CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-386

CHEMISTRY REVIEW(S)

MEMORANDUM

DATE: June 18, 2008

TO: NDA 22-386 and ——— Files for Prandimet (repaglinide/metformin HCL) Tablets b(4)

From: Sheldon Markofsky, Chemistry Reviewer (ONDQA I Branch II)

SUBJECT: Establishment Inspection

The relevant manufacturing and testing facilities for Prandimet (repaglinide/metformin HCL) tablets have been given an acceptable Establishment Inspection Report, dated 6-18-08. There are no remaining Chemistry issues. Therefore, from a Chemistry, Manufacturing, and Control (CMC) point of view, NDAs 22-386 ——— are recommended for approval. b(4)

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/s/

Sheldon Markofsky
6/18/2008 01:41:34 PM
CHEMIST

PrandiMet (repaglinide/metformin HCl) Tablets

NDA 22-232

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: NOVO NORDISK PHARMACEUTICALS INC
100 COLLEGE ROAD WEST
Princeton NJ 08536

Indication: PrandiMet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual repaglinide and metformin therapy is appropriate.

Presentation: PrandiMet (repaglinide/metformin HCl) tablets are supplied as scored, biconvex tablets available in 1 mg/500 mg (yellow) and 2 mg/500 mg (pink) strengths. Tablets are debossed with the Novo Nordisk (Apis) bull symbol and colored to indicate strength. The tablets are packaged in [redacted] bottles containing a desiccant and closed with a child-resistant-tamper-evident [redacted] cap. b(4)

EER Status: Pending.

Consults:
EA – Categorical exclusion provided
Statistics – N/A
Methods Validation – Deemed not necessary to be forwarded to Agency laboratory.
Microbiology – N/A
EES- **Pending**

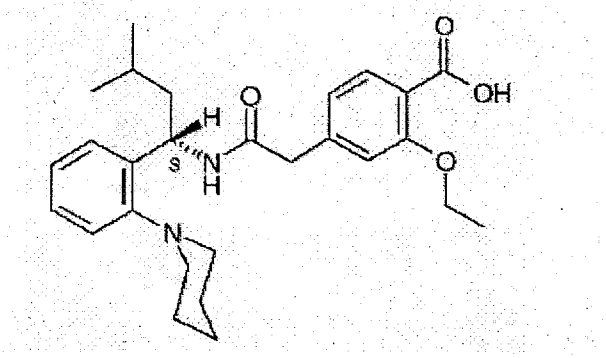
Original Submission: 10-Aug-2007
Re-submissions: N/A
Post-Approval Agreements: None beyond the typical stability commitment.

Drug Substance: The NDA contains two drug substances for the fixed dose combaination tablets i.e. repaglinide and metformin HCl.

Repaglinide

Repaglinide is a chiral molecule with one asymmetric center in the "S" configuration. This material is a white to off-white substance whose aqueous solubility is strongly pH dependent. Thus, it is slightly soluble in 0.1 M HCl, practically insoluble in water, and slightly soluble in 1M sodium hydroxide. Repaglinide is polymorphic. [redacted] b(4)

[redacted] Adequate Chemistry, Manufacturing, and Control (CMC) information for repaglinide was provided in DMF [redacted] and the stability data in the DMF support a [redacted] month retest period for this drug substance.

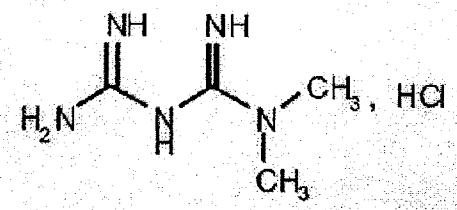


Name: (USAN): (+)-2-Ethoxy-a[[(S)-α-isobutyl-o-piperidinobenzyl] carbonyl]-p-toluolic acid

Molecular formula: $C_{27}H_{36}N_2O_4$
Molecular weight: 452.61

Metformin HCl

Metformin HCl is a white hygroscopic crystalline powder that is freely soluble in water (1:2). This drug substance has been reported to exist in two polymorphic forms, A and B. Form A is stable and form B metastable. Form B has only been observed under very unusual experimental conditions and converts very quickly to the stable form A. Adequate (CMC) information for this drug substance was provided in DMF —, and the stability data in the DMF support a —month retest period for metformin HCl. b(4)



Chemical Name (IUPAC): 1,1dimethylbiguanide hydrochloride

Molecular formula: $C_4H_{11}N_5$. HCl
Molecular weight: 165.6

Drug Product:

The manufacturing procedure of the tablet consists of — processes: preparation of the repaglinide —— by the same process approved in NDA 20-741 (repaglinide tablets), preparation of the metformin ⌜ ⌟ and tablet formation ⌜ ⌟. b(4)

[ ]

PrandiMet (repaglinide/metformin HCl) tablets are supplied as scored, biconvex tablets available in 1 mg/500 mg (yellow) and 2 mg/500 mg (pink) strengths. Tablets are debossed with the Novo Nordisk (Apis) bull symbol and colored to indicate strength. The tablets are packaged in [ ] bottles containing a desiccant and closed with a child-resistant-tamper-evident [ ] cap. Besides the two drug substances the drug product contains the following inactive ingredients: Povidone, Meglumine, Microcrystalline Cellulose, Poloxamer 188 [ ], Sorbitol, Polyethylene glycol, Polacrillin Potassium, Magnesium Stearate, Hypromellose, Talc, Titanium Dioxide, and red or yellow iron oxide. Propylene glycol is present only in the 2/500 PrandiMet tablets. All of the inactive ingredients are compendial. Process controls, such as appropriate limits on manufacturing parameters and the — content of a key ingredient [ ] help assure the consistency of the product. In addition, monitoring of the [ ] tablets for hardness, average mass, thickness, friability, and disintegration time are employed to achieve acceptable properties of the PrandiMet tablets. b(4)

The applicant provided stability data which support an 18 month expiry. However, Novo Nordisk may extend the expiry to — months in an Annual Report provided they have stability data from a — month time point which meets their proposed acceptance criteria, including their revised (15 minute) dissolution specification. b(4)

Conclusion: Drug product is satisfactory.

Overall Conclusion: From a CMC perspective, the application is recommended for approval pending an acceptable recommendation from the Office of Compliance regarding GMPs. Currently, the recommendation is PENDING.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Ali Al-Hakim
5/23/2008 10:56:50 AM
CHEMIST

NDA 22-232

Prandi*Met* (repaglinide/metformin HCl) Tablets

Novo Nordisk Inc.

Sheldon Markofsky, Ph.D.
Division of Metabolism and Endocrine Drug Products (HFD-510)

and

Office of New Drug Quality Assessment I
Branch II

File: n22232e

Table of Contents

Chemistry Review Data Sheet

1. NDA #: 22-232

2. REVIEW #: 1

3. REVIEW DATE: 14-April-2008

4. REVIEWER: Sheldon Markofsky, Ph.D.

5. PREVIOUS DOCUMENTS:

Original	10-AUG-2007
Amendment	19-OCT-2007
Amendment	06-DEC-2007
Amendment	21-DEC-2007
Amendment	14-JAN-2008
Amendment	11-FEB-2008
Amendment	13-FEB-2008
Amendment	10-April-2008
Filing letter	12-OCT-2007
IR letter	04-Nov-2007
IR letter	01-JAN-2008
IR letter	03-JAN-2008
IND 70,959 letter from Mary Parks, MD responding to CMC questions	06-DEC-2006
Chemistry Review # 1 for NDA 20-741	29-OCT-1997

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	10-Aug-2007
Amendment	19-OCT-2007[1]
Amendment	06-DEC-2007[2]
Amendment	21-DEC-2007[3]
Amendment	14-JAN-2008[4]
Amendment	11-FEB-2008[5]
Amendment	13-FEB-2008[6]
Amendment	10-April-2008[7]

1) The 10-19-07 amendment provided updated-draft-labeling.
2) The 12-6-07 amendment updated information on the acceptance criteria of metformin HCl.
3) The 12-21-07 amendment provided additional film coating information for Prandi*Met* tablets.
4) The 1-14-08 amendment updated the specification and Post-Approval-Stability Commitments for Prandi*Met* tablets.
5) The 2-11-08 amendment provided a new dissolution specification.
6) The 2-13-08 amendment provided new information related to manufacturing and the stability of the drug product.
7) The 4-10-08 amendment provided updated-draft carton and container labels

7. **NAME & ADDRESS OF APPLICANT:**

Name:	NOVO NORDISK PHARMACEUTICALS INC
Address:	100 COLLEGE ROAD WEST Princeton NJ 08536
Representative:	Sabina Sheikh
Telephone:	609-9875420

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Prandi*Met*
   b) Non-Proprietary Name: Repaglinide/Metformin Hydrochloride
   c) Code Name/# (ONDC only): NN4440
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 4
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: §505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of type 2 diabetes mellitus.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 1 mg/500 mg and 2 mg/500 (repaglinide/metformin HCl)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

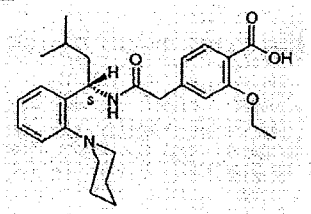
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Repaglinide



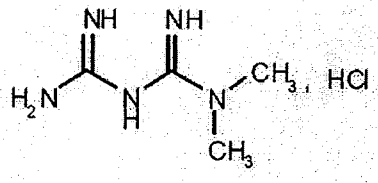
Chemical Names
(IUPAC): (S)-2-ethoxy-4-[2-[[methyl-1-[2-(1- piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid

(USAN): (+)-2-Ethoxy-α[[(S)-α-isobutyl-o-piperidinobenzyl] carbonyl]-p-toluolic acid

(Other): S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid

Molecular formula:	$C_{27}H_{36}N_2O_4$
Relative molecular mass:	452.61

Metformin HCl



Chemical Name (IUPAC): 1,1dimethylbiguanide hydrochloride

Molecular formula:	$C_4H_{11}N_5 \cdot HCl$
Relative molecular mass:	165.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs[a]:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	Adequate	2-1-08	b(4)
[redacted]	II	[redacted]	[redacted]	1	Adequate	3-12-08	
[redacted]	IV	[redacted]	[redacted]	4	Adequate		
[redacted]	III	[redacted]	[redacted]	4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	Repaglinide/Metformin HCl Tablets
NDA	20-741	Prandin (Repaglinide) Tablets

b(4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	Satisfactory (FDA labs. not needed)	4-14-08	S. Markofsky
DMETS	Approval of proprietary name is pending		
EA	Satisfactory	4-14-08	S. Markofsky
Microbiology	N/A		

The Chemistry Review for NDA 21-521

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA is recommended for approval, pending an acceptable cGMP status for the relevant manufacturing and testing facilities.
[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

There are two drug substances used for the fixed-dose-combination tablets of this NDA, i.e. repaglinide and metformin HCl; and both drug substances have been employed alone for initial therapy of type 2 diabetes mellitus.

Repaglinide

Repaglinide is a chiral molecule with one asymmetric center in the "S" configuration. This material is a white to off-white substance whose aqueous solubility is strongly pH dependent. Thus, it is slightly soluble in 0.1 M HCl, practically insoluble in water, and slightly soluble in 1 M sodium hydroxide. Repaglinide is polymorphic. [redacted] b(4)

Adequate Chemistry, Manufacturing, and Control (CMC) information for repaglinide was provided in DMF [redacted] and the stability data in the DMF support a — month retest period for this drug substance. b(4)

counts. Although the firm proposed a ——— expiry for tablets which are not stored above 25° C (77° F), the stability data support an 18 month expiry. Novo Nordisk may extend the expiry to ——— in an Annual Report provided they have stability data from ——— time point which meets their proposed acceptance criteria, including their revised (15 minute) dissolution specification. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The application can be approved pending a satisfactory Establishment Inspection Report. Thus, the NDA can be approved from a Chemistry point of view on the following basis:

- Adequate information was provided in referenced DMFs for the synthesis, purification and controls of the drug substances.
- Adequate manufacturing information to support the proposed to-be-marketed drug product
- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product
- Adequate stability package to support the recommended expiry period of the drug product

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

III. Administrative

A. Reviewer's Signature

N/A

B. Endorsement Block

N/A

C. CC Block

N/A

81 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Sheldon Markofsky
5/6/2008 09:44:48 AM
CHEMIST

Ali Al-Hakim
5/7/2008 09:47:34 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 22386/000	Action Goal:	
Stamp:	23-MAY-2008	District Goal:	16-APR-2008
Regulatory Due:	15-JUN-2008	Brand Name:	PRANDIMET (REPAGLINIDE +
Applicant:	NOVO NORDISK INC	Estab. Name:	METFORMIN HCL)
	100 COLLEGE RD WEST	Generic Name:	REPAGLINIDE METFORMIN
	PRINCETOWN, NJ 08540		
Priority:	4S	Dosage Form:	(TABLET)
Org Code:	510	Strength:	1/500 AND 2/500

Application Comment: [redacted] b(4)

FDA Contacts:

J. MARCHICK	(HFD-510)	301-796-1280	, Project Manager
S. MARKOFSKY		301-796-1412	, Review Chemist
S. TRAN		301-796-1764	, Team Leader

Overall Recommendation: ACCEPTABLE on 18-JUN-2008by S. ADAMS (HFD-325)301-796-3193

Establishment: CFN [redacted] FEI [redacted] b(4)

[redacted] b(4)

DMF No: [redacted] AADA: [redacted] b(4)

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JUN-2008				TRANS
OC RECOMMENDATION	10-JUN-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS

Profile: TCM OAI Status: NONE

stone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JUN-2008				TRANS
SUBMITTED TO DO	10-JUN-2008	10D			ADAMSS
DO RECOMMENDATION	10-JUN-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	12-JUN-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9613235 FEI 3003037054

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ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

NOVO NORDISK A/S

NOVO NORDISK PARK

MAALEOV, , DA DK-2760

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CTX OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JUN-2008				TRANS
OC RECOMMENDATION	10-JUN-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS

Establishment: CFN [redacted] FEI [redacted] b(4)

[redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile: TCM OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JUN-2008				TRANS
SUBMITTED TO DO	10-JUN-2008	GMP			ADAMSS
ASSIGNED INSPECTION T	10-JUN-2008	GMP			ADAMSS
ECTION SCHEDULED	10-JUN-2008		10-JUN-2008		ADAMSS
INSPECTION PERFORMED	12-JUN-2008		12-JUN-2008		ADAMSS
DO RECOMMENDATION	18-JUN-2008			ACCEPTABLE INSPECTION	ADAMSS

BASED ON INVESTIGATOR'S RECOMMENDATION, REVIEW OF 483. AWAITING EIR AND FIRM'S RESPONSE.

OC RECOMMENDATION 18-JUN-2008 ACCEPTABLE ADAMSS

DISTRICT RECOMMENDATION

Establishment: CFN FEI b(4)

b(4)

MF No: AADA:

Responsibilities: b(4)

Profile: TCM OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JUN-2008				TRANS
OC RECOMMENDATION	10-JUN-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS

Establishment: CFN FEI

b(4)

DMF No: AADA: b(4)

Responsibilities:

ile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
INSPECTION PERFORMED	02-JUN-2008		02-JUN-2008		ADAMSS
SUBMITTED TO OC	09-JUN-2008				TRANS
SUBMITTED TO DO	10-JUN-2008	GMP			ADAMSS
ASSIGNED INSPECTION T	10-JUN-2008	GMP			ADAMSS
INSPECTION SCHEDULED	10-JUN-2008		27-MAY-2008		ADAMSS
DO RECOMMENDATION	18-JUN-2008			ACCEPTABLE INSPECTION	ADAMSS
BASED ON INVESTIGATOR'S RECOMMENDATION, REVIEW OF 483. AWAITING EIR AND FIRM'S RESPONSE.					
OC RECOMMENDATION	18-JUN-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN FEI

b(4)

b(4)

DMF No: [redacted] AADA: b(4)

Responsibilities: [redacted] b(4)

Profile: CSN OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
INSPECTION PERFORMED	02-JUN-2008		02-JUN-2008		ADAMSS
SUBMITTED TO OC	09-JUN-2008				TRANS
SUBMITTED TO DO	10-JUN-2008	GMP			ADAMSS
ASSIGNED INSPECTION T	10-JUN-2008	GMP			ADAMSS
INSPECTION SCHEDULED	10-JUN-2008		02-JUN-2008		ADAMSS
DO RECOMMENDATION	18-JUN-2008			ACCEPTABLE	ADAMSS
				INSPECTION	

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

BASED ON INVESTIGATOR'S RECOMMENDATION, REVIEW OF 483 AND FIRM'S RESPONSE. AWAITING EIR.

OC RECOMMENDATION	18-JUN-2008	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	

Profile: NEC OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
INSPECTION PERFORMED	02-JUN-2008		02-JUN-2008		ADAMSS
SUBMITTED TO OC	09-JUN-2008				TRANS
SUBMITTED TO DO	10-JUN-2008	GMP			ADAMSS
GNED INSPECTION T	10-JUN-2008	GMP			ADAMSS
INSPECTION SCHEDULED	10-JUN-2008		02-JUN-2008		ADAMSS
DO RECOMMENDATION	18-JUN-2008			ACCEPTABLE	ADAMSS
				INSPECTION	

BASED ON INVESTIGATOR'S RECOMMENDATION, REVIEW OF 483 AND FIRM'S RESPONSE. AWAITING EIR.

OC RECOMMENDATION	18-JUN-2008	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	

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Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

OND Division of Metabolism and Endocrinology Products

NDA:	**22-232**
Applicant:	Novo Nordisk, Inc.
Stamp Date:	15-AUG-2007
PDUFA Date:	**15-JUN-2008**
Proposed Proprietary Name:	PrandiMet
Established Name:	Repaglinide and metformin hydrochloride
Dosage form and strength:	Fixed-dose combination tablet – 1 mg repaglinide and 500 mg metformin HCl 2 mg repaglinide and 500 mg metformin HCl
Route of Administration:	oral
Indications:	Treatment of type 2 diabetes mellitus
PAL:	Su (Suong) Tran, Branch II/DPA I/ONDQA
ONDQA Fileability:	**Yes**
Comments for 74-Day Letter:	**On the last page of this document**

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be determined by Primary Reviewer.
CDRH	*Not Applicable*
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER sent to Office of Compliance on 29-AUG-2007
DMETS	*Labeling consult request will be sent as part of DMEP's request.*
Methods Validation	*Validation may be requested of FDA labs after test methods are finalized.*
Microbiology	*Not Applicable*
Pharm/Tox	To be determined by Primary Reviewer.

Summary:

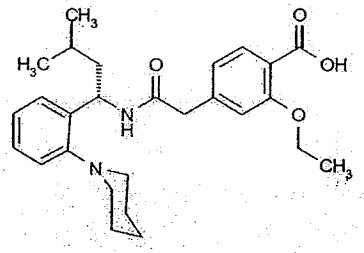
This is an electronic NDA, [redacted]. The associated IND is IND 70959. b(4)
Reference is made to the approved NDA 20741.

The product is a fixed dose combination tablet available in two strengths: 1 mg repaglinide and 500 mg metformin hydrochloride, and 2 mg repaglinide and 500 mg metformin hydrochloride. Each drug substance has been approved in other products as blood glucose-lowering drugs. This new fixed dose combination combines these two anti-hyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes. Its main purpose is to increase patient convenience and compliance by combining two medications into one. In support of efficacy, one single-dose bioequivalence study, NN4440-1753, was conducted to compare the combination tablet (2/500 strength) to the concomitantly administered individual tablets of 2 mg repaglinide and 500 mg metformin hydrochloride. The study also aimed at showing the dose proportionality of the two dosage strengths 1/500 and 2/500.

Maximum daily dose is 10 mg repaglinide and 2500 mg metformin hydrochloride.

Route of administration	Oral
Dosage form	Immediate release tablet
Package type	Plastic bottles with child-resistant screw caps and mounted desiccant inserts. The primary container/closure systems are: For commercial distribution: Bottles of 20- and 100-count.
Potency	Fixed-dose combination of: 1 mg repaglinide and 500 mg metformin hydrochloride, or 2 mg repaglinide and 500 mg metformin hydrochloride
Color	Yellow: 1 mg repaglinide and 500 mg metformin hydrochloride Pink: 2 mg repaglinide and 500 mg metformin hydrochloride
Shape	— biconvex
Coating	[redacted] b(4)
Size	8 mm by 16 mm
Scoring	Scored
Imprint codes	Debossed: dosage strength
Symbols	Debossed: Apis bull

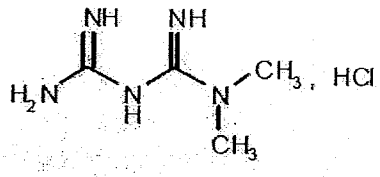
Drug substance: repaglinide



Repaglinide, USP, is a white crystalline powder that is non-hygroscopic, insoluble in water, and highly permeable (BCS Class II). There is one chiral center, and the drug substance is the S enantiomer. b(4)
[ ] This drug substance has been approved as a single entity in NDA 20741 Prandin (repaglinide) Tablets.

There is no chemistry, manufacturing, and controls information in the NDA. Reference is made to the Drug Master File [ ] This DMF will require a chemistry review because there is none on file. b(4)

Drug substance: metformin hydrochloride



Metformin hydrochloride, USP, is a white crystalline powder that is hygroscopic, soluble in water, and low in permeability (BCS Class III). There is no chiral center. There are two polymorphic forms, which b(4)
[ ] This drug substance has been approved in many products as a single entity as well as in combinations with other active ingredients.

There is no chemistry, manufacturing, and controls information in the NDA. Reference is made to the Drug Master File [ ]. This DMF will require a chemistry review because there is none on file. b(4)

Drug product:

The drug product is a fixed-dose combination tablet composed of repaglinide and metformin hydrochloride in two dosage strengths: 1 mg/ 500 mg and 2 mg/ 500 mg. The 1/500 tablet is yellow, — biconvex, ⌜ ⌟ and debossed with "1/500" on one side and the Apis bull on the other. The 2/500 tablet is pink, — biconvex, ⌜ ⌟ and debossed with "2/500" on one side and the Apis bull on the other. Both tablets are scored. b(4)

The manufacture of the tablet has three processes: preparation of the repaglinide —— by the same process approved in NDA 20-741 (repaglinide tablets), preparation of the metformin ⌜ ⌟ and tablet formation ⌜ ⌟ b(4)

Container closure systems for product distribution:

20-count	—— '30-mL/round bottle with 35-mm child-resistant — cap with 2 g desiccant (as a cap insert)
100-count	—— '125-mL/round bottle with 45-mm child-resistant — cap with 2 g desiccant (as a cap insert)

b(4)

The drug product is stored at 20-25 °C. The following primary stability data are provided in the NDA: 12-month data at 25 °C/60% RH and 6-month data at 40 °C/75% RH for the three stability batches of each dosage strength, and 3-month data at each storage condition for three additional stability batches of the lower 1/500 strength. See Discussion under Critical Issues.

Table 1 Composition of Repaglinide 1 or 2 mg, Metformin HCl 500 mg tablet

Component	Amount per Tablet (mg)		Function	Reference to Standards
	1/500	2/500		
Drug Product				
Repaglinide	1.00	2.00	Active ingredient	Ph. Eur./ USP
Poloxamer 188				Ph. Eur./ NF
Povidone				Ph. Eur./ USP
Meglumine				Ph. Eur./ USP
				Ph. Eur./ USP
Cellulose, Microcrystalline				Ph. Eur./ NF[3]
Metformin Hydrochloride	500	500	Active ingredient	Ph. Eur./ USP
Povidone				Ph. Eur./ USP
				Ph. Eur./ USP
Sorbitol				Ph. Eur./ NF
Macrogol				Ph. Eur./ NF[3]
Excipients				
Cellulose, Microcrystalline				Ph. Eur./ NF[2]
Polacrilin Potassium				NF
Magnesium Stearate				Ph. Eur./ NF
Hypromellose 6cP				Ph. Eur./USP
Talc				Ph. Eur./USP
Titanium Dioxide				Ph. Eur./USP
Macrogol				Ph. Eur. /NF[4]
Iron Oxide Yellow				NF[5]
				Ph. Eur./USP
Hypromellose 3cP				Ph. Eur./ USP
Talc				Ph. Eur./ USP
Titanium Dioxide				Ph. Eur./ USP
Propylene Glycol				Ph. Eur./ USP
Iron Oxide Red				NF[5]
Hypromellose 6cP				Ph. Eur./ USP
Titanium Dioxide				Ph. Eur./ USP
Macrogol				Ph. Eur./NF[4]
				Ph. Eur./ USP

b(4)

b(4)

b(4)

b(4)

2. Microcrystalline Cellulose NF
3. Polyethylene Glycol NF
4. Polyethylene Glycol NF
5. Conforms to the monograph of Ferric Oxide, NF

- Relevant batches of drug product:

See Discussion under Critical Issues.

1/500 strength: **SBBN012** SBBN013 SBBN014	Batch SBBN012 was used in the Bioequivalence study Primary stability batches. The formulation differs from the commercial formulation [ ] metformin hydrochloride.
1/500 strength: SBBN068 SBBN069 SBBN083	Primary stability batches. Commercial formulation. Limited stability data from these batches serve to bridge the three batches manufactured with [ ] the target amount of metformin HCl.
2/500 strength: **SBBN018** SBBN019 SBBN020	Batch SBBN018 was used in the Bioequivalence study Primary stability batches. Commercial formulation.

b(4)

b(4)

Critical Issues:

- **Has all information requested during the IND phases, and at the pre-NDA meetings been included?** Yes.
  - On 28-NOV-2005, the sponsor submitted a question on whether the dissolution test of the product can be dissolution of repaglinide only and not of metformin. (See the meeting minutes in DFS for details). The FDA's response dated 03-FEB-2006, which was reiterated on 03-MAR-2006, stated that all fixed dose combination oral dosage forms must have dissolution specifications for each active ingredient present in the combination product.

    As per FDA's request, the drug product specification includes separate dissolution specifications for each active ingredient.
  - On 14-JUL-2006, the sponsor submitted questions on the stability studies. The questions and FDA's response dated 06-DEC-2006 are copied below.

    Questions 1 and 2 are no longer relevant because the amount of stability data submitted in the NDA and the stability container closure systems are different from what were proposed in the guidance request. Question 3 [ ] is no longer relevant because the commercial product will be packaged in bottles. As agreed by FDA to Question 4, the expiry of the drug product will be determined from the data of primary stability batches manufactured at the pilot plant Novo Nordisk (i.e., not at the commercial site) [ ]

b(4)

1. Based on the extensive stability data available on the repaglinide and metformin tablets and twelve (12) months supporting stability data, does the Agency agree that nine (9) month long term (25°C/60%RH) and nine (9) month accelerated (40°C/75%RH) stability data on the NDA stability batches at the time of submission with additional data (up to 12 months) being provided during review period and a post approval commitment for a long term NDA stability program is sufficient to support a proposed shelf life of ⌜ ⌟ for repaglinide/metformin FDA products? b(4)

Depending on the demonstrated stability of the tablets and the ability to extrapolate the data with reasonable certainty, ⌜ ⌟ expiry may be supported. The final expiration dating period will be a NDA review issue. b(4)

2. Can the Agency confirm that the long term (25°C/60%RH) and accelerated (40°C/75%RH) stability data in large — containers ⌜ ⌟ with a post approval commitment for a long term (25°C/60%RH) NDA stability program for small — containers ⌜ ⌟ of identical material is sufficient for the NDA submission? b(4)

Your proposal to provide a post approval commitment for packaging tablets in the small — containers appears reasonable. b(4)

3. ⌜

b(4)

⌟

⌜

b(4)

⌟

4. If there is no change in the principles of manufacturing equipment, does the Agency agree that the stability data from the primary stability batches manufactured at Novo Nordisk A/S pilot plant is sufficient to launch the repaglinide/metformin FDC product with a post approval commitment to provide data for a stability program [long term (25°C/60%RH) and accelerated (40°C/75%RH stability] on the commercial batches manufactured at — and packaged in small — containers? b(4)

Your proposal to use the same expiry for drug products manufactured at the Novo Nordisk A/S and — facilities and packaged in small — containers appears reasonable. We recommend that stability data for product manufactured at the — facility be provided during review period, when available. b(4)

- **Repaglinide**. The applicant indicates in the tablet composition section that this active ingredient is Repaglinide, USP. Reference is made to the Drug Master File [redacted] for all chemistry, manufacturing, and controls information. This DMF will require a chemistry review because there is none on file. b(4)

- **Metformin hydrochloride**. The applicant indicates in the tablet composition section that this active ingredient is Metformin Hydrochloride, USP. Reference is made to the Drug Master File [redacted] for all chemistry, manufacturing, and controls information. This DMF will require a chemistry review because there is none on file. b(4)

- **Repaglinide** [redacted] Reference is made by the applicant to the approved NDA 20-741 (repaglinide tablets) for information on this repaglinide [redacted] used in the fixed dose combination tablet. b(4)

- **Dosage strength.** The dosage strength is correctly correlated with the established name of each active ingredient. The composition of the tablet is 1 mg of "repaglinide" and 500 mg of "metformin hydrochloride", or 2 mg of "replaglinide" and 500 mg of "metformin hydrochloride".

- **Impurities and degradants**. The reviewer will confirm that the limits on impurities in the drug substance repaglinide and metformin hydrochloride are the same as or better than those in the USP monographs. The proposed limits on degradants in the drug product are below the applicable ICH qualification thresholds (taking into account the maximum daily dose of 10 mg repaglinide and 2500 mg metformin hydrochloride). Therefore, a formal PharmTox consult may not be needed. The reviewer will assess whether the tests methods are adequately stability-indicating.

- **Moisture sensitivity**. The tablet is moisture-sensitive because degradation is found to be moisture-driven during stress stability testing (i.e., open containers under accelerated conditions). The reviewer will evaluate the adequacy of the container closure, which includes a desiccant, in protecting the product from moisture as part of the stability assessment. The reviewer will also determine whether the [redacted] is adequately stability-indicating, or a more direct method such as [redacted] should be required as a post-approval agreement. b(4)

- **Microbial limits.** A formal Microbiology consult may not be needed because the dosage form is a solid tablet for oral administration. The primary chemist (S. Markofsky) indicated that the product specification lacks microbial limit testing. The applicant states that "All components of the drug product are tested for microbial contamination before manufacture", and that batch release data as well as stability data show no microbial growth. The reviewer will assess whether the data adequately justify the omission of microbial limit testing. It is noted that moisture content is controlled because degradation of the product is moisture-driven, and the limits on moisture should also decrease the likelihood of microbial proliferation.

- **Dissolution of the drug product**. There is no IVIC being claimed. Because dissolution is used for quality control purposes only, a formal ClinPharm consult may not be needed. The applicant applies the USP dissolution specification for repaglinide tablets and metformin HCl tablets. Because the fixed dose combination tablet is a new product, the compendial criteria are not applicable. The primary chemist (S. Markofsky) indicated that the dissolution specification (test method and/or acceptance criteria) may not be adequately discriminating because close to 100% dissolution is obtained for both active ingredients at the 15-minute time point. The applicant should provide a justification for the proposed criteria as per ICH Q6A guidelines. ICH allows a dissolution specification that lacks discriminating power if certain criteria are met. If the justification is found to be inadequate by the primary chemist, a revised test method and/or criteria may be required as a post-approval agreement.

Comment to applicant: Because the fixed dose combination tablet is a new product, the compendial dissolution criteria for repaglinide tablets and metformin HCl tablets are not applicable. Provide a justification for the proposed dissolution criteria as per ICH Q6A guidelines. If we find your justification inadequate, a revised test method and/or criteria may be required.

- ⌜

b(4)

- **Container closure components.** Review of DMF — for the 30-mL and 125-mL — bottles, and child-resistant — caps with desiccant insert may not be necessary if the reviewer deems adequate the information included in the NDA on the safety and suitability of the product-contact components used to package this solid oral dosage product. b(4)

Bottle: 30-mL and 125-mL	Suitability: tested by USP <661> light transmission, nonvolatile residue, heavy metals, and buffering capacity, and by USP <671> container permeation as a "tight container" with the designated cap.
⌜ ⌟	Safety: compliant with 21CFR177.1520
⌜ ⌟	Safety: compliant with 21CFR177.1520 and 21CFR178.3297
Child-resistant caps with desiccant inserts (product-contact surface: paperboard)	Suitability: tested by USP <661> light transmission, nonvolatile residue, heavy metals, and buffering capacity, and by USP <671> container permeation as a "tight container" with the designated cap.
⌜ ⌟	Safety: compliant with 21CFR177.1520
⌜ ⌟	Safety: compliant with 21CFR177.1520 and 21CFR178.3297
Desiccant insert: ⌜ ⌟	Safety: compliant with 21CFR177.1520, 21CFR178.3297, 21CFR172.480, and 21CFR176.170

b(4)

- **Stability of the drug product.**
  - The drug product is stored at 20-25 °C. The following primary stability data are provided in the NDA: 12-month data at 25 °C/60% RH and 6-month data at 40 °C/75% RH for the three stability batches of each dosage strength, and 3-month data at each storage condition for three additional stability batches of the lower 1/500 strength. The three additional batches of the lower strength (SBBN068, SBBN069, and SBBN083) were placed on stability to bridge the first three batches (SBBN012, SBBN013, and SBBN014) that were manufactured with — less than the target amount of metformin hydrochloride. The difference in formulation was conveyed to the

b(4)

ClinPharm team on 05-SEP-2007. Additional stability data will be requested from the applicant for the additional bridging batches SBBN068, SBBN069, and SBBN083. If the difference is not clinically relevant, and if there is no significant difference in trends when comparing batches with the correct amount of metformin HCl and batches with — less, a shelf life for the 1/500 strength can be determined from the stability data of the primary batches SBBN012, SBBN013, and SBBN014. b(4)

- As agreed by FDA on 06-DEC-2006, the expiry of the drug product will be determined from the data of primary stability batches manufactured at the pilot plant Novo Nordisk (i.e., not at the commercial site —. b(4)

Comment to applicant: Provide additional stability data for the bridging batches SBBN068, SBBN069, and SBBN083 before Month 4 of the review cycle.

Supporting NDA or IND:
IND 70959 and NDA 20741

Supporting DMF:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
—	II		Repaglinide, USP	LOA is provided. This DMF has not been reviewed and will need a Chemistry assessment. b(4)
—	II		Metformin hydrochloride, USP	LOA is provided. This DMF has not been reviewed and will need a Chemistry assessment. b(4)
—	III			LOA is provided. Review of the DMF may not be necessary: the NDA includes information on the safety and suitability of the product-contact components used to package this solid oral dosage product. b(4)

As per request from the primary chemist (S. Markofsky) and concurred by the Branch Chief, the comment below will be included in the 74-day letter.
Comment to applicant: Regarding the — Yellow , Red excipients used in the — of your tablets, provide letters of authorization from the manufacturers to allow us access to information in the appropriate Drug Master Files. b(4)

Appears This Way
On Original

Manufacturers: EER was sent to the Office of Compliance on 29-AUG-2007

The information tabulated below is from the drug substance DMF. It should be included in the NDA.

Drug substance Metformin hydrochloride	
[redacted]	Manufacturing
[redacted]	Testing

b(4)

b(4)

The information tabulated below is from the drug substance DMF. It should be included in the NDA.

Drug substance Repaglinide	
[redacted]	Manufacturing and testing

b(4)

Appears This Way
On Original

Appears This Way
On Original

The information below is copied directly from the NDA. With the exception noted below, all sites were entered into the EER on 29-AUG-2007.

- [redacted] was NOT entered into EER because the Office of Compliance determined that this site is the headquarter office with no production work on site. b(4)

Table 1 Manufacturing of Drug Product

[redacted] b(4)

[redacted]

Appears This Way
On Original

Table 2 Quality Control of Drug Product

b(4)

Novo Nordisk AS * Novo Nordisk Park DK-2760 Måløv Denmark	Drug product release and stability testing according to specification

From: CDER EESQUESTIONS
Sent: Monday, August 27, 2007 3:11 PM
To: Tran, Suong T
Cc: Markofsky, Sheldon B
Subject: RE: new facilities

Su,

The first two sites will be added to EES by COB today. The third location is the headquarters which

b(4)

according to the website http://www. — no/English/Headquarter.htm all departments not directly
related to production are situated therefore this site does not need to be added to EES.

Thank you,

Shawnte L. Adams
Program Analyst
Division of Manufacturing and Product Quality
International Compliance Team, HFD 325
301-827-9051 (Office)
301-827-2063 (Fax)
FWAP: Tuesday and Thursday

From: Tran, Suong T
Sent: Monday, August 27, 2007 12:46 PM
To: CDER EESQUESTIONS
Cc: Markofsky, Sheldon B
Subject: new facilities

Please confirm that these three facilities are not in your databases. I checked in EES and there is nothing. Please enter
them as new facilities so I can finish filling out the EER for this new NDA.
NDA 22-232 repaglinide/metformin hydrochloride

b(4)

Thanks!
2
Su
Su (Suong) Tran, PhD
Pharmaceutical Assessment Lead
(Div. Metabolism/Endocrinology Products)
Office of New Drug Quality Assessment
CDER/FDA
301.796.1764

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		All facilities are listed.
6	Has an environmental assessment report or categorical exclusion been provided?	X		Exclusion request per 21 CFR 25.31(b) is included.
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?			Not applicable.

74-Day Letter – Draft Comments to the Applicant:

1. Because the fixed dose combination tablet is a new product, the compendial dissolution criteria for repaglinide tablets and metformin HCl tablets are not applicable. Provide a justification for the proposed dissolution criteria as per ICH Q6A guidelines. If we find your justification inadequate, a revised test method and/or criteria may be required.
2. Provide additional stability data for the bridging batches SBBN068, SBBN069, and SBBN083 before Month 4 of the review cycle.
3. Regarding the —— Yellow ⌜ ⌟ Red ⌜ ⌟ excipients used in the —— of your tablets, provide letters of authorization from the manufacturers to allow us access to information in the appropriate Drug Master Files. b(4)

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

/s/

Suong Tran
9/26/2007 12:21:27 PM
CHEMIST

as we agreed.

Ali Al-Hakim
9/26/2007 03:08:41 PM
CHEMIST