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APPLICATION NUMBER:

212595Orig1s000

NON-CLINICAL 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: 212595

Supporting document/s: SDN-1 (Original NDA)

Applicant's letter date
(CDER Stamp Date): 2 November, 2018

Product: Metformin HCl for Extended-Release Oral
suspension

Indication: Type 2 Diabetes Mellitus treatment

Applicant: Sun Pharmaceutical Industries Ltd.

Review Division: Metabolism and Endocrinology Products

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Review Completion Date: 6/17/19

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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.

Key: Metformin HCl (metformin); metformin HCl extended release (metformin XR); XR (extended release); type 2 diabetes mellitus (T2DM); MRHD (maximum recommended human dose); United States Pharmacopeia (USP)

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1 Executive Summary

1.1 Introduction

Sun Pharmaceuticals (Sun Pharma) submitted this NDA for metformin hydrochloride (metformin HCl; metformin) extended release oral suspension under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The metformin drug substance is identical to the referenced listed drug owned by Sun Pharma (Glucophage®; metformin HCl extended release tablet) indicated for treatment of type 2 diabetes mellitus.¹ The proposed drug product contains a slightly different extended release formulation that is reconstituted as a liquid suspension for oral dosing and which contains no new excipients. The proposed formulation was compared to the reference extended release drug in a bioequivalence clinical trial but no new nonclinical studies were conducted or submitted to the NDA.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical pharmacology or toxicology study data were provided. The Sponsor is relying on the Agency's prior findings of safety and effectiveness for the metformin drug substance. The metformin nonclinical toxicity profile is well established and described in the labels of listed products. There are no new nonclinical safety concerns about the metformin HCl drug substance. The proposed oral suspension drug product formulation is novel but the extended release pellets contain qualitatively similar excipients as the reference listed extended release drug tablets. Primary issues in the nonclinical review concerned the safety of excipients at proposed concentrations and any potential drug product impurities, including extractable or leachable compounds in the liquid suspension formulation. A notable potential clinical effect of the liquid oral suspension formulation is intestinal discomfort and/or a laxative effect.

Potential for intestinal discomfort was identified early in the drug development process and the Sponsor addressed the potential concerns in the NDA. High amounts of ethyl cellulose and other non-digestible fiber will be consumed under the recommended liquid suspension dosing regimen. Similar compounds have been used in the reference listed drug's extended release formulation and in other listed drugs.² Total daily exposure to non-digestible fibers, including ethyl cellulose, will be approximately 3.1 g. Current recommended daily dietary fiber intake is 25 g/d or more for adults, while the Sponsor cited published references estimating daily fiber intake of 14 g/d in children and 17 g/d in adults. Oral suspension fiber supplements are also marketed without a prescription to increase daily fiber exposure and as laxatives. The additional 3.1 g/d fiber exposure expected from the oral suspension is modest compared to actual or recommended daily

¹ Approved under NDA 021202 (see also referenced DMF (b) (4)) and Glucophage XR® reference listed drug (see www.accessdata.fda.gov)

² NDA 21591 (RIOMET®; see <https://www.accessdata.fda.gov/scripts/cder/daf/>)

fiber intake. Nevertheless, transient or long-term intestinal discomfort from increased fiber consumption is possible in some individuals.

Xylitol, a sugar alcohol low-calorie sweetener included as an excipient in the liquid formulation, was not addressed by the Sponsor as a potential contributor to intestinal discomfort. The maximum 9 g/d xylitol exposure is similar to exposure from the Sponsor's listed metformin solution, RIOMET®.³ However, intestinal absorption of sugar alcohols may be impaired when ingested in large doses which can result in a laxative effect and/or diarrhea. Additive effects of intestinal discomfort may occur in sensitive individuals or in an episodic manner (e.g., due to varied dietary conditions) due to concomitant exposure to large amounts of xylitol and non-digestible fiber in the oral suspension formulation

Publicly available nonclinical data and current dietary guidelines regarding the proposed levels of ethyl cellulose, total fiber content, and xylitol do not raise approvability concerns, but this Reviewer cautions that intestinal tolerability is a potential concern with widespread use and adoption of the new liquid formulation.

