CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212595Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	212595
Priority or Standard	Standard
Submit Date(s)	November 2, 2018
Received Date(s)	November 2, 2018
PDUFA Goal Date	September 2, 2019
Division/Office	DMEP
Reviewer Name(s)	Andreea Lungu
Review Completion Date	August 29, 2019
Established/Proper Name	Metformin hydrochloride extended release
(Proposed) Trade Name	(Riomet ER)
Applicant	Sun Pharma
Dosage Form(s)	Oral solution 500 mg/5 mL
Applicant Proposed Dosing Regimen(s)	Starting dose: 500 mg (5 mL) orally once daily, with the evening meal Increase the dose in increments of 500 mg (5 mL) weekly, up to a maximum dose of 2000 mg (20 mL) once daily, with the evening meal
Applicant Proposed Indication(s)/Population(s)	RIOMET ER is a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and above with type 2 diabetes mellitus
Recommendation on Regulatory Action	Approve the round bottle presentation (b) (4)
Recommended Indication(s)/Population(s) (if applicable)	RIOMET ER is a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in patients 10 years of age and older with type 2 diabetes mellitus

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CMC	chemistry, manufacturing, and controls
CV	cardiovascular
DPP-4	Dipeptidyl peptidase-4
ER	extended release
FDA	Food and Drug Administration
GCP	good clinical practice
GLP-1	glucagon-like peptide 1
GLP-1 RA	GLP-1 receptor agonist
IND	Investigational New Drug Application
iPSP	initial pediatric study plan
IR	Immediate release
NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
TEAE	treatment emergent adverse event
TZD	thiazolidinedione
T2DM	type 2 diabetes mellitus

1. Executive Summary

1.1. Product Introduction

Metformin is a biguanide used as a first-line treatment for type 2 diabetes mellitus (T2DM). It was approved in 1994 in the US, and its efficacy and safety are well known. It is currently available in tablet form [immediate release (IR) and extended release (ER) formulations], and liquid form (IR formulation).

The applicant has developed a formulation of Metformin Hydrochloride Extended Release Oral Suspension 100 mg/ml, as an alternative for patients who have difficulty in swallowing such as elderly and pediatric patients. The proposed trade name for the product is Riomet ER. The applicant filed a 505(b)(2) application using Glucophage, and Glucophage XR as reference listed drugs. Glucophage was approved by the US FDA on October 22, 1998, and Glucophage XR on October 13, 2000.

The applicant is proposing the following indication for Riomet ER:

> *Metformin hydrochloride for extended-release oral suspension is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus.*

1.2. Conclusions on the Substantial Evidence of Effectiveness

No efficacy studies were performed with the drug product under review. The metformin extended release oral suspension (Riomet ER) product was bridged to the Glucophage XR product via a bioequivalence (BE) study, and therefore the findings of effectiveness with Glucophage XR can be extended to Riomet ER.

Glucophage XR is only approved for use in adults, but shares approved labeling with Glucophage IR which is metformin immediate-release and is indicated to improve glycemic control in adult and pediatric patients 10 years of age and older with T2DM. The reason behind Glucophage XR not being specifically approved for pediatric use is not clear but it is unrelated to safety and efficacy, possibly pertaining to potential swallowability issues or to business reasons by the innovator. In adults with T2DM, Glucophage XR and Glucophage IR are switched for one another, and this is reflected by the following statement in the approved product labeling, under the Dosage and Administration section, Adult Dosage section: “Patients receiving [Glucophage IR] may be switched to [Glucophage XR] once daily at the same total daily dose, up to 2000 mg once daily”. The Pharmacokinetics section, Absorption subsection states: “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 IR] tablets 1000 mg twice daily." The Clinical Studies section describes a 24-week double-blind, randomized study of Glucophage XR taken once daily and Glucophage IR taken twice daily. The totality of this information allows for adequate bridging between Glucophage XR and Glucophage in adults.

Further, Glucophage use in pediatrics is supported, per the prescribing information, "by evidence from adequate and well-controlled studies of [Glucophage IR] in adults with additional data from a controlled clinical study in pediatric patients 10 to 16 years old with type 2 diabetes mellitus which demonstrated a similar response in glycemic control to that seen in adults. In this study, adverse reactions were similar to those described in adults." This supports the finding that the safety and efficacy of Glucophage IR in adult and pediatric patients with T2DM is similar.

As a result, the Riomet ER drug product was adequately bridged to Glucophage XR via a bioequivalence bridge, and further bridged to Glucophage via clinical and clinical pharmacology information outlined in the prescribing information. Therefore, the indication of use for Glucophage can be extended to the drug product under review. This is supportive of an indication for Riomet ER for use in patients with T2DM age 10 and (b) (4).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Diabetes mellitus is a serious disease that affects 22 million people in the United States. Diabetes mellitus can lead to macrovascular and microvascular complications that can reduce the quality of life and longevity of afflicted patients. There are currently 12 classes of diabetes medications approved for the treatment of type 2 diabetes mellitus including multiple metformin products.

Since this is a 505(b)(2) product with the application based on a clinical pharmacology study and literature evidence to support a pediatric indication, a standard benefit risk assessment does not apply here. The reference metformin products, both ER and IR formulations have been approved in the US since 1994, and the risk benefit balance is well known.

