CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208751Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval
(Including the Facility Review/Manufacturing Inspection Recommendation)

NDA 208751
Review 2
Review Date: 8/17/17

Drug Name/Dosage Form	Insulin aspart injection/Solution for injection
Trade Name	Fiasp® (10mL vial presentation); Fiasp FlexTouch (3 mL prefilled pen)
Strength	100 units/mL (U-100)
Route of Administration	Subcutaneous or intravenous injection
Rx/OTC Dispensed	Rx
Applicant	Novo Nordisk
Indication	Mealtime insulin.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and Amendments *Resubmission*	*12/08/15, 3/10/16, 6/09/16, and 8/05/16* *8/16/17*	*Quality (Module 3.2.P.3 and 1.1)*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	N/A
Drug Product	Muthukumar Ramaswamy	New Drug Products II/ONDP
Process	Erin Kim	Process Assessment/OPF
Microbiology	Koushik Paul	Microbiology Assessment/OPF
Facility	Juandria Williams	Inspectional Assessment/OPF
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management/OPRO
Application Technical Lead	Muthukumar Ramaswamy	New Drug Products II/ONDP
Facility	Crystal Lewis	CDRH Compliance
ORA Lead	N/A	N/A
Environmental Analysis (EA)	Muthukumar Ramaswamy	New Drug Products II/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Sufficient information provided in NDA		LOA 2/24/16
	Type III					LOA 2/24/16
	Type III					LOA 2/24/16
	Type III					LOA 3/02/16
	Type III					LOA 2/10/15
	Type III					LOA 3/04/16
	Type III					LOA 2/24/16
	Type III					12/28/06
	Type V			Adequate. Refer to microbiology review		LOA 5/22/15
	Type V					LOA 5/22/15

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	106878	NN1218 FIAsp (faster acting insulin aspart)
NDA	20-986	NovoLog® (insulin aspart [rDNA origin] injection); Drug Substance

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Complete	Acceptable	8/29/16	Dr. Miyun Tsai-Turton
CDRH- Compliance	Complete	Acceptable, See review in DARRTS 4/26/16	4/26/16	Crystal Lewis

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is approval. Labeling comments will be finalized during the multi-disciplinary review managed by OND.

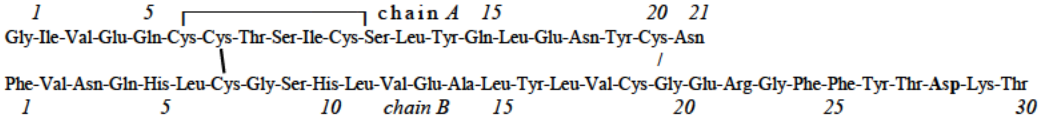
II. Summary of Quality Assessments

This NDA is a 505(b)(1) application for insulin aspart injection. Insulin aspart was approved under NDA 20-986. This NDA relies on available CMC information for drug substance insulin aspart provided under NDA 20-986, which is acceptable.

The proposed multi-dose product is a clear, colorless solution filled in 10mL vial or in 3mL cartridge preassembled in a pen injector for subcutaneous or intravenous injection. The prefilled pen-injector has a range of 1 to 80 units adjustable in increments of 1 unit. The product is intended use as a mealtime insulin with altered early glucose lowering compared to NovoLog® (insulin aspart injection). Excipients proposed for use are of compendial grade excipients. For maximum daily dose information, please refer to CDTL's memo.

Drug Substance Quality Summary

Insulin aspart is a human insulin analog produced with modification at B28 position. Insulin aspart has the following structural formula:



The Applicant has referenced NDA 020986 Novolog (insulin aspart injection) for all CMC information on the drug substance and is adequate to support the proposed NDA.

Drug Product

Insulin aspart injection is a sterile solution for subcutaneous use in adults with Type 2 diabetes. Drug product contains 100 units of insulin aspart, glycerol USP (3.3 mg), phenol USP (1.50 mg), metacresol USP (1.72 mg); zinc (as zinc acetate) USP (19.6 mcg); disodium phosphate dehydrate USP (0.53 mg); arginine (as L-arginine hydrochloride) USP (3.48 mg); niacinamide USP (20.8 mg) and water for injection USP. Hydrochloric acid or sodium hydroxide may be added to adjust pH to 7.1.