No genotoxic impurities or other impurity concerns were identified. Four compounds in the extractable/leachable study exceeded 'analytical evaluation thresholds' but further analysis showed none of the compounds exceeded calculated individual 'acceptable daily intake' levels. The compounds were only observed after exaggerated storage conditions and none were considered to present a toxicity concern under recommended use of the drug product.

1.3 Recommendations

1.3.1 Approvability

Approval recommended from a nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

No changes are proposed to the nonclinical sections of the reference listed drug label for the new drug product formulation. No nonclinical labeling changes are recommended to the proposed label. Any potential minor labeling changes can be addressed during label discussions with the Sponsor.

³ RIOMET® (see current prescribing information at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm#>)

2 Drug Information

2.1 Drug

Metformin hydrochloride

2.1.1 CAS Registry Number

1115-70-4

2.1.2 Generic Name

Metformin HCl; metformin

2.1.3 Code Name

Metformin EROS (extended release oral suspension)

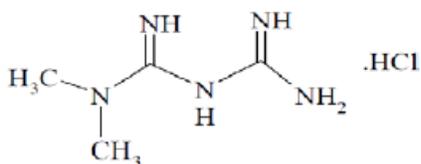
2.1.4 Chemical Name

Imidodicarbonimidic diamide; N,N-dimethyl-mono-hydrochloride; 1,1-dimethylbiguanide mono-hydrochloride; N,N-dimethylbiguanide mono-hydrochloride; N'-dimethylguanylguanide mono-hydrochloride

2.1.5 Molecular Formula/Molecular Weight

$C_4H_{11}N_5 \cdot HCl$ / 165.62 g/mol

2.1.6 Structure (or Biochemical Description)



2.1.7 Pharmacologic class

Biguanide

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

IND 127945 (metformin HCl extended-release oral suspension; Sun Pharma)

NDA 021202 (metformin HCl extended-release; Glucophage XR®)

DMF (b) (4) (metformin HCl; Sun Pharma)

Other DMF's are cross-referenced for container closure system components ('Right of Reference' letters are included for all cross-referenced components)