The recommended approval is based on a three-way bridge between Riomet ER, Glucophage XR, and Glucophage IR. The applicant successfully bridged the Riomet ER drug product to the currently marketed Glucophage XR via a bioequivalence study. Glucophage XR is indicated to improve glycemic control in adult patients with T2DM. Therefore, the risk benefit profile of Glucophage XR in adults can be extended to Riomet ER. Since Glucophage XR is not approved for use in pediatrics, for unclear reasons unrelated to safety and efficacy, a further bridge to Glucophage IR, which is an immediate release metformin formulation approved for use in both adults and pediatric patients, had to be achieved. This was important since Riomet ER is a drug product specifically designed for patients with potential swallowability issues, which includes pediatric patients. Glucophage XR and Glucophage IR share the prescribing information, which is supportive of similar efficacy and safety between metformin IR and ER formulations in adults. In adults with T2DM, Glucophage XR and Glucophage are used interchangeably and this is reflected by the following statement in the product label: “Patients receiving Glucophage may be switched to Glucophage XR once daily at the same total daily dose, up to 2000 mg once daily”. Additional support of the interchangeability between metformin immediate release and extended release in adults with T2DM is provided by peer-reviewed literature submitted by the applicant, as well as professional association guidelines such as the American Diabetes Association Standards of Medical Care in Diabetes Guidelines who do not differentiate between metformin immediate release and extended release formulations. Additionally, available data is supportive of similar efficacy, safety, and clinical pharmacology parameters of metformin IR between adults and pediatric patients with T2DM. Per the Glucophage IR prescribing information, metformin IR has similar glycemic control and similar adverse profile in adults and pediatric patients 10-16-year-old with T2DM. All this information suggests that it can be inferred that the safety and efficacy of metformin extended release will be similar between adult and pediatric patients.

Notably, the applicant proposed two presentations for the to-be-marketed drug product, (b) (4) a round bottle pack. (b) (4) the round bottle pack can be approved at this time.

In conclusion, the product currently under review (Riomet ER) was successfully bridged to Glucophage XR, and Glucophage IR. All immediate release metformin drug products are approved for use in adult and pediatric patients age 10 and above with T2DM. Therefore, this 3-way bridge allows us to infer that Riomet ER will be safe and efficacious for use in adult and pediatric patients with T2DM age 10 and (b) (4).

I recommend approval of metformin extended release oral suspension for improving glycemic control in patients with T2DM age 10 and (b) (4), in the round bottle formulation. (b) (4)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2014, the Center for Disease Control estimated that 22 million people in the United States have diabetes. • Diabetes is associated with multiple complications including macrovascular and microvascular complications which may shorten and affect the quality of life of patients. • Studies have shown that improving glycemic control in patients with diabetes improved clinical outcomes (e.g., reduction in retinopathy). • Many diabetic patients also have additional risk factors such as smoking, obesity, hypertension and hyperlipidemia which contribute to their overall health burden.	• Diabetes is a serious condition associated with chronic morbidity and premature death. • Glycemic control of diabetes improves microvascular complications.
Current Treatment Options	• Twelve classes of drugs, including multiple metformin formulations, are FDA approved in the United States to improve glycemic control in patients type 2 diabetes. • The extended release formulations are currently available only in	• There are multiple effective treatment options available for the treatment of type 2 diabetes, including multiple IR and ER metformin formulations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	tablet form, cannot be crushed, and that may limit use in patients with swallowing issues.	•
Benefit	• Oral suspension formulation would allow use in patients who cannot swallow large pills. • Metformin formulation (ER) allows for once daily use vs metformin IR which is administered twice daily.	• Riomet ER is the first metformin extended release oral suspension formulation, which can potentially expand the usability of metformin extended release to populations with swallowing issues such as the elderly and pediatric populations. • Since Riomet ER is recommended for once daily use, this could potentially increase compliance when compared to metformin IR (used twice daily).
Risk and Risk Management	• The safety of Riomet ER is expected to be similar to all other extended release metformin products. • The applicant proposed two container presentations, however one container presentation raised concerns regarding patient safety (b) (4) • Alcohol dumping studies show that taking the drug product with alcohol 5% or will impact the dissolution profile.	• Riomet ER is a metformin extended release product, and the risks with the reference drug are well described in the prescribing information. • (b) (4) • Alcohol dissolution issues can be mitigated via labelling.

1.4. Patient Experience Data

Not applicable.

2. Therapeutic Context

2.1. Analysis of Condition

Type 2 diabetes mellitus (T2DM) is a disease of impaired glucose homeostasis resulting in chronic hyperglycemia that is associated with significant morbidity and mortality due to microvascular and macrovascular pathologies, and is a major cause of hospitalization, blindness, renal failure, amputations and cardiovascular (CV) disease. Patients have varying degrees of insulin resistance and are unable to maintain euglycemia with endogenous insulin secretion.

There is no cure for T2DM, but therapies aimed at improving glycemic control are available. Currently approved therapies in T2DM aim to improve glycemic control by improving insulin resistance, enhancing insulin secretion, or increasing glucose excretion.

2.2. Analysis of Current Treatment Options

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes include:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 receptor agonists (GLP-1 RA)
- SGLT2 inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)

- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colesevelam hydrochloride)

Despite the relatively large number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug.

