# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA Number: | 212595 SDN 0001 (Related IND 127945) |
| Submissions Date: | 11/02/2018 |
| Submission Type: | 505(b)(2) |
| Proposed Brand Name: | RIOMET ER |
| Generic Name: | Metformin hydrochloride |
| Sponsor: | Sun Pharmaceutical Industries Ltd. |
| Route of Administration: | Oral |
| Dosage Form: | Extended-release suspension |
| Dosage Strength: | 100 mg/mL |
| Proposed Dosing Regimen: | • Adult Dosage for metformin hydrochloride for extended-release oral suspension:<br>o Starting dose: 500 mg (5 mL) orally once daily, with the evening meal<br>o 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<br>o Patients receiving metformin immediate-release treatment may be switched to metformin hydrochloride for extended-release oral suspension once daily at the same total daily dose, up to 2000 mg (20 mL) once daily<br><br>• Pediatric Dosage for metformin hydrochloride for extended-release oral suspension:<br>o Starting dose: 500 mg (5 mL) orally once daily, with the evening meal<br>o Increase dosage in increments of 500 mg (5 mL) weekly up to a maximum of 2000 mg (20 mL) once daily, with the evening meal |
| Proposed Population and Indication(s): | As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and (b) (4) with type 2 diabetes mellitus |
| OND Divisions: | Division of Metabolism and Endocrinology Products |
| OCP Division: | Clinical Pharmacology 2 |
| Reviewer: | Yunzhao Ren, M.D., Ph.D. |
| Team Leader: | Manoj Khurana, Ph.D. |

# TABLE OF CONTENTS



## 1. EXECUTIVE SUMMARY

Sun Pharmaceutical Industries Ltd. submitted NDA 212595 under 505(b)(2) on 11/02/2018 seeking approval of metformin hydrochloride extended-release oral suspension (100 mg/mL) 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 Listed Product in this NDA is 750 mg Glucophage® XR extended-release tablet from NDA 020357.

The 100 mg/mL metformin hydrochloride extended-release oral suspension contains (b) (4) mg/mL metformin hydrochloride as (b) (4) pellet and (b) (4) mg/mL metformin hydrochloride as (b) (4) formulation.

The proposed dosing regimens are:

- Adult Dosage for metformin hydrochloride for extended-release oral suspension:
  - 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
  - Patients receiving metformin immediate-release treatment may be switched to metformin hydrochloride for extended-release oral suspension once daily at the same total daily dose, up to 2000 mg (20 mL) once daily

- Pediatric Dosage for metformin hydrochloride for extended-release oral suspension:
  - Starting dose: 500 mg (5 mL) orally once daily, with the evening meal
  - Increase dosage in increments of 500 mg (5 mL) weekly up to a maximum of 2000 mg (20 mL) once daily, with the evening meal

- Renal Impairment:
    - Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR)
    - Do not use in patients with eGFR below 30 mL/minute/1.73 $m^2$
    - Initiation is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 $m^2$
    - Assess risk/benefit of continuing metformin hydrochloride for extended-release oral suspension if eGFR falls below 45 mL/minute/1.73 $m^2$

In this submission package, the sponsor included one clinical pharmacology study MFM_100S_0508_17 conducted in India. It was an open-labeled, randomized, single-dose, three-treatment, three-period, crossover study comparing the bioavailability of metformin systemic exposure following 750 mg extended-release oral suspension and 750 mg Glucophage® XR extended-release tablet in healthy subjects. In total, 60 subjects were planned, and 60 males were enrolled with 52 of them completed the study. The 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 $C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$ were all within the pre-defined 0.8 to 1.25 range.

During the review cycle, Division of New Drug Bioequivalence Evaluation (DNDBE) within Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time, because the clinical site (Sun Pharmaceutical Industries, Clinical Pharmacology Unit) was inspected in March 2017 and the analytical site (Sun Pharmaceutical Industries, Clinical Pharmacology & Pharmacokinetics) was inspected in January 2018, which falls within the surveillance interval. The final classification for the inspections was No Action Indicated (NAI).

### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the NDA 21595 original submission (SDN 0001) submitted on 11/02/2018 and recommends approval.

### 1.2 Phase 4 Commitments

None

### 1.3. Summary of Clinical Pharmacology Findings

#### 1.3.1 Background

The sponsor initiated the IND 127945 on 09/29/2015 by requesting a pre-IND meeting. A Written Response was guaranteed and issued on 11/24/2015. The clinical pharmacology-related question and response from the Written Response were listed as following:

> **Question 1:** Considering that Metformin is recommended to be taken with meals, Sun pharma intends to conduct "Single-dose three-way crossover study to assess bioequivalence of Metformin Extended Release Powder for Oral Suspension 100 mg/mL with Glucophage XR (Metformin HCl) Extended-Release tablets 750 mg under Fed condition and to assess the effect of Food on bioavailability of Metformin Extended Release Powder for Oral Suspension 100 mg/mL (7.5 mL) in healthy adult human subjects." Does the Agency concur on adequacy of the proposed human pharmacokinetic and bioequivalence study for approval of the drug product?