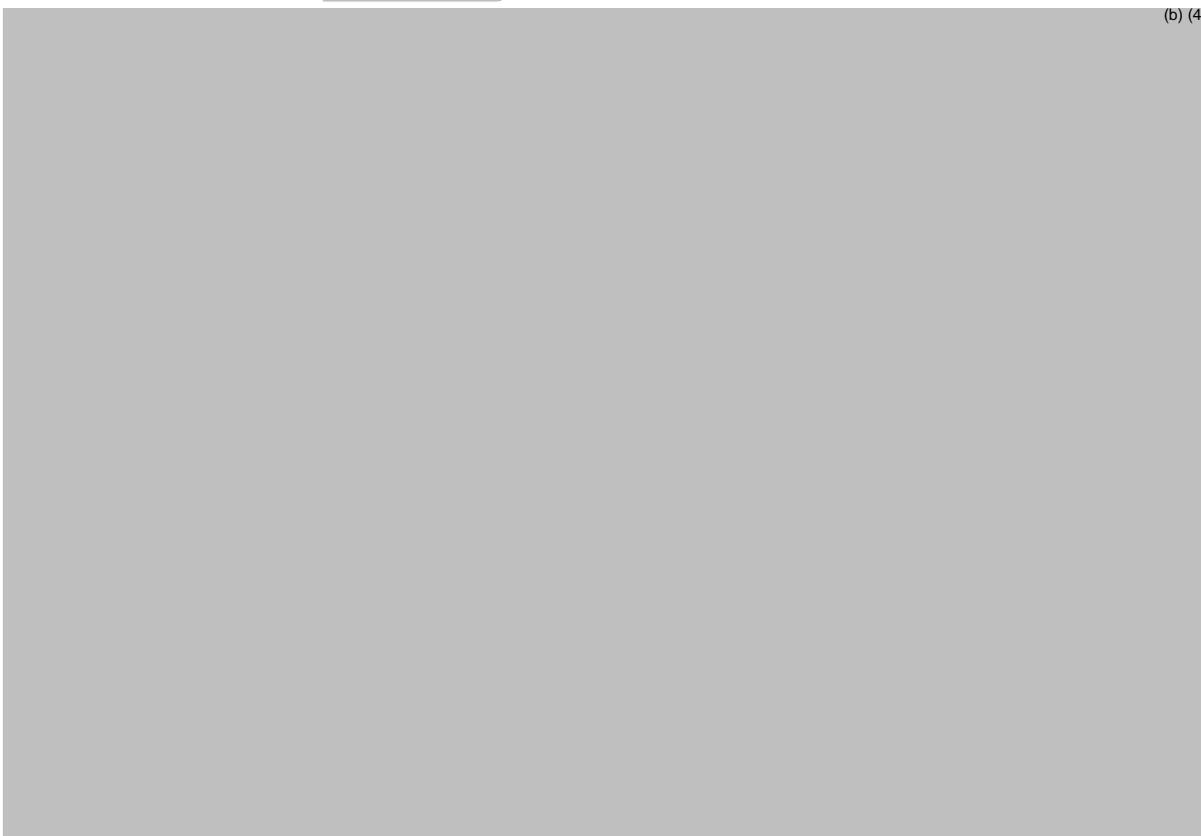
2.3 Drug Formulation

Metformin HCl drug substance is compendial (USP) and is identical to drug substance used by the Sponsor (abbreviated "SPIL" in the Sponsor's quality documents) in other listed drugs.⁴ The drug product consists of extended release pellets suspended in a vehicle for reconstitution and administration as a liquid suspension. The formulation is novel but the extended release pellets contain qualitatively similar excipients to the reference listed drug which allows once daily liquid administration after reconstitution and bioequivalent clinical exposures. A summary of the drug product formulation is shown below (Figure 1). Different types of packaging and reconstitution "packs" are provided which are not described in detail here (see the Quality Review for details of container closure systems and methods for extractables and leachables characterization). Potential toxicity of identified extractables and leachables is discussed below (Review Section 2.5 Comments on Impurities/Degradants of Concern).

⁴ Detailed drug substance information included in Drug Master File No. (b) (4)

Figure 1 – Drug product formulation summary

SPIL's test formulation is an extended release (b) (4) oral suspension formulation of metformin 100 mg/mL, which is bioequivalent to RLD 'Glucophage XR 750 mg'. The reference product, Glucophage® XR (metformin hydrochloride) of Bristol-Myers Squibb is an extended release (ER) tablet formulation (b) (4). However, SPIL's test product, Metformin Hydrochloride for Extended Release Oral Suspension 100 mg/mL is an extended release liquid dosage form having advantage of ease of swallowability and dose flexibility. This product is based on Sun Pharma's extended release suspension technology which constitutes of the following (b) (4)



Sponsor summaries of drug product composition (Table 1, Table 2, Table 3) and excipient qualification (Table 4) are shown below. The excipient qualification table illustrates that all excipients in the current extended release formulation have been used in other listed drug products.

The maximum recommended human dose (MRHD) of the extended release drug product will result in approximately 3.1 g daily ingestion of non-digestible fiber from microcrystalline cellulose, Hypromellose, carboxymethyl cellulose, and ethyl cellulose, (Table 3, Table 4). The approximately (b) (4) g ethyl cellulose expected to be ingested daily exceeds excipient levels found in previously approved US listed drugs. Ethyl cellulose levels were discussed during the investigational phase and potential for intestinal discomfort from daily fiber ingestion in the drug product excipients was addressed by the Sponsor and is discussed in the Safety Pharmacology section below (Review Section 4.3 Safety Pharmacology).