Relevant for this application, metformin was approved by US FDA in December 1994. It is now widely used alone as immediate release tablets, extended release tablets and oral solution; and in combination with a range of oral hypoglycemic agents.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Riomet ER is not approved in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant submitted a pre-IND meeting request on September 29, 2015 to discuss the proposed development plan, clinical studies, and the filing strategy for the prospective NDA for Riomet ER. Written responses were issued by the FDA on December 1, 2015. The FDA generally agreed with the applicant regarding the proposed cross-over bioequivalence study to Glucophage XR. At that time, the applicant expressed the desire to claim pediatric indication for Riomet ER based on available literatures studies demonstrating safety and efficacy of metformin in pediatric patients and asked whether a waiver would be appropriate for this age group. The FDA stated that there was insufficient information to agree with the proposed waiver and advised the applicant to submit an initial pediatric study plan (iPSP).

The IND was submitted on May 17, 2017, and it contained the protocol for the proposed bioequivalence study, as well as an iPSP with the proposal to conduct a pharmacokinetic (PK) study in pediatric patients with T2DM to support use of the metformin extended release oral suspension product in patients age 10-17. On August 14, 2017, the FDA sent comments to the iPSP, and stated the following:

> *Assuming that you are able to demonstrate bioequivalence of your product to the proposed listed drug in adults, we believe that you may be able to utilize the existing data bridging metformin immediate-release to metformin extended-release to conduct an assessment of efficacy in children for your product rather than conducting a clinical study. We note that you are proposing to utilize existing data to support that your drug product will have an acceptable safety profile in adolescent patients with type 2 diabetes mellitus. This approach*

is acceptable, but you should be aware that the adequacy of this data will be determined during the NDA review. With your NDA, you should include a detailed summary of the existing data, and also justify why data from a different population is appropriate to inform the safety profile in the target population.

The applicant submitted revisions to the pediatric study plan on September 29, 2017 proposing full waiver for the pediatric age group of birth to 16 years. The FDA did not agree with the waiver, and proposed the following:

- Partial waiver for the pediatric age group of birth to <10 years
- Assessment based on existing data in pediatric patients (10 to 16 years) with type 2 diabetes mellitus

The letter of agreement with the iPSP was sent on November 16, 2017.

3.3. Foreign Regulatory Actions and Marketing History

Riomet ER is not approved for marketing in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

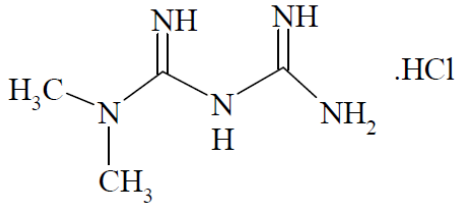
4.1. Office of Scientific Investigations (OSI)

No inspection was performed as part of this NDA. The clinical site where the bioequivalence study was performed was previously inspected in March 2017 and the analytical site was inspected in January 2018, under ANDAs 209735 and 210838. These dates fall within the surveillance interval.

4.2. Product Quality

Below are the nomenclature, molecular structure, molecular formula, CAS number, molecular weight, and pharmacological class of the drug.

United States Adopted Name (USAN)	**:**	Metformin Hydrochloride
Recommended International Non-Proprietary Name (rINN)	**:**	Metformin Hydrochloride
Compendial Name	**:**	Metformin Hydrochloride

Chemical Name (s)	**:**	Imidodicarbonimidic diamide, N,N-dimethyl-, monohydrochloride (or) 1,1-dimethylbiguanide monohydrochloride (or) N, N-dimethylbiguanide monohydrochloride (or) N'-dimethylguanylguanide monohydrochloride
Chemical Abstracts Service(CAS) Registry Number	**:**	[1115-70-4]
Structure of the Molecule	**:**	
Molecular Formula	**:**	$C_4H_{11}N_5.HCl$
Molecular Weight	**:**	Metformin Base: 129.17 Metformin Hydrochloride: 165.62
Pharmacological Class	**:**	Antihyperglycemic agent

Sun Pharmaceutical Industries Limited's Metformin Hydrochloride for Extended-Release Oral Suspension 100 mg/mL, subject of this NDA, is an Extended-Release Oral Suspension formulation with the following description:

Before reconstitution:

- Extended-Release Pellets in Top Chamber/drug pellets bottle: White to off-white pellets
- Immediate Release vehicle in bottom chamber/drug diluent bottle: White to off-white dispersion

After reconstitution: White to off white suspension containing white to off white pellets.

Metformin Hydrochloride for extended release Oral suspension 100 mg/mL is packed as follows

1) 10 mL Physician sample

2) 16 oz. (b) (4) bottle pack (Twin Chamber pack)

3) 16 oz. Round bottle pack.

Please see CMC review by Dr. Chris Galliford for details. Additionally, issues with the (b) (4) bottle pack will be discussed under Section 4.7 consumer study reviews.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

No new studies have been performed for the drug product under review, as the nonclinical pharmacology/toxicology profile of metformin is well known.

Dr David Carlson reported in his review:

> *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.*

The concerns about increase in intestinal discomfort and laxative effect come from the fiber content of the Riomet ER formulation, as well as the xylitol content. These are discussed

separately below.

