CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208026Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208026
Supporting document/s:	SDN-1
Applicant's letter date (CDER Stamp Date):	July 27, 2015
Product:	Linagliptin/metformin XR FDC
Indication:	Type 2 diabetes mellitus
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Review Division:	Metabolism and Endocrinology Products
Reviewer:	David B. Carlson, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
Division Director:	Jean-Marc Guettier, M.D.
Project Manager:	Richard Whitehead, M.S.
Review Completion Date:	4/20/16

Disclaimer

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Review Notes and Abbreviations/Key

Some of the sponsor's tables and figures from the electronic NDA submission have been included and cited in this review. All drug-related trends are discussed in relation to concurrent vehicle control groups in each study unless otherwise noted.

Key: Linagliptin (LINA); Metformin HCl extended release (metformin XR, aka metformin ER); fixed-dose combination (FDC), once daily dosing (QD); mg/kg (mg/kg/day); MRHD (maximum recommended human dose); IR (immediate release), XR (extended release); polyethylene oxide (PEO), polyethylene glycol (PEG); molecular weight (MW)

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1 Executive Summary

1.1 Introduction

Boehringer Ingelheim (BI) submitted NDA 208026 for a combination of two approved drugs, linagliptin and metformin extended release (metformin XR), in fixed-dose combination (FDC) tablets to be given once daily (QD) to treat type 2 diabetes mellitus. BI owns linagliptin (NDA 201280) and linagliptin plus metformin immediate release (metformin IR) FDC tablets (NDA 201281) and cites a complete 'right of reference' to all information supporting the metformin extended release (metformin XR) drug substance and drug product information under NDA 21748 (GLUMETZA®). Nonclinical support for the safety of the proposed FDC tablets is claimed from cross-referencing information in the approved drug products. Clinical studies supporting the new FDC drug product were limited to Phase I, bioequivalence trials in healthy men and women.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical information was submitted to support the proposed linagliptin and metformin XR FDC tablets. The Sponsor relied entirely on cross-referenced nonclinical data from previously approved monotherapy drugs (linagliptin, metformin XR) and linagliptin plus metformin IR FDC. The drug substances in the proposed FDC tablets are identical to those previously approved. Cross-referenced extended release metformin is marketed as GLUMETZA® and the metformin drug substance is identical to that in the proposed drug product. A slight formulation modification is proposed for the extended release drug product compared to the referenced drug product. Clinical bioequivalence of the drug substances in the current formulation were confirmed and human exposures at the maximum recommended human dose (MRHD) are consistent with exposure to individual drug substances – $AUC_{0\text{-}24h}$ = 158 nM*h linagliptin (5 mg QD) and $AUC_{0\text{-}24h}$ = 159 µM*h metformin XR (1000 mg QD).

There are no existing or new pharmacology or toxicology concerns about the listed drug substances proposed in the new FDC drug product. The pivotal nonclinical issues in the proposed drug product are (b) (4) compared to referenced metformin XR and (b) (4) The Sponsor stated that no novel excipients were used in the drug product formulation and that no new impurities, degradation products, (b) (4) were identified.

Nonclinical review of the drug product excipients and specifications independently verified that there are no new excipients or impurities in the proposed drug product. The polyethylene oxide used in the drug product, (b) (4)

(b) (4) PEGs and PEOs are marketed over-the-counter (OTC; i.e., without a prescription) as laxatives. The OTC laxatives are typically in the range of (b) (4) g/mol with recommended dosage of approximately (b) (4) g/day. No absorption or systemic toxicity are predicted from the (b) (4) g/mol PEOs in the listed and proposed metformin XR formulations compared to the OTC laxatives. Laxative effects are not expected from the approximately (b) (4) mg/day PEO excipient exposures, (b) (4) than OTC laxatives. Any potential laxative effects for the XR tablets would be expected to be simply a clinical tolerability issue and not a toxicity issue.

