful assessment of several daily blood glucose readings throughout the day might help select which patient will respond better to BIAsp50. From the early 0-2 hr time points, there is significant pK and PD distinction between these two products but the label should emphasize that glycemic control at later time periods are less distinct.

The applicant has suggested that the differences in findings between Study 1086 and Study 1746 reflected two different populations: healthy versus type 1 diabetics. A higher dose of insulin used in Study 1746 may also result in a greater chance at observing PK/PD differences. It is also important to note that Study 1086 has several deficiencies noted by DSI that were considered relevant to determination of efficacy. While deficiencies were also summarized for Study 1746, Dr. Wei has considered these and found that data from this study can still be relied upon.

Table 5. PK and PD parameter ratios of IAsp vs. BIAsp50

Pharmacokinetics				
Product	**[a]Mean AUC $_{0\text{-}2h}$**	**[b]Ratio (IAsp/BIAsp 50)**	**95% CI**	**90% CI**
IAsp	284.93	2.00	180.96;	184.05;
BIAsp 50	134.03		221.08	217.37
	[a]Mean AUC$_{4\text{-}12h}$	**[b]Ratio (IAsp/BIAsp 50)**	**95% CI**	**90% CI**
IAsp	112.97	0.63	51.57;	53.35;
BIAsp 50	161.19		76.95	74.40
Pharmacodynamics				
Product	**[a]Mean AUC GIR $_{0\text{-}2h}$**	**[b]Ratio (IAsp/BIAsp 50)**	**95% CI**	**90% CI**
IAsp	573.75	1.45	127.52;	130.44;
BIAsp 50	403.38		166.69	162.96
	[a]Mean AUC GIR $_{4\text{-}12h}$	**[b]Ratio (IAsp/BIAsp 50)**	**95% CI**	**90% CI**
IAsp	671.34	0.64	50.14;	52.3;
BIAsp 50	968.84		82.68	79.26

[a] Mathematic mean
[b] Ratios are calculated from WinNonlin using LnAUC data.

The applicant has been informed of the decision to not approve BIAsp70 (NovoLog mix 30/70) and has submitted a letter stating its intent to withdraw this application. The agency has acknowledge this letter and conveyed deficiencies of NDA 21-809 to the applicant as follows:

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2. [redacted] b(4)

From a clinical perspective, NDA 21-810 for NovoLog Mix 50/50 can be approved. Labeling from clinical, CMC, and Clinical Pharmacology disciplines have been deemed acceptable. However, given DMETS concerns for medication errors regarding the recent change to the carton and container labels, I concur that this application is approvable until the applicant changes the color scheme of NovoLog Mix 50/50 to be more distinct from the currently marketed NovoLog Mix 70/30.

Appendix

PD in early time period

Study 1086

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Study 1746

Table 1. Area under the GIR curve during the first 2 hours after s.c. injection of trial products ($AUC_{GIR,\ 0\text{-}2\ hr}$) in trial 1746 (from Table 14.2-8)

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P value	0.0038	0.0933	<0.001	<0.001

PD in intermediate time period
Study 1086

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Study 1746

$AUC_{GIR, 4\text{-}12\ hr}$ (mg/kg)								
N	31	31	31	31				
mean	543	876	846	1029				
ratio					0.62	1.04	0.82	0.85

PK in early time period
Study 1086

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Study 1746

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PK in intermediate time period
Study 1086

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