Cross-Discipline Team Leader Review

Date	August 29, 2019
From	Mitra Rauschecker
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	212595-1 (b) (4)
Applicant	Sun Pharmaceutical Industries, Limited
Date of Submission	November 2, 2018
PDUFA Goal Date	September 2, 2019
Proprietary Name	Riomet ER
Established or Proper Name	Metformin hydrochloride extended release
Dosage Form(s)	Oral solution 500 mg/5 mL
Applicant Proposed Indication(s)/Population(s)	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
Applicant Proposed Dosing Regimen(s)	Starting dose 500 mg (5 mL) orally once daily, increase in dose increments of 500 mg (5 mL) weekly, up to a maximum dose of 2000 mg (20 mL) once daily
Recommendation on Regulatory Action	Approval of the round bottle design (NDA 212595-1) (b) (4)
Recommended Indication(s)/Population(s) (if applicable)	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
Recommended Dosing Regimen(s) (if applicable)	Starting dose 500 mg (5 mL) orally once daily, increase in dose increments of 500 mg (5 mL) weekly, up to a maximum dose of 2000 mg (20 mL) once daily

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Type 2 diabetes mellitus (T2DM) is a serious, chronic medical condition, which has been increasing in prevalence in the US, and can lead to secondary complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Current approved therapies for T2DM include biguanides, which acts to improve insulin sensitivity by increasing peripheral glucose uptake and utilization, suppress hepatic gluconeogenesis, and slow gastric emptying thereby slowing glucose absorption and reducing food intake. Metformin hydrochloride is a biguanide that was first approved in 1994, and its efficacy and safety have been previously established.

The Applicant has submitted a NDA under the 505(b)(2) pathway for metformin extended release (ER) oral solution (Riomet ER), using Glucophage (metformin immediate release), which was approved in the US in the US in 1998, and Glucophage XR (metformin HCl ER) which was approved in the US in October 2000, as the reference listed drugs. The Applicant conducted a bioequivalence study to successfully bridge Riomet ER to one of the reference products, Glucophage XR. Although Glucophage is indicated in both adults and pediatric patients ages 10 and older, Glucophage XR is only indicated in adults with T2DM. It is not clear why Glucophage XR is not indicated for pediatric patients with T2DM, although it is not for reasons of safety or efficacy, but it may be related to the need for swallowability studies for Glucophage XR at the time of approval. As Riomet ER is an oral liquid formulation, it offers greater ease of swallowability for pediatric populations. The Applicant submitted literature references in support of similar safety and efficacy between Glucophage and Glucophage XR to support use of Riomet ER (which is bridged to Glucophage XR via bioequivalence study) in pediatric subjects. Additionally, the product labeling (which is shared for Glucophage and Glucophage XR), including clinical pharmacology data, is supportive of switching one for the other, which supports the bridge between Glucophage, Glucophage XR, and Riomet ER in adults. With respect to pediatric use, the pediatric use section for Glucophage described data with Glucophage in pediatric patients, in which a similar glycemic response and similar adverse event profile were seen in comparison to adults. This data supports the Agency's findings of safety and efficacy of Glucophage in adult and pediatric patients with T2DM is similar. Therefore, it is reasonable to further conclude that the safety and efficacy of Glucophage XR is similar between adult and pediatric patients. Overall, the data is supportive of a bridge between Riomet ER and Glucophage and Glucophage XR, and support the Applicant's reliance on Glucophage for pediatric use.

The Applicant submitted [redacted] (b) (4) the "round bottle" [redacted] (b) (4) (b) (4) . A Human factors validation study was performed [redacted] I recommend approval of Riomet ER in the "round bottle" presentation (NDA 212595 Original-1) 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, (b) (4)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2DM) is a disease characterized by hyperglycemia, insulin resistance, and relative impairment of insulin secretion. • It is a relatively common disease that is estimated to affect approximately 30 million people in the United States as of the 2015 Center for Disease Control report. • T2DM is often associated with other metabolic derangements, such as dyslipidemia, hypertension, and obesity. • Chronic complications of T2DM include cardiovascular disease, retinopathy, nephropathy, and neuropathy.	T2DM is a serious, life-threatening condition that can lead to serious morbidity and mortality if left untreated.
Current Treatment Options	• Treatment options for T2DM includes lifestyle modifications, usually followed by the addition of one or multiple different medications. • There are currently multiple classes of pharmacologic treatments for T2DM, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose linked transporter (SGLT)-2 inhibitors. • Metformin, a biguanide, is considered to be a first line treatment for T2DM. • Metformin extended release is currently available only in tablet form, which cannot be crushed.	There are multiple different classes of medication for patients with T2DM.
Benefit	• Riomet ER is an oral formulation, which would allow use in patients with difficulty swallowing • Riomet ER is administered once daily.	Riomet ER offers the potential for use in populations (such as pediatric patients) with difficulty swallowing large pills, and offers once daily administration.
Risk and Risk Management	• Bioequivalence was established between Riomet ER and the reference listed product, Glucophage XR. • Glucophage and Glucophage XR can be switched for each other for adult use in product labeling • Glucophage has similar safety and efficacy profile in adult and pediatric	The safety of Riomet ER is expected to be similar between adult and pediatric patients with T2DM, and to that of other approved metformin products, which is described in product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients.	

2. Background

Metformin Hydrochloride (HCl) is indicated for the treatment of type 2 diabetes mellitus (T2DM), and was first approved in the US in 1994. It is a biguanide, and works by decreasing hepatic glucose production, reducing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. It is currently available in immediate release (IR), and extended release (ER) tablets, as well as IR oral solution.

Sun Pharmaceuticals Industries Limited, hereafter referred to as the Applicant, has submitted a NDA under the 505(b)(2) pathway for metformin ER oral solution (Riomet ER), using Glucophage (NDA 20357) and Glucophage XR (NDA 21202) as the reference listed drugs, which were approved in the US in 1998 and 2000. The indication for Riomet ER proposed by the Applicant is *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*. The Applicant is proposing a starting dose of 500 mg (5 mL) orally once daily, to be taken with the evening meal, to be increased in dose increments of 500 mg (5 mL) weekly, up to a maximum dose of 2000 mg (20 mL) once daily. The drug product is available in (b) (4) a 16 oz. round bottle.

In support of this application, the Applicant conducted a bioequivalence study between Riomet ER and Glucophage XR.In addition, the Applicant submitted literature references in support of the safety and efficacy of Glucophage XR in pediatric patients with T2DM which were not necessary for approval, but were supportive. The Applicant also conducted human factors validation studies to support the proposed product presentations. Please see the Benefit Risk Framework for a discussion of the bridging strategy for this application.

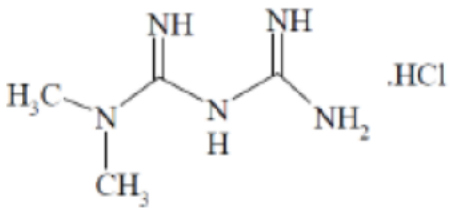
3. Product Quality

Drug Substance:

The drug substance of Riomet ER is an oral suspension of metformin hydrochloride, which is a biguanide. Metformin hydrochloride is a white crystalline solid that is freely soluble in water, with a molecular weight of 165.6. The molecular formula is $C_4H_{12}ClN_5$.

The chemical structure of metformin hydrochloride is shown below, in Figure 1.

Figure 1: Chemical Structure of Metformin Hydrochloride



Source: from CMC review

The Applicant referenced their DMF for their approved product Riomet (which is an immediate release form of the drug) for the CMC information for the drug substance metformin hydrochloride for this NDA application. Due to the applicant's extensive manufacturing experience with the drug substance, the CMC information for the drug substance is considered adequate.

Drug Product

The drug product for Riomet ER is a combination of a diluent solution and (b) (4) pellets. Following reconstitution, the oral suspension is formed. A diagram displaying the composition of the (b) (4) pellets in Riomet ER drug product is shown below, in Figure 2.

Figure 2 (b) (4) Pellet for Riomet ER

(b) (4)

(b) (4) Pellet (b) (4)

Source: from Applicant's eCTD 2.3.P Drug Product Overall Summary

The contents of Riomet ER are listed below, in Table 1. Note that metformin hydrochloride is present in both the (b) (4) pellets, as well as in the (b) (4) diluent. All excipients are present in approved products, and were reviewed by Dr. Galliford and found to be adequate. Excipients are also discussed in more detail in Section 4.

Table 1: Riomet ER Composition

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

Source: from Applicant's eCTD 2.3.P Drug Product Overall Summary

Based on the provided 12-month primary stability data, Dr. Galliford recommends an expiration period of 24 months when stored at room temperature, and in-use stability of 100 days.

The drug product is a nonsterile oral solution in a two-part container closure system. The microbiology reviewer, Dr. Jennifer Patro, reviewed the antimicrobial effectiveness testing, the manufacturing methods for microbial control of a non-sterile product containing a preservative, and stability data to support the maintenance of microbiological quality during storage. Her review concluded that the product quality microbiology is adequate to support the NDA.

For detailed discussion of the drug substance and drug product manufacturing process, see Dr. Galliford's review. The Office of Product Quality (OPQ) CMC review concludes that the overall recommendation is for approval. For further details, please see the OPQ review.

The Applicant performed a human factors validation study to evaluate [redacted] container closure systems; the "round bottle" [redacted] As Riomet ER needs to be reconstituted by a pharmacist prior to dispensing, [redacted] contain a bottle with Riomet ER drug pellets, and a second bottle containing diluent. [redacted]

(b) (4)

he study included pharmacists and pharmacy technicians, who were tasked with reconstituting Riomet ER, and patients and caregivers, who were tasked with dosing the medication.

(b) (4)

Facilities:
Pre-approval inspections at the drug product manufacturing facility (Sun Pharmaceutical Industries Limited) were performed by Dr. Ramesh Dandu. The drug substance is also manufactured at the same facility, and was previously inspected in 2017, and the facility was found to be acceptable. The CMC reviewers concluded that information provided in process and facilities is acceptable to support the approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any new nonclinical pharmacology or toxicology studies for Riomet ER, and is relying on the nonclinical information for Glucophage XR. The proposed oral suspension Riomet ER has a novel formulation, but does not contain any new excipients. Dr. Carlson, the nonclinical reviewer, evaluated the safety of the excipients at the proposed concentrations, along with any potential drug product impurities, specifically extractable or leachable compounds from the liquid suspension.

Ethyl cellulose, a nondigestible dietary fiber, is an excipient included in the proposed drug product. While it has not been used at the proposed (b) (4) g/d, ethyl cellulose has been used in over the counter drug products and is a part of a normal diet. Xylitol, which is a sugar alcohol, has also been included as an excipient at similar levels to those in an approved product, Riomet oral solution (immediate release). Dr. Carlson notes the potential for a laxative effect

or diarrhea with high exposures to xylitol. Overall, Dr. Carlson concluded the potential for intestinal effects for xylitol or ethyl cellulose are likely to be transient. Since intestinal effects are a known AE related to metformin and are included in labeling, I do not think potential transient intestinal effects related to xylitol and ethyl cellulose are likely to pose a safety concern.

5. Clinical Pharmacology

The Applicant conducted a single bioequivalence study, which was an open-labeled, randomized, single-dose, three treatment, three-period, crossover study which compared the bioavailability of Riomet ER and Glucophage XR tablets. In Study MFM-100S-0508-17, healthy adult subjects were given a single dose of 750 mg/7.5 mL Riomet ER suspension with 240 mL 20% glucose after an overnight fast, a single dose of 750 mg/7.5 mL Riomet ER suspension with 240 mL 20% glucose 30 minutes after a high fat breakfast, or single dose of 750 mg Glucophage ER tablet with 240 mL 20% glucose 30 minutes after a high fat breakfast. The 90% CI of geometric mean ratios (suspension/tablet) of AUC_{0-t}, AUC_{0-inf}, and C_{max} were all within the range of 0.8 and 1.25, therefore bioequivalence between Riomet ER and Glucophage XR was established. See Table 2 for more details.