Xylitol, a sugar alcohol, has been included as an excipient at similar levels in other listed drugs including the Sponsor’s own RIOMET® (metformin HCl solution) which they reference in the NDA (Table 4). High exposures to sugar alcohols may have a laxative effect or induce diarrhea, typically transiently during initial exposures. Potential for the xylitol excipient to contribute to intestinal discomfort is also discussed along with ethyl cellulose and non-digestible fiber in the Safety Pharmacology section, below (Review Section 4.3 Safety Pharmacology).

Table 1 – Drug product components qualitative summary

Ingredients	Compendial Reference	Function
(b) (4)		
Metformin Hydrochloride	USP	(b) (4)
Xylitol (b) (4)	USNF	
Microcrystalline Cellulose (b) (4)	USNF	
(b) (4)		
Xanthan Gum (b) (4)	USNF	
Methyl Paraben	USNF	
Propyl Paraben	USNF	
(b) (4) Strawberry Type FL # 28082	In-House	
Sucralose (b) (4)	USNF	
Colloidal Silicon dioxide (b) (4)	USNF	
(b) (4)	USP	

From Quality Overall Summary, Drug Product (Section 2.3.P)

Table 2 – Drug product composition (b) (4) Strawberry Type FL #28082)

(b) (4) Strawberry Type FL # 28082	
Components	Compendial Reference(s)
(b) (4)	

From Quality Overall Summary, Drug Product (Section 2.3.P)

Table 3 – Drug product components quantitative summary

Ingredients	mg/mL	%w/w
(b) (4)		
Metformin Hydrochloride USP #		(b) (4)
Xylitol USNF	(b) (4)	
Microcrystalline Cellulose	(b) (4)	
	(b) (4)	
Xanthan Gum USNF	(b) (4)	
Methyl Paraben USNF		
Propyl Paraben USNF		
(b) (4) Strawberry Type FL # 28082		
Sucralose USNF	(b) (4)	
Colloidal Silicon dioxide USNF	(b) (4)	
	(b) (4)	
Total	(b) (4)	100.00
(b) (4)		

From Quality Overall Summary, Drug Product (Section 2.3.P)

Table 4 – Excipient qualification summary



(b) (4)

(b) (4)



From Quality Overall Summary, Drug Product (Section 2.3.P)

2.4 Comments on Novel Excipients

The Sponsor claimed the drug product contains no novel excipients and referenced the FDA Inactive Ingredients Database (IID) for all excipients in the formulation (summarized in Table 4 above).⁵ This Pharmacology/Toxicology reviewer confirmed all excipients have been used previously in US listed drug products and are listed in FDA's Inactive Ingredients Database in similar or lower concentrations with any exceptions assessed in this review.

The proprietary flavor, (b) (4) Strawberry Type FL # 28082, is not listed in IID but it has been used in a previously listed drug product by the Sponsor (NDA 21591) at higher daily exposures (maximum (b) (4) mg) compared to estimated exposures (see Table 4).⁶ The Sponsor's submission also included a list of individual ingredients in the strawberry flavoring and a 'Declaration' that all individual flavor ingredients are present at below 0.1% w/w with the exception of propylene glycol and glycerine. The Sponsor noted the 0.1% w/w limit is consistent with "the justification limit for current 'FDA review practice' for generic drugs reviewed under Abbreviated New Drug Applications" and those levels are also consistent with ICH Q3B(R2) Guidance for 'degradation products' as drug product impurities.⁷ Levels of propylene glycol and glycerine in the strawberry flavoring are also consistent with prior excipient use in the IID. No toxicity concerns were identified from the flavoring or its individual components.

2.5 Comments on Impurities/Degradants of Concern

Potential impurities in the drug product contributed by the metformin drug substance have been assessed in the previously described USP manufacturing process for the reference listed drug.⁸ No new impurities or degradants which may pose a safety concern were identified in the proposed drug product.

The Sponsor described results from extraction experiments under extreme conditions in a report on the potential extractable and leachable compounds from the container closure system. Risk assessments were conducted for impurities and 'extractable' compounds from the extraction experiments and described in a Risk Assessment Report provided in the application. No elemental impurities were observed at levels that exceeded permitted daily exposure (PDE) in ICH Q3D Guidance.⁹ Four chemicals were identified in the Sponsor's risk assessment that exceeded the analytical evaluation threshold (AET). None of the compounds were genotoxic in either rule-based or statistically-based in silico analyses. 'Acceptable Daily Intake' (ADI) levels were

⁵ U.S. Food and Drug Administration, Inactive Ingredient Search for Approved Drug Products, <http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm>

⁶ NDA 21591 (RIOMET®); see <https://www.accessdata.fda.gov/scripts/cder/daf/>

⁷ ICH Guidance for Industry, Q3B(R2) Impurities in New Drug Products, 2006

⁸ See referenced NDA 021202 and DMF (b) (4)

⁹ ICH Guidance for Industry, Q3D Elemental Impurities, 2015

estimated for each compound and all estimated daily exposures fell below the estimated ADI (summarized in Sponsor's Table 5 and Table 6).

Table 5 – Extractable compounds above Analytical Evaluation Threshold

Summary of Extractable detected above AET during GC/MS screening of extracted samples from Pack (b) (4) under Experiment C.

Component Name	Concentration in $\mu\text{g}/\text{CCS}$	Concentration in $\mu\text{g}/\text{day}$
(b) (4)		

Table 6 – Exposure and ADI summary for extractables

Sr. No.	Extractables	Concentration ($\mu\text{g}/\text{day}$)	Acceptable daily intake ($\mu\text{g}/\text{day}$)	Structure	DEREK and TOPKAT concern (Remark)
(b) (4)					

Assessment of the above extractable/potential leachable was done through software DEREK: Rule based and TOPKAT: Statistics based and also from literature. From the data gathered through different source it has been revealed that all of the above mentioned extractable are nonirritant, non-sensitizing, non-genotoxic and have low toxicity potential. The observed concentration (μg) of each extractable per day is below the ADI limit.

2.6 Proposed Clinical Population and Dosing Regimen

Metformin is considered the “first-line” oral therapy to treat type 2 diabetes mellitus uncontrolled on a modified diet and exercise regimen. Indicated populations are identical to those in the reference listed metformin XR formulation (NDA 021202).

2.7 Regulatory Background

Initial NDA review cycle. Investigated under IND 127945.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies were submitted.

3.2 Studies Not Reviewed

No nonclinical studies were submitted.

3.3 Previous Reviews Referenced

Nonclinical communications related to the drug product formulation were discussed and reviewed under IND 127945.¹⁰ See also reviews in the referenced DMF (b) (4) and NDA 021202.

¹⁰ Carlson DB. Pharmacology/Toxicology Review and Evaluation, 6/15/17.

4 Pharmacology

4.1 Primary Pharmacology

Metformin is currently the recommended “first-line” oral therapy for type 2 diabetes mellitus. Metformin is listed in the U.S. and worldwide as various immediate release and extended release oral formulations. The proposed metformin formulation is a (b) (4) mg/ml metformin HCl oral suspension designed for extended release and once daily dosing.

Metformin is a biguanide indicated for use in non-insulin dependent diabetes mellitus (i.e., type 2 diabetes mellitus (T2DM)) patients to improve insulin sensitivity when modified diet and exercise are insufficient to control blood glucose. The exact mechanisms of improved insulin sensitivity and decreased intestinal glucose absorption are not completely understood.