It appears that the oral suspension formulation of metformin contains high amounts of ethyl cellulose and other non-digestible fiber, up to a total of 3.1 grams of fiber/day. However, since the daily recommended fiber intake for adults is 25 grams, and most adults consume on average less than the recommended amount, the addition of 3.1 grams is not likely to be a significant issue.

Xylitol, a sugar alcohol low calorie sweetener, is added to as an excipient in the metformin extended release oral suspension, with a maximum daily exposure of 9 grams. This is no different from metformin immediate release solution Riomet, however, when administered all at once it may result in increased incidence of gastrointestinal symptoms especially when added to the non-soluble fiber.

Dr Carlson noted that although the proposed levels of ethyl cellulose, total fiber content, and xylitol did not raise any approvability concerns based on publicly available nonclinical data, along with current dietary guidelines, he notes that intestinal tolerability is a potential concern with use of the new liquid formulation.

Please see full review by Dr David Carlson for details.

Reviewer comment: I believe that Dr Carson's concerns are well justified, and that these excipients may limit tolerability of this new metformin formulation. No clinical data is available to evaluate the clinical impact at this time.

4.5. Clinical Pharmacology

The applicant conducted an open-label single-dose three-way crossover study to assess the effect of food on bioavailability of Metformin Hydrochloride for extended release oral suspension 100 mg/mL (7.5 mL) and to assess the bioequivalence of Metformin Hydrochloride for extended release oral suspension 100 mg/mL (7.5 mL) with Glucophage XR (Metformin HCl) Extended-Release tablets 750 mg in healthy adult human subjects under fed condition. The study was conducted in India.

Of the 60 subjects enrolled in the study, 52 were completers. Of the remaining 8 patients, 4 were withdrawn, and 4 dropped out.

Each subject completing the study was dosed with test (Treatment A - fasting and Treatment B - fed) and reference (Treatment R - fed) products. All periods were separated by a 6-day washout period.

Pharmacokinetic (PK) results

Table 1 PK parameters of test product (A or B) and reference product (R)

T_{max} (hr)			C_{max} (ng/mL)			AUC_{0-t} (hr *ng/mL)		
R	A	B	R	A	B	R	A	B
7.4330	4.3654	5.5962	766.48	1067.56	815.39	8932.2920	7472.0207	7694.7811

$AUC_{0-\infty}$ (hr *ng/mL)			Half-life (hr)		
R	A	B	R	A	B
9252.3278	7662.8521	7894.0374	3.9897	4.6352	4.1916

Source: Section 2.5.2 Clinical Overview

The ratios of the log transformed PK parameters for products administered under fed conditions are presented in the table below.

Parameter	Test (B) vs Reference (R)
C_{max}	106.40 % (102.21 % – 110.75%)
AUC_{0-t}	87.11 % (83.95 % – 90.39 %)
$AUC_{0-\infty}$	86.33 % (83.15 % – 89.64%)

Source: Section 2.5.2 Clinical Overview

The Clinical Pharmacology reviewer concluded that bioequivalence was established between 750 mg extended-release oral suspension and 750 mg Glucophage XR extended-release tablet, as the 90% confidence interval (CI) of geometric mean ratios of Cmax, AUC_{0-t} and AUC_{0-inf} were all within the pre-defined 0.8 to 1.25 range. In this context, it is notable that there was a significant difference observed in the Tmax for the Riomet ER (fasting or fed) when compared to Glucophage XR. The Tmax for the reference product Glucophage XR was 7.4330 hours, and Tmax for the Riomet ER product was 4.3654 hours under fasting conditions, and 5.5962 hours under fed conditions.

Reviewer comment: It is not clear how the difference in Tmax will be reflected, if at all, in the efficacy and safety of the Riomet ER product in clinical practice.

Biopharmacology

An in vitro alcohol dissolution study was performed by the applicant, as required by the FDA for all extended release products. The results show that in the presence of high concentration of alcohol, the in vitro drug dissolution profiles of metformin extended-release oral suspension are

very different from the reference profile. At 20 minutes, about 20%, 20%, 21%, 33%, and 73% of metformin was released in the presence of 0%, 5%, 10%, 20%, and 40% alcohol. At 2 hours, about 62%, 69%, 77%, 93%, and 99% of metformin was released in the presence of 0%, 5%, 10%, 20%, and 40% alcohol.

This indicates that co-administration of the drug product under review with alcohol above 5% concentration would substantially accelerate the release of metformin from its extended-release formulation, resulting in a relatively earlier Tmax with higher Cmax and a potentially lower Ctrough. This profile may impact the efficacy of the drug product used as a once daily extended release formulations, and therefore will be reflected in the prescribing information.

Reviewer comment: Dose dumping may affect both safety (increase gastrointestinal adverse events) and efficacy of Riomet ER. Information will be added to the prescribing information to adequately define and mitigate the risks of dose dumping.

Additionally, the applicant submitted clinical pharmacology literature in support of the similarity of PK parameters between metformin IR and ER, as well as between pediatric and adult patients as follows.

1. Comparative PK of metformin IR and ER

Per the Glucophage prescribing information, following a single oral dose of metformin extended release, Cmax 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 metformin immediate release, however, the AUC is comparable to metformin immediate release.