Originally this NDA was filed on 12/8/2015. CMC review for this NDA was completed on 9/9/16 and the OPQ CMC recommendation for this NDA was approval. For details, please refer to CMC Executive Summary in Panorama dated 9/9/16.

Expiration Date & Storage Conditions: An expiration period of 30 months is granted for the finished product in vials and in prefilled pen when stored at 2-8 °C with an in-use period of up to 28 days at room temperature (below 86° F (30 °C) after first use. Shelf-life is based on real-time stability data for the primary batches with the commercial formulation.

Chemistry review also concluded that faster-acting insulin aspart injection stored in intravenous (IV) infusion bags is stable for 24 hours at room temperature post dilution.

This NDA received Complete Response Letter (CRL) from the Agency on October 7, 2016 citing deficiencies in Clinical Pharmacology and Immunogenicity. On 3/29/2017, the applicant resubmitted this application, addressing these deficiencies. There are no CMC updates in this resubmission.

Trade Name proposed for the insulin aspart injection is Fiasp ((b) (4) vial) and Fiasp FlexTouch. Carton labels proposed for the finished product are as shown below. Non-proprietary name, composition and storage information are adequately described in the label.

Fiasp and Fiasp FlexTouch Carton Labels **Adequate**

(b) (4)

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES:

From CMC perspective, the proposed product is recommended for approval.

Muthukumar Ramaswamy, 8/17/17

Application Technical Lead Name and Date:

Muthukumar Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 8/17/2017 10:36:46AM
GUID: 508da7210002a0c0870017f6c83398f4

Recommendation: Approval

(Including the Facility Review/Manufacturing Inspection Recommendation)

NDA 208751
Review 1
Review Date: 9/9/16

Drug Name/Dosage Form	Insulin aspart injection/Solution for injection
Trade Name	(b) (4)
Strength	100 units/mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Novo Nordisk
Indication	Mealtime insulin (b) (4)

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and Amendments	*12/08/15, 3/10/16, 6/09/16, and 8/05/16*	*Quality (Module 3.2.P.3 and 1.1)*

Quality Review Team

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Drug Substance	N/A	N/A
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Environmental Analysis (EA)	Muthukumar Ramaswamy	New Drug Products II/ONDP

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	Type III					LOA 3/04/16
	Type III					LOA 2/24/16
	Type III					12/28/06
	Type V			Adequate. Refer to microbiology review		LOA 5/22/15
	Type V					LOA 5/22/15

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	106878	NN1218 FIAsp (faster acting insulin aspart)
NDA	20-986	NovoLog® (insulin aspart [rDNA origin] injection); Drug Substance

(b) (4)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER

Pharmacology/Toxicology	Complete	Acceptable	8/29/16	Dr. Miyun Tsai-Turton
CDRH- Compliance	Complete	Acceptable, See review in DARRTS 4/26/16	4/26/16	Crystal Lewis

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is approval. Labeling comments will be finalized during the multi-disciplinary review managed by OND. CDRH Review of the pen injector device is pending at this time.

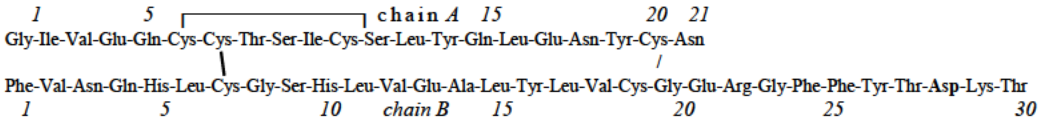
II. Summary of Quality Assessments

This NDA is a 505(b)(1) application for insulin aspart injection. Insulin aspart was approved under NDA 20-986. This NDA relies on available CMC information for drug substance insulin aspart provided under NDA 20-986, which is acceptable.