Table 2: PK Parameters for Riomet ER and Glucophage XR After a Single Oral Dose of 750 mg

Parameter	ER-Suspension	Glucagon-XR Tablet	Ratio (S/T)	90% CI	Intra-Subject Variation
C_{max} (ng/mL)*	796.7	748.8	1.064	1.022 – 1.108	12.2%
AUC_{0-t} (ng·h/mL)*	7515.3	8627.2	0.871	0.840 – 0.904	11.2%
AUC_{0-24h} (ng·h/mL)*	7714.5	8935.4	0.863	0.832 – 0.896	11.4%

* Least square mean

The fitted model (log-scale) for each parameter includes the fixed effects period, sequence and treatment, subject as random effect.

Source: Table 4.7 from Applicant's CSR

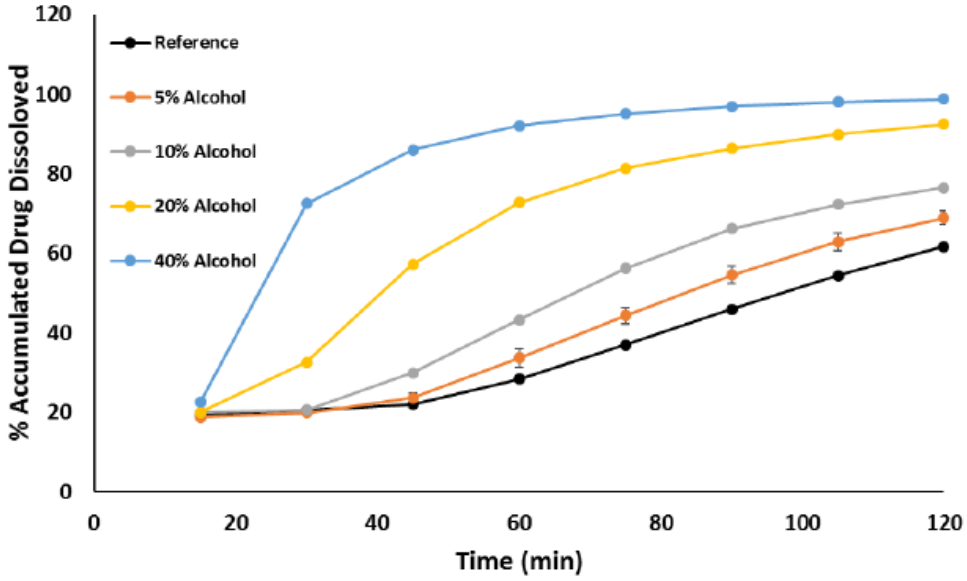
It was noted the median T_{max} following a single dose of Riomet ER is 5.5 hours post-dose, which is about 2.5 hours earlier than after a single dose of Glucophage XR. However, it was unclear whether there was any clinical relevance to the earlier onset of T_{max}. The study results also supported that, while there was a decrease of approximately 20% in peak plasma exposure (C_{max}), there was no effect on total systemic plasma exposure (AUC) after a high fat meal, in comparison to fasted condition.

Dose Dumping Study:

An *in vitro* drug dissolution study (in 0.1 N hydrochloric acid) was conducted to evaluate the effects of alcohol on dose dumping. In the presence of high concentrations of alcohol (20% or greater), the *in vitro* drug dissolution profiles of Riomet ER are different from the reference

profile. As seen in Figure 3, at 20 minutes, approximately 20%, 20% and 21% Riomet ER was released in the presence of 0%, 5%, and 10% alcohol, in contrast to 33% and 73% for 20% and 40% alcohol. After 2 hours, 62%, 69%, and 77% of Riomet ER was released in the presence of 0%, 5%, and 10% alcohol, while for 20% and 40% alcohol, 93% and 99% was released.

Figure 3: *In Vitro* Drug Dissolution Profile



Source: Clinical Pharmacology Review

As a result, in the presence of 20% alcohol or higher concentrations, there will be an earlier T_{max} with higher C_{max}, and potentially lower C_{trough}, resulting in an accelerated release of Riomet ER. This would result in the potential for a maximum of 2000 mg of Riomet ER with a profile similar to metformin IR, which is labeled for use in doses up to a maximum of 2500 mg per day. Therefore, the Clinical Pharmacology reviewer, Dr. Ren, concludes this can adequately be communicated with labeling. I agree with his assessment.

Based on the reviewed clinical pharmacology data, which support the bioequivalence of Riomet ER with Glucophage XR, Dr. Ren and Dr. Khurana support approval of Riomet ER 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. The Office of Study Integrity and Surveillance (OSIS) determined that an inspection was not warranted, as both the clinical and analytical site had been inspected recently.

6. Clinical Microbiology

This section is not applicable.

7. Clinical/Statistical- Efficacy

This section is not applicable, as the Applicant did not submit any clinical efficacy data.
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8. Safety

This section is not applicable, as the Applicant did not submit any clinical safety data.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Glucophage (NDA 20357) is currently approved for use in adults and children with T2DM ages 10 years and older, while Glucophage XR (NDA 21202) is approved for use in adults with T2DM. It is not clear why Glucophage XR is not approved for use in children with T2DM, although it is unrelated to issues concerning safety or efficacy, but rather is likely due to issues concerning swallowability. Glucophage XR pills are large, and there was the potential concern that pediatric populations would have difficulty swallowing them.

The Applicant submitted an initial PSP (iPSP) on May 17, 2017, which included a proposal to conduct a PK study with Riomet ER in pediatric subjects ages 10-17 years. On August 14, 2017, the FDA sent comments to the iPSP, and stated the following:

We note that you are planning to conduct a pharmacokinetic study in pediatric patients with type 2 diabetes mellitus to support use of your product in adolescents (age 10 to 17 years)with type 2 diabetes mellitus. 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 the revised iPSP on September 29, 2017, containing a request for a full waiver for pediatric subjects from birth to 16 years. The FDA sent comments back to the Applicant, and proposed a partial waiver for pediatric patients from birth to less than 10 years of age, and a pediatric assessment for pediatric subjects aged 10 to 16 years with T2DM, based on existing literature data. On November 16, 2017, the letter of agreement for the iPSP was

sent to the Applicant. With this NDA submission, the Applicant has now submitted the available data concerning the use of Glucophage XR in pediatric patients from literature references to support a pediatric indication for Riomet ER, which is consistent with the agreed iPSP.

Although there are no published data available on the use of Glucophage XR in pediatric patients with T2DM, the submitted literature includes two studies evaluating Glucophage XR in obese adolescents. In the first study by Clarson, et al,[1] obese adolescents ages 10 to 16 years old were randomized to receive Glucophage XR 2000 mg daily versus placebo for 24 months, and either vigorous or moderate exercise for the first 3 months. The study randomized 69 adolescent subjects, and reported two non-serious adverse events; one event of transient elevations in transaminases at 1 year, and one event of persistent diarrhea at 1 year. An additional 6 subjects were unable to tolerate the full dose of 2000 mg, and had dose reductions to 1000-1500 mg. A second study by Wilson, et al,[2] was conducted in obese adolescents aged 13 to 18 years old, in which 77 subjects were randomized to Glucophage XR versus placebo for 48 weeks (with an additional 48 week follow-up period), after completing a lifestyle intervention program. The study reported one serious adverse event of appendectomy in a subject treated with metformin during the study treatment period which was considered unrelated to study treatment. An additional serious adverse event of deep vein thrombosis was reported in a subject treated with metformin during the follow-up period. Additional non-serious adverse events reported during the study which were more common in metformin-treated subjects were headache, nausea, and vomiting. These are consistent with the known safety profile of Glucophage XR. Although these studies were not conducted in pediatric subjects with T2DM, and offer a limited safety database, the data they provide is reassuring that the safety of Glucophage XR in pediatric subjects is similar to that which is observed in adults.

The Applicant also submitted data to support the similarity of the PK parameters of Glucophage and Glucophage XR, as well as the similarity of the PK parameters between adult and pediatric patients. As seen in Table 2, the PK parameters after a single oral dose of Glucophage in pediatric subjects is similar to the PK parameters after a single oral dose of Glucophage in healthy adults, as well as the PK parameters after a single oral dose of Glucophage XR in healthy adult subjects.

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[1] Clarson CL, Brown HK, De Jesus S, Jackman M, Mahmud FH, Prapavessis H, et al. Effects of a Comprehensive, Intensive Lifestyle Intervention Combined with Metformin Extended Release In Obese Adolescents. *International Scholarly Research Notices*. 2014, Nov 10.

[2] Wilson DM, Abrams SH, Aye T, Lee PD, Lenders C, Lustig RH, et al. Metformin Extended Release Treatment of Adolescent Obesity: a 48-week Randomized, Double-Blind, Placebo-Controlled Trial with 48-week Follow-Up. *Archives of Pediatric and Adolescent Medicine*. 2010; 164(2):116-23.

Table 2: Comparison of Pharmacokinetics of Metformin IR in Pediatric T2DM and Healthy Adult Subjects versus Metformin ER in Healthy Adult Subjects

	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

Although the Applicant submitted literature references in support of the pediatric assessment for Riomet ER, this data was considered supportive. The shared product labeling for Glucophage and Glucophage XR provide the scientific justification for bridging between Riomet ER and Glucophage, and therefore for pediatric use. The Pediatric Use section of the Glucophage label describes data from a controlled clinical study in pediatric subjects (aged 10-16 years old), in which the glycemic response was similar to the glycemic response seen in adults. The adverse reactions seen in the pediatric study were also similar to those described in adults. Therfore, since the safety and efficacy of Glucophage is similar in adults and pediatric patients, and Glucophage and Glucophage XR are similar in adults in the approved product labeling, it is reasonable to conclude that the safety and efficacy of Glucophage XR is similar between adults and pediatric patients with T2DM. Since Riomet ER established bioequivalence to Glucophage XR, and Glucophage XR and Glucophage are similar in pediatric and adult patients, this allows us to infer the safety and efficacy of Riomet ER in pediatrics.

The pediatric assessment in pediatric patients with T2DM ages 10 and older, along with their request for a waiver for study in children under the age of 10 was discussed with PeRC on April 17, 2019. The applicant's pediatric assessment for children ages 10 and older based on literature was found to be acceptable. The PeRC concurred with a partial waiver in pediatric patients birth to less than 10 years of age because studies would be impractical.

Overall, the data is supportive of a bridge between Riomet ER and Glucophage and Glucophage XR, and support the Applicant's reliance on Glucophage for pediatric use.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Prescribing Information

The applicant is relying on the reference listed products, Glucophage and Glucophage XR, and has proposed the same indication for Riomet ER: as an adjunct to diet and exercise to improve glycemic control in patients 10 years of age and older with type 2 diabetes. I agree that the literature references along with the reference product labeling, supports the use of Riomet ER for the proposed indication for pediatric subjects aged 10 and older.

The applicant has proposed the same contradindications, and Warnings and Precautions as for the reference product Glucophage XR. In Drug Interactions, I recommend an additional statement about the effect of alcohol intake on Riomet ER (increases the rate of absorption), in addition to the language currently in the label warning against excessive alcohol consumption, due to the results of the dose dumping studies.

The applicant has included reference to (b) (4) "round bottle" system. (b) (4) (b) (4) approval of the "round bottle" presentation. (b) (4) .

The clinical trial data and description of clinical studies proposed by the applicant is the same as the approved reference product.

Other Labeling:
The applicant has proposed the proprietary name Riomet ER. This name was reviewed by Dr. Ariane Conrad of DMEPA, who has found the name to be acceptable.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No REMS is recommended for Riomet ER. No serious safety concerns associated with the use of Riomet ER were identified that would require a REMS.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

There are no additional PMRs or PMCs recommended for this product.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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08/29/2019 12:56:44 PM

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