Additionally, literature data suggests that the PK parameters of metformin immediate release in pediatric patients are similar to the PK parameters of metformin IR and ER in healthy adults. These parameters are presented in **Error! Reference source not found.** below.

Table 2 Comparison of Pharmacokinetic Parameters of Metformin IR in Pediatric Patients with T2DM and Healthy Adults vs Metformin XR in Healthy Adults

	Metformin 500 mg Tablet, Single Dose	Metformin 500 mg Tablet, Single Dose	Metformin 500 mg XR Tablet, Single Dose
Source	Gao X et al. 2003	Gao X et al. 2003	Drug Approval Package, Glucophage XR
Parameters	Pediatric T2DM Patients (12-16 yrs)	Healthy Adult Subjects (20-45 yrs)	Healthy Adult Subjects (18-40)
C_{max} [ng/mL]	898	925	645
AUC_{inf} [ng*h/mL]	6311	6634	6666

Source: Table 2 Clinical Overview

Reviewer comment: While it is unlikely that bioequivalence could be demonstrated between any ER and IR metformin products due to inherent differences related to specific characteristics of the two products, it is not necessary to demonstrate this to support the bridge between the Riomet ER drug product and metformin IR. It is important to note that the clinical pharmacology parameters of metformin IR appear to be similar in adults and pediatric patients that represent the target population. By extension, it is likely that the clinical pharmacology parameters for metformin ER will be similar between adults and pediatric patients. This further supports the potential extrapolation of efficacy findings for metformin ER from adults to children.

2. Comparative PK of metformin in adult and pediatric patients

For Metformin IR, the PK parameters were similar in pediatric patients age 12-16, and healthy adult volunteers as evidenced in **Error! Reference source not found.**.

Reviewer comment: The information in the Glucophage prescribing information is also supportive of similar PK parameters following metformin IR exposure between pediatric patients and adults, suggesting that no dose adjustment is needed. The sponsor submitted additional literature supportive of this. This further supports the potential extrapolation of efficacy findings for metformin ER from adults to children.

In conclusion, the Riomet ER drug product was successfully bridged to Glucophage XR, and further to Glucophage IR. Additionally, the clinical pharmacology parameters are similar between metformin IR and ER, both in adults and pediatric patients. Please see Clinical Pharmacology review by Dr Yunzhao Ren for details and refer to biopharmaceutical reviewer Dr Sarah Ibrahim.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Human factors (HF) studies conducted to evaluate the usability of the device were reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). Per the review, the purpose of this HF validation study was to demonstrate that the (b) (4) bottle design and its associated materials supports safe and effective use by the intended user populations, in the intended use environments, for the intended use scenarios; and ensure that use-related risks associated with the (b) (4) bottle design have been effectively mitigated. The HF validation study included four groups of representative users of the product: 15 pharmacists, 15 pharmacy technicians, 15 patients, and 15 caregivers. Participants did not receive training.

The study results showed several use errors, close calls, and use difficulties that occurred with critical tasks for healthcare providers reconstituting the metformin hydrochloride extended release oral suspension that may result in harm to the patient, pertaining to the (b) (4) bottle container presentation. Communication between the FDA and the applicant did not reconcile the issues, although the applicant proposed changes to the Instructions for Pharmacists to mitigate the errors. The DMEPA team concluded that, in the absence of new HF validation data, they do not find that product user interface of the (b) (4) bottle design supports safe and effective use by the intended users. As a result, DMEPA recommends approval for the round bottle container only at this time, and a Complete Response for the (b) (4) bottle and physician sample designs.

Please see DMEPA review for details.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled/completed	Study Population
Bioequivalence study-	Open label, randomized, three treatment, three period, six sequence, single dose crossover food effect and bioequivalence study	**Reference product**: Glucophage XR 750 mg tablets **Test product**: Metformin Hydrochloride extended release oral suspension 100 mg/mL, 7.5 ml	PK parameters	60/52	Healthy adults

5.2. Review Strategy

The clinical program only included a clinical pharmacology study bridging the oral suspension to the metformin extended release tablet. I briefly discussed this study in Section 4.5, and a detailed review can be found in the Clinical Pharmacology review by Dr Yunzhao Ren.

Additionally, per agreement with the FDA the applicant submitted literature to support use of Riomet ER in pediatric patients with T2DM. I reviewed selected relevant studies in support of a bridge between Riomet ER and metformin IR in support of a pediatric indication for Riomet ER in the integrated review of efficacy section.

6. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable as no efficacy trials have been conducted with Riomet ER.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable as no efficacy trials have been conducted with Riomet ER.

7.1.1. Primary Endpoints

Not applicable.

7.1.2. Secondary and Other Endpoints

Not applicable.

7.1.3. Subpopulations

Not applicable.

7.1.4. Dose and Dose-Response

Not applicable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Riomet ER is an oral suspension extended release metformin product which could be used by patients who have issues swallowing the large metformin extended release tablets currently marketed. While many other metformin formulations are currently marketed, the extended release formulations are all in tablet form, and the tablets are quite large and cannot be crushed. This change in formulation may allow more patients to switch from immediate release metformin (twice a day) to extended release metformin (once a day) and may lead to better medication compliance.

7.2.2. Other Relevant Benefits

None.

7.3. Integrated Assessment of Effectiveness

The efficacy of Riomet ER in adults can be inferred from the BE bridge between Riomet ER and Glucophage XR. As Riomet ER was found to be bioequivalent to the first reference product, Glucophage XR, the findings of safety and efficacy of Glucophage XR in adults can be extended to the Riomet ER product.

Glucophage XR is not approved in pediatrics for reasons that are not related to safety or efficacy concerns. While the reasons are not clear, it is likely that they are due to issues of swallowability of the non-crushable Glucophage XR tablet in this patient population, and also possibly due to innovator business decisions. As a result, the efficacy of Riomet ER in pediatrics is based on a further bridge between Glucophage XR and Glucophage IR, as well as supportive literature data.

Bridge between Glucophage XR and Glucophage IR

Glucophage XR shares approved labeling (the prescribing information) with Glucophage, which is metformin immediate-release (Glucophage IR), which is indicated to improve glycemic control in adult and pediatric patients 10 years of age and older with T2DM. In adults with T2DM, Glucophage XR and Glucophage IR are switched for one another, and this is reflected by the following statement in the approved product labeling, under the Dosage and Administration section, Adult Dosage section: “Patients receiving [Glucophage IR] may be switched to [Glucophage XR] once daily at the same total daily dose, up to 2000 mg once daily”. The Pharmacokinetics section, Absorption subsection states: “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 IR] tablets 1000 mg twice daily." The Clinical Studies section describes a 24-week double-blind, randomized study of Glucophage XR taken once daily and Glucophage IR taken twice daily. Thus, there is adequate bridging information for Glucophage XR and Glucophage IR for adult use.

The Pediatric Use section, Glucophage IR subsection, states: "The use of [Glucophage IR] in pediatric patients 10-16 years old for the treatment of type 2 diabetes mellitus is supported by evidence from adequate and well-controlled studies of [Glucophage IR] in adults with additional data from a controlled clinical study in pediatric patients 10 to 16 years old with type 2 diabetes mellitus which demonstrated a similar response in glycemic control to that seen in adults. In this study, adverse reactions were similar to those described in adults." This supports this Agency's finding that the safety and efficacy of Glucophage IR in adult and pediatric patients with T2DM is similar.

Given the findings above, the Agency can conclude that the applicant can appropriately rely on Glucophage IR given the relationship between Glucophage XR and Glucophage IR described in the approved labeling with respect to adult use; and that Glucophage IR has similar glycemic control and similar adverse event profile in adults and pediatric patients 10-16 years old for treatment of T2DM. Therefore, it is reasonable to further conclude that the safety and efficacy of Glucophage XR is similar between adult and pediatric patients.

In conclusion, Riomet ER can be considered adequately bridged to both Glucophage XR and Glucophage, and this constitutes the basis for my findings of efficacy.

Supportive literature data

Additionally, per the agreed iPSP, the applicant compiled available data to support a clinical bridge between metformin ER and metformin IR, to ultimately justify a pediatric indication for Riomet ER. This information is supportive and does not constitute a basis for the conclusion of efficacy.

A summary of the information submitted by the applicant with reviewer comments is presented below.

The applicant used the following arguments in support of the required bridge:

1. Similar disease progression and response to intervention between adult and pediatric patients with T2DM

The applicant argues that pediatric and adult patients with T2DM have similar disease

presentation, pathophysiology, progression, and similar efficacy outcome measures. In both adult and pediatric populations, the phenotype of T2DM appears similar, with insulin resistance, dyslipidemia, and obesity. The applicant states that there is currently no information in the literature to suggest fundamental differences exist between the adult and pediatric populations in disease characteristics or outcomes.

Reviewer comment: The information provided by the applicant is not entirely correct. It is not clear whether the disease is similar in adults and pediatric patients with T2DM, as the data in children is limited. The only large study in pediatric patients with T2DM, the TODAY study, suggested that, although the pathophysiology of the disease may be the same, T2DM in pediatric patients may have more aggressive rate of progression compared to patients diagnosed later in life. Specifically, treatment failure with metformin was seen in approximately half of the TODAY study participants over the course of 5 years, compared to 21% reported in adults (ADOPT trial). Regardless of whether such differences exist, metformin IR is used in treatment of T2DM in pediatric patients with similar efficacy and safety as for adult patients as reflected in the prescribing information.

2. Comparable efficacy and safety between metformin ER and IR

Adult patients

The applicant submitted an abstract of a systematic review[1] of 9 studies including 6316 adult patients to assess the efficacy, safety, and treatment adherence of metformin extended release in prediabetes or T2DM. It appears that the comparator was metformin IR in at least 4 studies, and the authors' conclusion was that there are no significant differences between metformin IR and XR regarding efficacy. The review concludes that metformin XR has at least similar efficacy and improved safety and adherence compared to metformin IR.

A multicenter study[2] evaluating the glycemic effects of a switch from metformin IR to ER in adults with T2DM age 27-77 years, concluded that the patients who were switched achieved comparable glycemic control on either metformin formulation.

In another study[3], adults with newly diagnosed T2DM were randomly assigned to receive extended release, or immediate release metformin in a double blind, 24-week trial. The safety and efficacy of the two metformin formulations was found to be similar.