The reference listed drug label notes:¹¹

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

4.2 Secondary Pharmacology

No new data from secondary pharmacology studies were submitted. Known risks from metformin secondary pharmacology potential or interactions with metformin are included in WARNINGS (boxed), CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections, including listing of potential drug-drug interactions in Tables 5 and 6, are described in the reference listed drug label.¹²

4.3 Safety Pharmacology

No new safety pharmacology information was submitted. An evaluation of potential intestinal discomfort from the ethyl cellulose excipient was provided in response to the

¹¹ Glucophage XR®. See <https://www.accessdata.fda.gov/scripts/cder/daf/>

¹² *IBID*

Agency's prior recommendation.¹³ Ethyl cellulose ((b) (4)) has not been used at the proposed (b) (4) g/d in listed drug product excipients according to the IID but it and other non-digestible fiber have been used in prescription and over-the-counter drug products and are encountered in a normal diet. Ethyl cellulose and related non-digestible fiber have been reviewed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and no acceptable daily intake (ADI) was specified and no daily dietary limit was considered necessary due to its very low toxicity.¹⁴ Fiber supplements are used 'over the counter' in the US as laxatives or for appetite control with dosage recommendations of 2.5 to 7.5 g/serving up to a maximum 30 g/d from divided oral dosing, consistent with daily dietary guidelines.¹⁵

The Sponsor estimated a maximum daily intake of approximately 3.1 g of non-digestible dietary fiber, consisting of approximately (b) (4) amounts ethyl cellulose (b) (4) and microcrystalline cellulose (b) (4) (Table 7). The additional daily non-digestible fiber in the drug product formulation is approximately (b) (4) % of the recommended daily dietary fiber intake of 25 to 38 g/d (females and males, respectively).¹⁶ The Sponsor cited various published references which found average daily fiber intake of less than 14 g/d in children and adolescents and 17 g/d for adults. Thus, estimated additional fiber intake of 3.1 g/d from the drug product formulation would still result in average daily fiber intake below current recommendations for daily fiber intake. Published references provided by the Sponsor note intestinal signs (bloating, diarrhea, or upset stomach) were absent in people who consumed 33 g to 50 g non-digestible fiber daily for various treatment periods. The additional approximately 3 g/d fiber intake could potentially cause intestinal discomfort in patients whose fiber intake is below recommended levels. However, any intestinal discomfort would be expected to be transient and not a long-term concern based on negligible contribution of dietary fiber to the recommended healthy intake levels.

Table 7 – Non-digestible fiber daily intake estimate

A large rectangular area of the document is redacted with a solid grey background. The redaction covers the entire content of Table 7. In the top right corner of this redacted area, the text "(b) (4)" is visible.

¹³ IND 127945, Pre-IND Meeting Written Responses, Meeting Minutes, 11/24/15

¹⁴ JECFA. 1989. Ethyl ether of cellulose, Report TRS 789-JECFA 35/24 (accessed 05/09/19 at http://www.inchem.org/documents/jecfa/jecval/jec_730.htm)

¹⁵ Psyllium. MedlinePlus (accessed 05/09/19 at <https://medlineplus.gov/druginfo/meds/a601104.html>)

¹⁶ Institute of Medicine. 2005. Dietary reference intakes for energy, carbohydrates, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: The National Academies Press. <https://doi.org/10.17226/10490>

An additional excipient, xylitol, is notable for the potential to have intestinal effects. Xylitol is a sugar alcohol that is used as a non- or low-caloric sweetener in foods, including foods marketed to diabetic patients. Intestinal absorption of sugar alcohols can be limited when consumed in large quantities, resulting in intestinal discomfort (e.g., cramping) and/or diarrhea. Xylitol is listed as an “osmogent” but it is likely included because of its sweetening effect on the liquid formulation. It has been used as an excipient in high concentrations, with up to 2 g to 4 g per dose listed in the IID, which are below the anticipated total 9 g/d exposure in the oral suspension. The Sponsor noted the maximum (b) (4) g daily exposure to xylitol in their listed metformin solution exceeds the 9 g/d in the current oral suspension (Table 4).¹⁷ In addition, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) did not set a maximum daily limit on xylitol consumption from food (i.e., no tolerability limit was identified to establish a maximum ‘acceptable daily intake’).¹⁸ Similar to ethyl cellulose and other fiber excipients in the drug product formulation, potential intestinal effects from xylitol are likely to be transient.

Publicly available nonclinical data and references provided by the Sponsor support the safety of individual excipients including ethyl cellulose and xylitol, however, concomitant exposure to non-digestible fiber and xylitol in the drug product formulation may have an additive effect on intestinal tolerability.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No nonclinical pharmacokinetic or toxicokinetic data were submitted. Clinical pharmacokinetics are described in the current reference listed drug label (summary reproduced below) and updated in the proposed label for the oral suspension extended release product.^{19,20}

Metformin HCl Absorption and Bioavailability

The absolute bioavailability of a GLUCOPHAGE 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of GLUCOPHAGE 500 to 1500 mg, and 850 to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption

¹⁷ RIOMET® (current prescribing information accessed at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm#>)

¹⁸ Joint FAO/WHO Expert Committee on Food Additives, Summary of Evaluations, (accessed at http://www.inchem.org/documents/jecfa/jecval/jec_2404.htm)

¹⁹ Glucophage XR®. See www.accessdata.fda.gov

²⁰ NDA 212595, eCTD 1.14.3 Listed Drug Labeling

rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Following a single oral dose of GLUCOPHAGE XR, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of GLUCOPHAGE, however, the extent of absorption (as measured by AUC) is similar to GLUCOPHAGE.

At steady state, the AUC and C_{max} are less than dose proportional for GLUCOPHAGE XR within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 $\mu\text{g/mL}$ for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from GLUCOPHAGE XR at a 2000 mg once-daily dose is similar to the same total daily dose administered as GLUCOPHAGE tablets 1000 mg twice daily. After repeated administration of GLUCOPHAGE XR, metformin did not accumulate in plasma.

Within-subject variability in C_{max} and AUC of metformin from GLUCOPHAGE XR is comparable to that with GLUCOPHAGE.

Although the extent of metformin absorption (as measured by AUC) from the GLUCOPHAGE XR tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of GLUCOPHAGE XR.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of GLUCOPHAGE 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of GLUCOPHAGE, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally $< 1 \mu\text{g/ml}$. During controlled clinical trials of GLUCOPHAGE, maximum metformin plasma levels did not exceed $5 \mu\text{g/ml}$, even at maximum doses.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance

(see Table 1) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

6 General Toxicology

No nonclinical studies were conducted or submitted to the NDA. Nonclinical sections of the reference listed drug substance describe known pharmacology and toxicology data for metformin and reflect FDA's prior findings of safety and effectiveness.

7 Genetic Toxicology

No genetic toxicology studies were conducted or submitted to the NDA.

8 Carcinogenicity

No carcinogenicity studies were conducted or submitted to the NDA.

9 Reproductive and Developmental Toxicology

No reproductive or developmental toxicology studies were conducted or submitted to the NDA.

11 Integrated Summary and Safety Evaluation

The proposed metformin extended release oral suspension was submitted in accordance with 21 USC 505(b)(2) for treatment of type 2 diabetes mellitus.

The drug substance is a currently listed drug owned by the Sponsor. The Sponsor is relying on the Agency's prior findings of safety and effectiveness as described in the listed drug label for extended release metformin. No new pharmacology or toxicology data were submitted. The Sponsor included reviews of available peer-reviewed literature and public data pertaining to metformin HCl nonclinical pharmacology and toxicology. All supporting nonclinical information was reviewed for this NDA, including prior submissions under the IND (which are cited in this review as appropriate).

The drug product formulation contains similar excipients to the reference listed drug product, but the oral suspension formulation is novel. Potential impurities, degradation products, residual solvents, excipients, and extractable or leachable compounds from the container closure system were described by the Sponsor. This Pharmacology/Toxicology review did not identify any new safety concerns with the proposed drug product components. Potential for intestinal discomfort in patients is possible due to concomitant exposure to large amounts of non-digestible fiber and the sugar alcohol xylitol in the drug product formulation. The clinical team should be informed about potential clinical intestinal issues, including a laxative effect and/or diarrhea.

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/s/

DAVID B CARLSON
06/17/2019 10:25:01 AM
Recommend approval - Nonclinical

TODD M BOURCIER
06/17/2019 03:50:32 PM
I concur