The proposed multi-dose product is a clear, colorless solution filled in 10mL vial or in 3mL cartridge preassembled in a pen injector for subcutaneous injection (b) (4) The prefilled pen-injector has a range of 1 to 80 units adjustable in increments of 1 unit. The product is intended use as a mealtime insulin with altered early glucose lowering compared to NovoLog® (insulin aspart injection). Excipients proposed for use are of compendial grade excipients. For maximum daily dose information, please refer to CDTL's memo.

Drug Substance Quality Summary

Insulin aspart is a human insulin analog produced with modification at B28 position (Asp instead of proline). It is produced by recombinant DNA technology utilizing Saccharomyces cerevisiae (baker's yeast) as the production organism. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8. Insulin aspart has the following structural formula:



The Applicant has referenced NDA 020986 Novolog (insulin aspart injection) for all CMC information on the drug substance and is adequate to support the proposed NDA.

Drug Product

Insulin aspart injection is a sterile solution for subcutaneous use in adults with Type 2 diabetes. Drug product contains 100 units of insulin aspart, glycerol USP (3.3 mg), phenol USP (1.50 mg), metacresol USP (1.72 mg); zinc (as zinc acetate) USP (19.6 mcg); disodium phosphate dehydrate USP (0.53 mg); arginine (as L-arginine hydrochloride) USP (3.48 mg); niacinamide USP (20.8 mg) and water for injection USP. Hydrochloric acid or sodium hydroxide may be added to adjust pH (to 7.1).

Excipients proposed for use in the drug product are known for use in pharmaceutical products. The Applicant provided safety literature data to support the levels of nicotinamide and L-arginine used in the insulin aspart injection. Pharm. /Tox. reviewer has reviewed this information and concluded that there are no significant safety concerns. Please refer to non-clinical review dated 8/29/16 in DARRTS.

During development, the applicant used several formulations containing nicotinamide and L-arginine in animal models. Based on data from pharmacokinetic studies in animal models, the applicant chose a formulation that showed earlier absorption and early glucose lowering for commercial development.

Dr. Koushik Paul has reviewed the (b) (4) data for (b) (4) and concluded that the proposed (b) (4) is adequate (b) (4). Please refer to microbiology review dated 7/25/16 in Panorama.

The drug product is filled in USP (b) (4) cartridge (3-mL) vial sealed with a (b) (4) rubber disc on one end and a (b) (4) rubber plunger on the other end. The drug product is also available in 10 mL vial sealed with a (b) (4) rubber (b) (4) The container closure system components proposed for use are the same as in approved insulin aspart injection.

The stability data provided in the application supported the compatibility of active ingredient with excipients and container closure components. Extractable and leachable data are reported in the NDA with supporting safety information Please refer to drug product review for additional information. Pharm. Tox. reviewer reviewed the safety information for excipient related impurities and leachables for container closure system and concluded that they do not to pose a safety risk to humans per ICH M7, ICH Q3B and ICH Q3C guidelines. Please refer to non-clinical review dated 8/29/16 in DARRTS.

The proposed manufacturing process involves (b) (4)

(b) (4)

and visual inspection are considered critical.

The manufacturing process was validated using three consecutive batches at commercial scale ((b) (4) L, (b) (4) cartridges or (b) (4) vials). The proposed commercial manufacturing process and the process used for manufacturing clinical batches are similar. For detailed information on the manufacturing process and process control, refer to Dr. Erin Kim's review in Panorama dated 1/27/16. Dr. Kim's review concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

The applicant utilized risk assessment techniques to identify the critical quality attributes (CQA) of product and assessed the impact of manufacturing process parameters (Critical process parameters and incoming materials) on critical quality attributes. Appearance, Drug content/ Assay, Impurities/ Degradants/ Aggregate content, (b) (4) content, Sterility, Endotoxins,

Particulate matter, pH, and Leachable/extractable are considered critical quality attributes of the drug product.

The critical quality attributes of the product are controlled through batch records instructions, process design, component specifications, in-process controls ((b) (4) adequate (b) (4) techniques, and through adequate finished product specification. The proposed control strategy is adequate to assure the quality of the product.