To summarize these findings, a publication by Jabbour S and Ziring B, 2011 compared the glycemic effects of metformin IR and ER in patients with T2DM (Table 3).

[1] Fujii RK et al, 2015
[2] Fujioka K et al, 2003
[3] Schwartz S et al, 2006

Table 3 Effects of Metformin Immediate Release and Extended-Release Metformin on Glycemic Parameters in Patients with Type 2 Diabetes Mellitus

Product	Treatment	n[a]	Study Duration (weeks)	Mean BL HbA_{1c} (%)	Mean Change From BL HbA_{1c} (%)	Mean BL FPG (mg/dL)	Mean Change From BL FPG (mg/dL)
Patients managed previously with diet							
Glucophage®	Metformin (up to 2250 mg/day)	141	29	8.4	–1.4[b]	241.5	–53.0[b]
	Placebo	145		8.2	0.4	237.7	6.3
Glucophage® XR	Metformin ER 500 mg qd	115	16	8.2	–0.4[b]	182.7	–15.2[b]
	Metformin ER 1000 mg qd	115		8.4	–0.6[b]	183.7	–19.3[b]
	Metformin ER 1500 mg qd	111		8.3	–0.9[b]	178.9	–28.5[b]
	Metformin ER 2000 mg qd	125		8.4	–0.8[b]	181.0	–29.9[b]
	Metformin ER 1000 mg bid	112		8.4	–1.1[b]	181.6	–33.6[b]
	Placebo	111		8.4	0.1	179.6	7.6
Patients managed previously with diet and/or other OADs[c]							
Glucophage®	Metformin 500 mg/day	73	14	10.1	0.3[d]	282	–27
	Metformin 1000 mg/day	73		10.0	0.01[b]	281	–39[d]
	Metformin 1500 mg/day	76		9.7	–0.5[b]	262	–49[b]
	Metformin 2000 mg/day	73		10.1	–0.8[b]	288	–86[b]
	Metformin 2500 mg/day	77		10.0	–0.4[b]	287	–70[b]
	Placebo	79		9.9	1.2	279	–8
Glumetza®	Metformin ER 1500 mg qd	169	24	8.2	–0.7	190.0	–38.5
	Metformin ER 500 mg am/ 1000 mg pm	175		8.5	–0.7	192.5	–31.8
	Metformin ER 2000 mg qd	159		8.3	–1.1	183.9	–42.0
	Metformin 500 mg am/ 1000 mg pm	170		8.7	–0.7	196.5	–32.1
Patients treated previously with metformin ("switch studies")							
Glucophage®	Metformin 500 mg bid	67	24	7.1	0.14 (–0.04 to 0.31)[e,f]	127.2	14.0 (7.0–21.0)[e]
Glucophage® XR[11]	Metformin ER 1000 mg qd	72		7.0	0.27 (0.11–0.43)[e]	131.0	11.5 (4.4–18.6)[e]
	Metformin ER 1500 mg qd	66		7.0	0.13 (–0.02 to 0.28)[e]	131.4	7.6 (1.0–14.2)[e]
Metformin	Metformin bid (titrated)	332	20	7.1	0.14	145.6	4.2
Fortamet®	Metformin ER qd (titrated)	327		7.0	0.40	146.8	10.0
	Difference between treatments				0.25 (0.14–0.37)[e]		6.43 (0.57–12.29)[e]

[a]n indicates the number of patients with data for HbA_{1c}.
[b]P < 0.001 vs placebo.
[c] These studies included patients managed previously with diet as well as patients previously treated with other OADs (Other oral Anti-diabetics Drugs). Prior medications were first discontinued during a washout period before patients were randomized to study treatment.
[d]P < 0.01 vs placebo.
[e]95% confidence interval.
[f]n = 68.
Abbreviations: bid, twice daily; BL, baseline; ER and XR, extended-release; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; qd, once daily.
Reference: Jabbour S and Ziring B, 2011.

Source: Table 1 Clinical Overview

Additional studies supporting comparable safety and efficacy of metformin IR and ER in adults with T2DM were included by the sponsor, but not included here as the information is redundant.

Reviewer comment: I agree with the applicant that there is a large body of literature pointing to the similarity in efficacy and safety between metformin IR and ER in adults. Most importantly, the similar efficacy and safety between metformin IR and ER in adults with T2DM is also supported by the Glucophage and Glucophage XR prescribing information. The Glucophage and Glucophage XR label also contains the following wording in support of the two metformin formulations being used interchangeably: "Patients receiving Glucophage may be switched to Glucophage XR once daily at the same total daily dose, up to 2000 mg once daily".

Pediatric patients
No efficacy studies have been performed using metformin ER in pediatric patients with T2DM.

The available data for the safety of metformin ER in pediatric patients without diabetes is summarized in Section 8.10.

This, in addition to the clinical pharmacology information presented in Section 4.5, is supportive of the similarity between adults and pediatric patients with T2DM regarding clinical efficacy and clinical pharmacology parameters when using metformin formulations (IR or ER).

In summary, the Riomet ER drug product was successfully bridged via a BE study to the reference drug Glucophage XR, which is, in turn, bridged to the Glucophage IR product via the shared prescribing information, which includes clinical and clinical pharmacology data. Since metformin IR is approved for use in children with T2DM, with efficacy and safety similar to what was observed in adult patients with T2DM, it may be reasonable to infer Riomet ER safety and efficacy in pediatric patients with T2DM.

8. Review of Safety

8.1. Safety Review Approach

No clinical studies were performed by the applicant in support of this application.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Not applicable.

8.2.2. Relevant characteristics of the safety population:

Not applicable.

8.2.3. Adequacy of the safety database:

Not applicable.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Not applicable.

8.3.2. Categorization of Adverse Events

Not applicable.

8.3.3. Routine Clinical Tests

Not applicable.

8.4. Safety Results

8.4.1. Deaths

Not applicable.

8.4.2. Serious Adverse Events

Not applicable.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Not applicable.

8.4.4. Significant Adverse Events

Not applicable.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Not applicable.

8.4.6. Laboratory Findings

Not applicable.

8.4.7. Vital Signs

Not applicable.

8.4.8. Electrocardiograms (ECGs)

Not applicable.

8.4.9. QT

Not applicable.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

Not applicable.

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

No assessment has been performed, however, metformin IR is a widely used drug in the proposed pediatric population (T2DM, age 10-18), and the safety is well described in the literature and prescribing information.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Riomet ER is not approved in any country.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety of Riomet ER is expected to be similar to the safety of the reference product Glucophage XR.

8.9.3. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

In adults, the safety of Riomet ER in adults can be inferred from the BE bridge between Riomet ER and Glucophage XR. Therefore, the safety of Riomet ER is expected to be similar to the safety of Glucophage XR in this patient population.

No direct safety information is available for metformin ER in pediatric patients with T2DM. However, Glucophage XR and Glucophage share the prescribing information which states that the products can be switched for one another. This statement is supported by both clinical and clinical pharmacology information outlined in the prescribing information and presented in Section 7.3 of this review. Additionally, the Glucophage safety in adults and pediatric patients age 10-16 with T2DM was found to be similar as confirmed by a similar adverse events profile in a controlled clinical study in pediatric patients. The totality of this information allows us to conclude that the safety profile of Glucophage XR in similar in adults and pediatric patients 10-16 years of age with T2DM, and extend these safety findings to Riomet ER, the drug product under review. This constitutes the basis of the safety bridge between Riomet ER and the listed drugs.

The applicant submitted additional supportive literature outlining the use of metformin ER in obese adolescents, without T2DM.

In one study[4], 69 obese adolescents age 10-16 were randomized to receiving metformin ER 2000 mg or placebo with either moderate or vigorous exercise. The study did not report any serious adverse events (SAEs), the only adverse events (AEs) reported were a transient increase in transaminases, and temporary discontinuation of the study drug in one patient due to diarrhea. In addition, 6 patients were unable to tolerate the 2000 mg of metformin ER and the dose had to be reduced.

[4] Clarson CL et al, 2014

A second study[5] evaluated the effect of 48 weeks of metformin ER treatment on weight loss in 77 obese adolescents ages 13-18 (39 of which received metformin ER). Nausea, vomiting and headache were more common with metformin ER compared to placebo, which is consistent with the known safety profile of metformin ER. One SAE of appendectomy was reported in a patient who received metformin but was considered unrelated to the study drug. Another SAE was reported in the follow up period (the patients were followed for additional 48 weeks after discontinuation of the study drug), leg vein thrombosis, considered to be unrelated to previous study drug use (metformin ER).

Reviewer comment: The information submitted by the applicant is further supportive of similar safety and tolerability of metformin ER in children and adults.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The applicant submitted a label based on the label of the reference drug, Glucophage XR. The indication of the Riomet ER product extends beyond that of Glucophage XR to pediatric patients age 10-18. This is adequate as it is supported by the literature allowing a bridge between Riomet ER and metformin IR which is approved for use in pediatrics.

Additionally, other changes were made to the prescribing information submitted by the applicant as follows:

- Drug Interactions: Added wording to reflect the results of the in vitro alcohol dissolution study showing that alcohol >5% increased the release and absorption of Riomet ER.
- Container presentations: The sponsor proposed 2 presentations for the Riomet ER drug product (a (b) (4) bottle pack, and a round bottle pack). Based on the results of the human factors study, DMEPA deemed the (b) (4) container to be prone to errors that could not be mitigated by the sponsor's proposal. As such, only the round bottle pack can be approved at this time.

[5] Wilson DM et al, 2010

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was recommended for this application.

12. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments were recommended for this application.

13. Appendices

13.1. References

1. Glucophage and Glucophage XR prescribing information US https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020357s034,021202s018lbl.pdf
2. Clarson CL et al, 2014
3. Fujii RK et al, 2015
4. Fujioka K et al, 2003
5. Gao X et al, 2003
6. Jabbour S and Ziring B, 2011
7. Schwartz S et al, 2006
8. Wilson DM et al, 2010

13.2. Financial Disclosure

The bioequivalence study was conducted at a single site, with only one investigator.

Covered Clinical Study (Name and/or Number): FM_100S_0508_17

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		

<table>
<tr><td colspan="3">Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0</td></tr>
<tr><td colspan="3">If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 0

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in Sponsor of covered study: 0</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐
Not applicable</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐
Not applicable</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐
Not applicable</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

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