Several commercial (b) (4) coating agents were used in different film-coat layers of the drug product. The exact (b) (4) formulations have not been previously used in listed drug products but the Sponsor provided qualitative and quantitative composition of the (b) (4) coating agents and printing ink. A review of all components of the (b) (4) formulations verified their use in approved drug products in the FDA Inactive Ingredients Guide[1] and no novel excipients were identified.

Combination toxicology studies of linagliptin and metformin coadministration in rats were previously reviewed and cross-referenced to support the new linagliptin plus metformin XR drug product. No unexpected toxicity or significant supra-additive or synergistic interactions from combination treatment were identified. As summarized in the Pharmacology/Toxicology Review for NDA 201281 (linagliptin plus metformin IR FDC):[2]

> "Toxicity in nonclinical studies was driven by metformin, as expected based on dosing ratios and large safety margins with linagliptin. Major target organs of metformin were heart and liver, as evidenced by heart hypertrophy with immune cell infiltration/inflammation and liver hypertrophy with concomitant hepatic injury and elevated LFT biomarkers, starting at approximately 10-times the expected clinical AUC exposures. Linagliptin coadministration did not have any apparent effect on heart, liver or other metformin-related toxicity on target organs including stomach and GI tract, salivary glands, lymphoreticular tissues, or reproductive tissues."

[1] U.S. Food and Drug Administration, Inactive Ingredient Search for Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm
[2] Carlson DB. NDA 201281, Pharmacology/Toxicology Review, 10/4/11

Embryofetal toxicity was observed in rats treated with metformin alone and with linagliptin and metformin coadministration as noted in the nonclinical review for NDA 201281. The current label for linagliptin plus metformin IR FDC (JENTADUETO®) includes the embryofetal rat findings and the information is maintained in the proposed label for this drug product. As noted in the Pharmacology/Toxicology Review for NDA 201281 (JENTADUETO®),[2]

> "The mechanism of metformin-induced teratogenicity was not investigated. Clearly there are differences in the embryofetal study results for this NDA compared to those described on the existing metformin labels and in other DPP4 inhibitor nonclinical programs. It is likely the maternal toxicity at teratogenic doses contributed to fetal findings, since there were no fetal malformations in the absence of metformin-induced maternal toxicity. It is equally important to emphasize that both metformin alone and the combined linagliptin plus metformin treatment were not teratogenic at approximate clinical exposures (by AUC), consistent with the current metformin label."

1.3 Recommendations

1.3.1 Approvability

Nonclinical data (cross-referenced from approved drugs) support the safe use of linagliptin plus metformin extended release FDC tablets under the proposed uses. The pharmacology/toxicology reviewer recommends approval.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are needed.

1.3.3 Labeling

No new nonclinical information was provided and no updates are necessary for nonclinical data described in existing labels. The Sponsor submitted proposed labeling updates in compliance with the 'Pregnancy and Lactation Labeling Rule' (PLLR). The proposed labeling is based on labels for linagliptin monotherapy, metformin XR monotherapy, and linagliptin/metformin IR FDC tablets. Labeling recommendations were provided directly on the Division's shared document.

2 Drug Information

2.1 Drug

Jentadueto XR™ (proposed)
Linagliptin and metformin HCl extended release (XR) FDC film coated tablets.

2.1.1 CAS Registry Number

Linagliptin – 668270-12-0
Metformin HCl – 115-70-4; metformin (free base) 657-24-9

2.1.2 Generic Name

Linagliptin / metformin HCl XR

2.1.3 Code Name

Linagliptin (BI 1356; BI 1356 BS)

2.1.4 Chemical Name

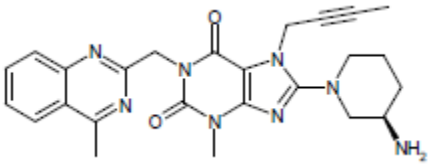
Linagliptin – 1H-purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butynyl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-
Metformin HCl – 1,1-dimethylbiguanide hydrochloride;
N,N-Dimethylimidodicarbonimidic diamide hydrochloride

2.1.5 Molecular Formula/Molecular Weight

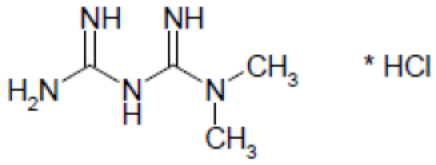
Linagliptin – $C_{25}H_{28}N_8O_2$ / 472.54 g/mol
Metformin HCl – $C_4H_{12}ClN_5$ / 165.62 g/mol

2.1.6 Structure (or Biochemical Description)

Linagliptin



Metformin HCl



* HCl

2.1.7 Pharmacologic class

Dipeptidyl peptidase 4 (DPP-4) inhibitor (linagliptin) /
Biguanide (metformin HCl)

2.2 Relevant IND/s, NDA/s, and DMF/s

IND [redacted] (b) (4)
IND [redacted] (b) (4)
NDA 201280 – Linagliptin (TRADJENTA®)
NDA 201281 – Linagliptin/metformin HCl FDC (JENTADUETO®)
NDA 021748 – Metformin HCl extended release (GLUMETZA®)

2.2 Drug Formulation

Two fixed-dose combination, film coated tablet strengths are proposed for QD dosing (see Sponsor's description in Table 1):

2.5 mg linagliptin / 1000 mg metformin XR
5 mg linagliptin / 1000 mg metformin XR

Table 1 – Key drug product information

Key information of linagliptin / metformin hydrochloride extended release (ER) coated tablets

Name of the drug product:	linagliptin / metformin hydrochloride extended release (ER) coated tablets
Drug substances:	Linagliptin Metformin hydrochloride
Company:	Boehringer Ingelheim
Dosage form:	Tablets (extended release coated tablets)
Indication:	Adult patients with type 2 diabetes mellitus
Strengths:	2.5 mg linagliptin + 1000 mg metformin hydrochloride 5 mg linagliptin + 1000 mg metformin hydrochloride
Route of administration:	Oral use

A schematic of the drug product, consisting of a metformin HCl extended release core and an immediate release layer of linagliptin is shown in the Sponsor's Figure 1.

Figure 1 – FDC Coated Tablet (Schematic)

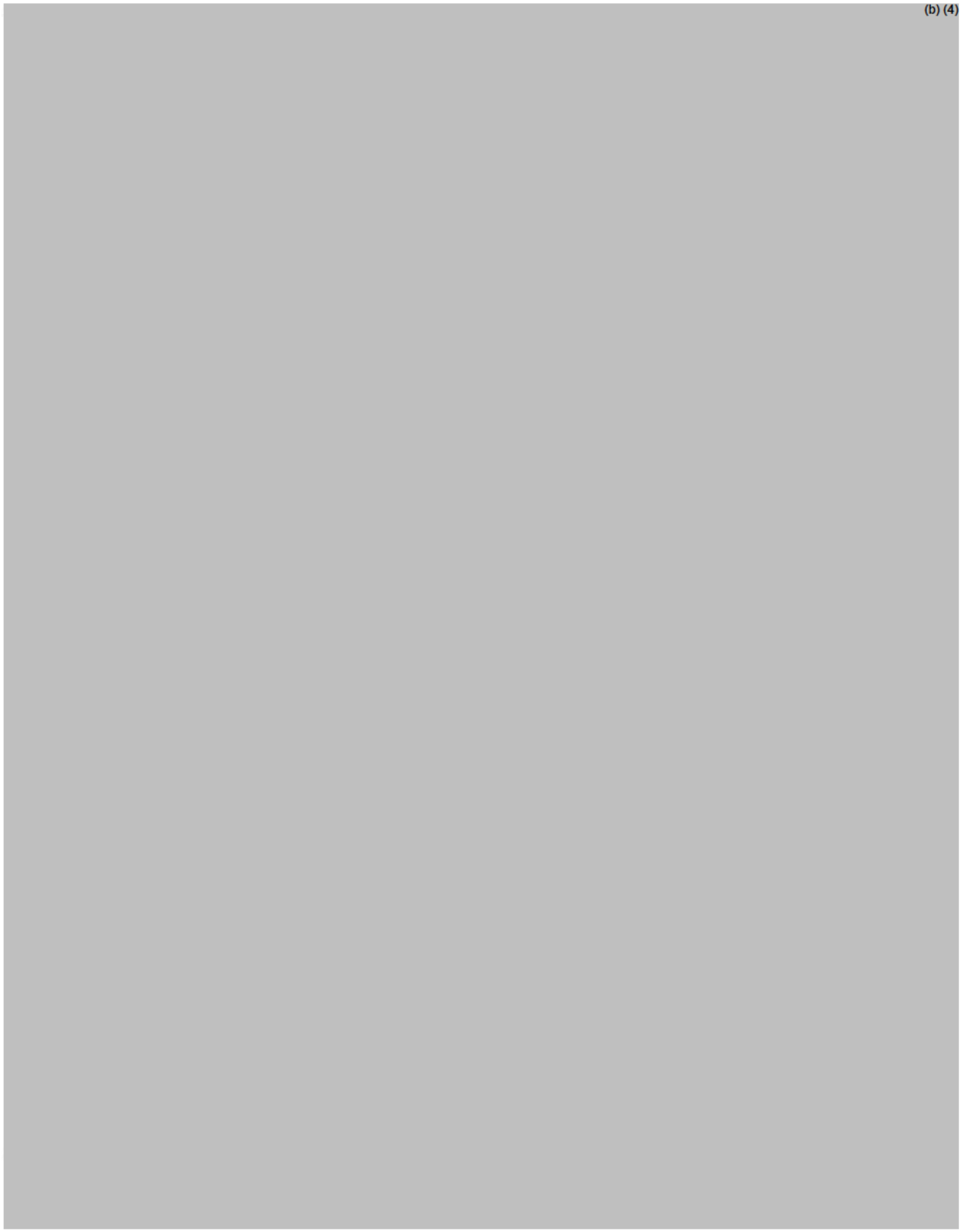
The Sponsor's summaries of inactive ingredients in the film coated tablets are shown in Table 2 and Table 3, below. The Sponsor stated the drug product formulation "uses excipients ((b) (4) , mixtures of excipients) that are commonly used in similar proportions in approved oral drug products. All excipients are compendial." An independent analysis of the drug product formulation by this Pharmacology/Toxicology Reviewer confirmed that all listed excipients are found in FDA's public Inactive Ingredients Guide (IIG)[3], (b) (4) (b) (4) The individual components in the commercial formulations were provided and all compounds were found in similar oral products described in the IIG. Discussion of notable individual excipients (b) (4) formulations are provided below.

[3] U.S. Food and Drug Administration, Inactive Ingredient Search for Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm, accessed 4/20/16

Table 2 – Drug Product Composition

Qualitative and Quantitative Composition of Linagliptin/Metformin HCl ER Coated Tablets, 2.5 mg/1000 mg and 5 mg/1000 mg

(b) (4)



(b) (4)

[redacted]

[4] Carlson DB. (b) (4), Pharmacology/Toxicology Memo to File, 6/14/13

The manufacturer stated that all excipients and colors in the (b) (4) formulations used in the linagliptin/metformin XR tablets are compendial and previously approved for human use. (b) (4) The Sponsor did provide the qualitative and quantitative composition of (b) (4) color used, which are shown in Table 3.

The individual components were verified by this Pharmacology/Toxicology Reviewer to be present in similar (b) (4) in the IIG. Table 3 notes the (b) (4) (b) (4) . However, the (b) (4) Black is used only as a printing ink and the total amount listed in the drug product (Table 2) is (b) (4) Thus, (b) (4) of ink used to label the approximately (b) (4) tablets will contain several orders of magnitude (b) (4) noted in the printing ink's formulation, does not present a significant oral exposure risk, and is in fact (b) (4) used in oral drug products listed in the IIG.

Table 3 – [redacted] Coating [redacted] Composition

Qualitative and Quantitative Composition of [redacted] Coating Agents [redacted]

[redacted]

2.4 Comments on Novel Excipients

The Sponsor claims that no novel excipients are used in the drug product. All excipients listed in the drug product information are compendial and controls according to the current compendial monograph for each excipient as noted by the Sponsor in their submission.

The Sponsor stated that (b) (4) coating agents and printing inks used in the drug product are non-compendial commercial excipient mixtures that meet regulatory and compendial requirements for their intended use.

2.5 Comments on Impurities/Degradants of Concern

Drug substances are identical to those previously approved and sourced from the same manufacturing sites as the approved products. Impurities and degradants in the approved drug substances have been qualified nonclinically and previously reviewed.[5,6] No drug product impurities or degradants of concern were noted by the Sponsor or the CMC/Quality Reviewer. The Sponsor stated that specifications comply with ICH Q6. This Pharmacology/Toxicology Reviewer did not identify any impurity concerns based on a review of the drug product specifications.

2.6 Proposed Clinical Population and Dosing Regimen

2.7 Regulatory Background

This is the original submission for linagliptin/metformin XR tablets. All drug substances have been previously approved and the Sponsor owns, or has a written 'right of reference' to all of the drug substances and drug product components.

3 Studies Submitted

3.1 Studies Reviewed

None. No pharmacology or toxicology studies submitted. All nonclinical studies supporting the NDA are cross-referenced from the Sponsor's other NDAs.

3.3 Previous Reviews Referenced

Carlson DB. NDA 201281, Pharmacology/Toxicology Review, 10/4/11.
Carlson DB. (b) (4), Pharmacology/Toxicology Memo to File, 6/14/13.
Carlson DB. (b) (4), Pharmacology/Toxicology Review #1, 3/26/13.

[5] Carlson DB. NDA 201281, Pharmacology/Toxicology Review, 10/4/11
[6] Carlson DB. (b) (4) Pharmacology/Toxicology Review #1, 3/26/13

11 Integrated Summary and Safety Evaluation

The proposed linagliptin/metformin XR FDC tablet NDA was submitted in accordance with 21 USC 505(b)(1) for treatment of type 2 diabetes mellitus. No nonclinical studies were submitted. An integrated summary of nonclinical information of individual drug substances and linagliptin/metformin immediate release coadministration studies was provided. The Sponsor relied on cross-referencing existing nonclinical data from several listed individual and FDC drugs.

Pivotal nonclinical review issues were limited to potential impurities and novel excipients. The drug substances are identical to listed drugs and the drug product is only slightly modified from the listed linagliptin/metformin IR FDC and the listed metformin XR drug product (GLUMETZA®). The Pharmacology/Toxicology review did not identify any new safety concerns. No novel excipients or unqualified impurities were identified.

Clinical bioavailability/bioequivalence studies confirmed similar pharmacokinetic profiles for linagliptin and metformin compared to individual drug substances and the listed linagliptin/metformin immediate release formulation. Pharmacology and toxicology studies conducted with linagliptin, metformin, and linagliptin/metformin coadministration support proposed use of the new extended release FDC clinical formulation.

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/s/

DAVID B CARLSON
05/03/2016
Nonclinical approval recommendation

TODD M BOURCIER
05/04/2016
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208026 **Applicant:** Boehringer Ingelheim **Stamp Date:** 27 July, 2015

Drug Name: linagliptin/ metformin XR FDC **NDA/BLA Type:** 505(b)(1)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Data required for review are incorporated by reference from NDAs 201280 (linagliptin), 201281 (linagliptin/metformin FDC), and right of reference to NDA 021748 (metformin XR).
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		Extended release FDC formulation incorporates appropriate pharmacology/ toxicology studies by reference.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		Statements of GLP compliance included in referenced NDAs.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A. No special studies were requested. Justification of novel inactive ingredient was discussed with sponsor during pre-NDA phase and is a review issue.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Preliminary review of label shows pharmacology/toxicology sections incorporate language from listed drugs in the FDC drug product.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)			N/A. No issues were previously uncovered. Any impurity or degradant issues in the formulation will be addressed in the review.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			N/A.

N/A – not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __ Yes**____**

No issues were identified for incorporation in the 74-day letter.

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/s/

DAVID B CARLSON
09/11/2015
Nonclinical information supports filing

TODD M BOURCIER
09/11/2015
I concur