Dr. Koushik Paul has reviewed the drug product manufacturing process from the microbiological controls perspective. Her review included information on (b) (4), drug product specification for (b) (4), sterility, and endotoxin, component sterilization, container closure integrity studies, and post-approval stability commitment. Her review concluded that microbiological controls are adequate to support the NDA. Refer to CMC (Microbiology) review by Dr. K. Paul dated 7/25/16 in Panorama.

The proposed specifications are based on batches used in pre-clinical, clinical and registration stability studies and are in accordance with ICH Q6B recommendations, pharmacopeial and/or regulatory guidelines. The proposed drug product attributes are typical for protein drugs formulated as an injectable solution. The proposed specifications for insulin aspart and its impurities conform to the specification approved for insulin aspart injection (NDA 20-986) or tighter than insulin aspart injection USP.

With the exception of one impurity ((b) (4)), the impurity profile for faster aspart injection is comparable or better than the marketed insulin aspart injection. Bioactivity of degradants correlating the potency of API by bioassay with the mass based HPLC assay is included in the NDA. Drug product reviewer has concluded that determination of potency based on mass based assay is acceptable.

The proposed finished product (pen injector) specification includes a test for dose accuracy and device functionality test. Refer to CDRH Review (pending at this time) for additional information.

Expiration Date & Storage Conditions: Stability information available for the proposed product in vials and cartridges was reviewed by drug product reviewer. An expiration period of 30 months is granted when stored at 2-8 °C for the finished product in vials and in prefilled pen with an in-use period of up to 28 days at room temperature (below 86° F (30 °C) after first use. Shelf-life is based on real-time stability data for the primary batches with the commercial formulation.

(b) (4)

The applicant also evaluated the compatibility of faster-acting insulin aspart injection in intravenous (IV) infusion bags. Microbiology and chemistry review concluded that the product is stable for 24 hours at room temperature post dilution.

Manufacturing process flow information and facility compliance status for device assembly sites was reviewed by CDRH compliance reviewer, Ms. Crystal Lewis. Her review dated 4/21/16 concluded that manufacturing facilities associated with device assembly are acceptable.

Facility compliance information for drug product and drug substance facilities was reviewed by Dr. Juandria Williams. Her review concluded that there are no outstanding manufacturing or facility risks that prevent approval of this application. Refer to J. Williams's review dated 8/24/16 in Panorama for details.

CMC Reviewer's risk assessment for critical attributes is shown at the end of the review. In conclusion, the final risk is low for the proposed product. No further mitigation necessary.

C. Summary of Drug Product Intended Use

Proprietary Name	(b) (4) (insulin aspart injection)
Non Proprietary Name of the Drug Product	Insulin aspart injection
Non Proprietary Name of the Drug Substance	Insulin aspart
Proposed Indication(s)	Treatment of diabetes
Duration of Treatment	
Maximum Daily Dose	See CDTL's memo.
Alternative Methods of Administration	

D. Life Cycle Knowledge Information

Final Risk Assessment - Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Drug content/ Assay	Formulation, Process, Container closure	H	stability studies/in-process controls	L	none
Impurities/ degradants/ Aggregates	Formulation, Process, Container closure	H	stability studies, in-process controls	L	none
Appearance	Formulation, Process, Container closure	H	stability studies	L	none
Sterility	Container closure Process	H	stability studies in-process controls	L	none
Endotoxins	Container closure Process	H	stability studies in-process controls	L	
Particulate matter	Formulation	H	stability studies in-process controls	L	none
pH	Formulation	H	Optimize formulation stability studies	L	none
Leachable/ Extractables	Formulation, Process, Container closure	M	Optimize formulation qualification of packaging components	L	Reference the pharmaceutical development for container closure

(b) (4)	Formulation, Process, Container closure	H	Optimize formulation stability studies, in-process controls	L	none
	Formulation, Process, Container closure	H	Optimize formulation stability studies, in-process controls	L	none

OVERALL ASSESSMENT AND SIGNATURES:

From CMC perspective, the proposed product is recommended for approval.

Muthukumar Ramaswamy -S

Digitally signed by Muthukumar Ramaswamy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000341660, cn=Muthukumar Ramaswamy -S
Date: 2016.09.09 11:00:32 -04'00'

Muthukumar Ramaswamy, 9/9/16

Application Technical Lead Name and Date: