CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208026Orig1s000

CHEMISTRY REVIEW(S)

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Recommendation:
Approval

NDA 208026
Review #1
Review Date (see page 5)

Drug Name/Dosage Form	linagliptin and metformin hydrochloride extended release tablet
Strength	5 mg/1000 mg and 2.5 mg/1000 mg linagliptin/metformin hydrochloride
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Boehringer Ingelheim

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	7/27/2015
0003	8/6/2015
0008	1/27/2016
0009	2/17/2016
0010	3/11/2016
0013	4/6/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Product	Muthukumar Ramaswamy	New Drug Products II/ONDP
Biopharmaceutics	Mei Ou	Biopharmaceutics/ONDP
Process	Shujun Chen	Process Assessment II/OPF
Microbiology	Shujun Chen	Process Assessment II/OPF
Facility	Vipulchandra Dholakia	Inspectional Assessment/OPF

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	Currently adequate to support the approved NDA 201281 (linagliptin/metformin HCl, by the same applicant; reference is provided)		
	III			by M.Ramaswamy/D. Christodoulou Per MAPP "CMC Reviews of Type III DMFs for Packaging Materials" the referenced Type III DMFs need not be reviewed for solid dosage forms.		
	III					
	III					
	IV					

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21748	Glumetza(metformin HCl) Authorized reference from applicant (Salix)
NDA	201280	Tradjenta (linagliptin) Same applicant
NDA	201281	Jentaduo ((linagliptin/metformin HCl) Same applicant

2. CONSULTS: not applicable

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Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (including the Overall Manufacturing Inspection Recommendation) is for **APPROVAL**.

Labeling comments will be finalized during the multi-disciplinary review managed by OND.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

B. Recommendation on Post-Marketing Commitments, Agreements, and/or Risk Management Steps- not applicable

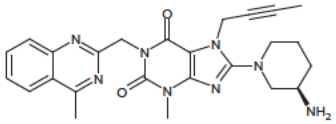
II. Summary of Quality Assessment

This is a 505(b)(1) application but not for an New Molecular Entity. The applicant has approved NDAs for the active ingredient linagliptin and full right of reference to the approved NDA for the active ingredient metformin HCl.

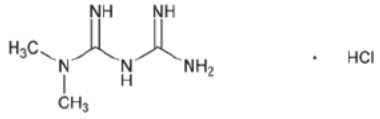
A. Drug Substance

Chemical Name or IUPAC Name/Structure:

Linagliptin is described chemically as 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-, the empirical formula is C25H28N8O2 and the molecular weight is 472.54 g/mol. The structural formula is:



Metformin hydrochloride is N,N-dimethylimidodicarbonimidic diamide hydrochloride, with a molecular formula of C4H11N5•HCl and a molecular weight of 165.63. The structural formula is:



NDA 201280 Tradjenta (linagliptin), by the same applicant, is referenced for all CMC information on the drug substance linagliptin. The NDA is currently approved and the reference is adequate.

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NDA 201281 Jentaduo ((linagliptin/metformin HCl), by the same applicant, is referenced for all CMC information on the drug substance metformin HCl. The NDA is currently approved and the reference is adequate.

B. Drug Product

The product is a film-coated tablet consist of immediate release saxagliptin and extended release metformin HCl, with two strengths: 5 mg/1000 mg and 2.5 mg/1000 mg linagliptin (immediate release)/metformin hydrochloride (extended release). (b) (4) . Polyethylene oxide is (b) (4)

2.5 mg/1000 mg - yellow oval tablet printed on one side in black ink with the BI logo and "D2" on the top line and "1000M" on the bottom line.
5mg/1000 mg - white oval tablet printed on one side in black ink with the BI logo and "D5" on the top line and "1000M" on the bottom line.

Excipients are
[Tablet core] polyethylene oxide, hypromellose, and magnesium stearate (b) (4) .
[Coatings] hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, arginine, polyethylene glycol, ferric oxide yellow (2.5 mg/1000 mg), carnauba wax, ferrosoferric oxide, propylene glycol, and isopropyl alcohol.

The product manufacturing process (b) (4)

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form. It includes content for Arginine, (b) (4)

Container Closure: HDPE bottles with desiccant (b) (4)

Expiration Date & Storage Conditions: 24 months at room temperature

C. Summary of Drug Product Intended Use

Proprietary Name	[not finalized by GRMP goal; see CDTL's memo]
Non Proprietary Name of the Drug Product	linagliptin and metformin hydrochloride extended

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