***FDA Response to Question 1:*** *Your approach seems reasonable to support the development of the proposed product.*

**Question 2:** Considering that controlled clinical studies of Glucophage in patients with type 2 diabetes has demonstrated comparable anti-hyperglycemic effect in Whites, Blacks, and Hispanics and this being a relative bioavailability study, the proposed bio study for Metformin hydrochloride extended release powder for oral suspension 100 mg/mL can be performed at any geographical location including India. Does the Agency concur?

***FDA Response to Question 2:*** *With cross-over bioequivalence (BE) study design, geographical location is less of a concern.*

Based on FDA's 2015 Written Response, the sponsor opened IND on 05/17/2017 with the protocol of the pivotal clinical pharmacology study MFM_100S_0381_17. During the review, following non-hold comments were conveyed to the sponsor:

- *You mentioned in the protocol of Study MFM_100S_0381_17that a chromatographic procedure only will be used for measuring metformin plasma concentration. However, your pilot study 3008_METFO_14 used a validated LCMS/MS method for measuring metformin plasma concentration. Please clarify in your protocol.*
- *Provide dose selection rationale in your BA/BE study protocol.*
- *Although you listed that subject with renal illness in the exclusion criteria, it's not specific. Renal clearance is the major elimination pathway of metformin, therefore it is more pertinent to list subjects with eGFR <90 mL/min/1.73m$^2$ or creatinine clearance <90 mL/min in the exclusion criteria. This will help reducing the PK variability.*

The initial Pediatric Study Plan (iPSP) was submitted by the sponsor on 05/17/2017. The sponsor proposed a partial waiver for pediatric patients <10 years of age and a PK study in children (10 to 16 years of age) with type 2 diabetes mellitus.

A Written Response on iPSP was issued on 08/14/2017. The following comments were conveyed to the sponsor:

*We agree with your plan to request a partial waiver for pediatric patients below the age of 10 (studies are highly impractical). 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.*

*Please re-submit your pediatric study plan to reflect these changes.*

The sponsor revised their pediatric plan and submitted the Agreed iPSP on 11/13/2017. The sponsor proposed a partial waiver for pediatric patients <10 years of age and an assessment based on existing data in pediatric patients (10 to 18 years) with type 2 diabetes mellitus.

FDA issued initial agreement on sponsor's Agreed iPSP on 11/16/2017. FDA PeRC concurred with the agreed iPSP on 11/28/2017.

### 1.3.2 Bioequivalence between metformin systemic exposure following 750 mg extended-release oral suspension and 750 mg Glucophage® XR extended-release tablet

Bioequivalence between extended-release oral suspension and Glucophage® XR extended-release tablet was established following 750 mg single dose oral administration in healthy males (PK set, N=52) in fed condition. The 90% CI of geometric mean ratios (suspension/tablet) of $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ are all within the range of 0.80 and 1.25 (Table 1.1). The median $T_{max}$ following single dose of extended-release oral suspension is 5.5 hours post-dose, which is about 2.5 hours earlier than following single dose of extended-release tablet (8 hours) (Figure 1.1). The clinical meaning of earlier onset of median $T_{max}$ is unclear. The median $T_{max}$ of sponsor's metformin hydrochloride immediate-release product (NDA 021591 Riomet®) is similar to Glucophage®. For details, refer to Clinical Pharmacology Review by Dr. Suliman I. Al-Fayoumi dated 9/10/2003.

**Table 1.1 Statistical Comparison of Metformin PK Parameters following 750 mg Single Dose Administration of ER-Suspension and ER-Tablet (PK Set, N=52)**

| 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

The geometric mean concentration-time profiles (PK set) of metformin following 750 mg single dose of extended-release oral suspension and extended-release tablet are depicted in Figure 1.1.

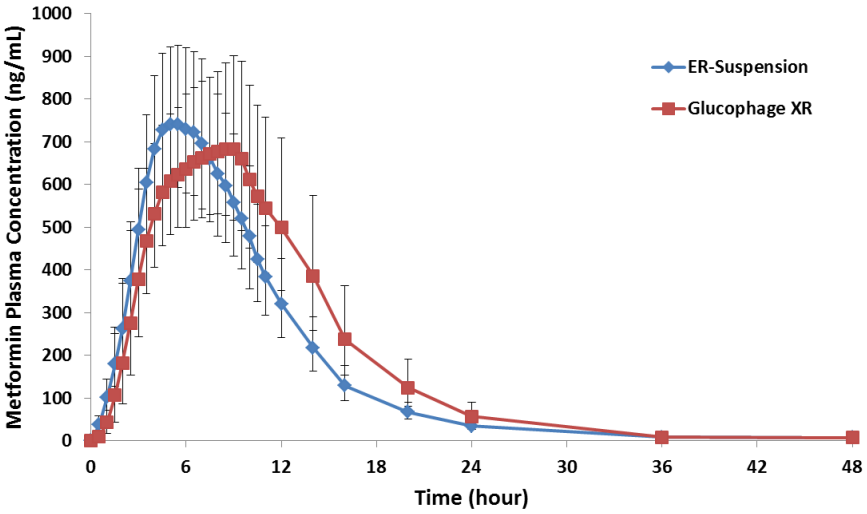


**Figure 1.1** Geometric mean (± SD) metformin plasma concentration-time profiles (PK set, N=52) following 750 mg single dose of ER-suspension (blue) and ER-tablet (red). BLQ samples were imputed with 1/2 LLOQ values (7.55 ng/mL). (Source: Figure 4.2)

Refer to the approved label of NDA 020357 Glucophage®: *Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender (males=19, females=16).*

Therefore, the bioequivalence result from this male-only PK study is acceptable from clinical pharmacology perspective.

### 1.3.3 Food effect on extended-release oral suspension

Following 750 mg single-dose administration of extended-release oral suspension in healthy adults, metformin AUCs are comparable between fed and fasting conditions as the 90% CI of geometric mean ratios (fed/fasting) of $AUC_{0-t}$ and $AUC_{0-inf}$ are all within the range of 0.80 and 1.25 (Table 1.2). Metformin $C_{max}$ is about 20% less in fed condition compared to fasting condition. The lower boundary of 90% CI of geometric mean ratio (fed/fasting) of $C_{max}$ is lower than 0.80. The median $T_{max}$ in fasting condition is 4.5 hours post-dose, which is 1 hour earlier than in fed condition (Figure 1.2).

**Table 1.2 Statistical Comparison of Metformin PK Parameters following 750 mg Single Dose Administration of ER-Suspension under Fed Condition and Fasting Condition (PK Set, N=52)**

| Parameter | Fed Condition | Fasting Condition | Ratio (Fed/Fasting) | 90% CI | Intra-Subject Variation |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL)* | 796.6 | 1002.0 | 0.795 | 0.747 – 0.846 | 19.1% |
| $AUC_{0-t}$ (ng·h/mL)* | 7506.8 | 7178.8 | 1.046 | 1.006 – 1.087 | 11.9% |
| $AUC_{0-24h}$ (ng·h/mL)* | 7706.4 | 7370.2 | 1.046 | 1.006 – 1.086 | 11.6% |

* 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

The geometric mean concentration-time profiles (PK set) of metformin following 750 mg single dose of extended-release suspension under fed and fasting conditions are summarized in Figure 1.2.

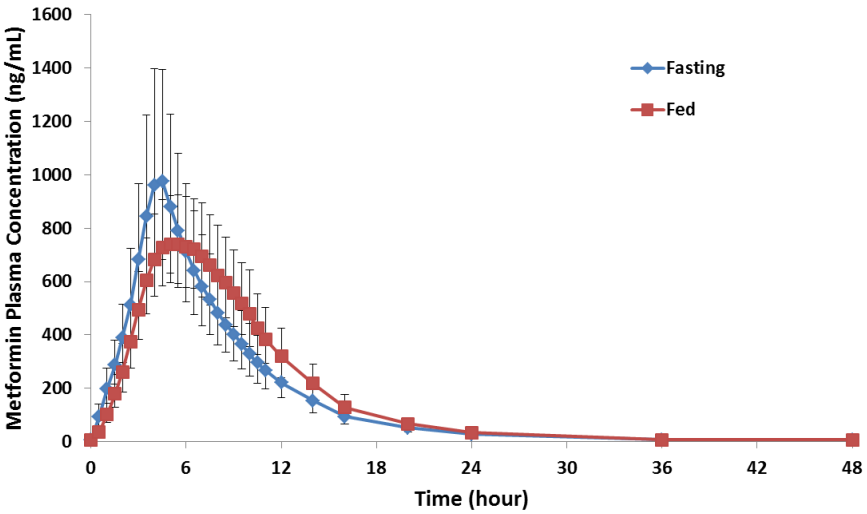


**Figure 1.2** Geometric mean (± SD) metformin plasma concentration-time profiles (PK set, N=52) following 750 mg single dose of ER-suspension under fasting condition (blue) and fed condition (red). BLQ samples were imputed with 1/2 LLOQ values (7.55 ng/mL). (Source: Figure 4.3)

### 1.3.4 Drug dose dumping result from *in vitro* dissolution profile

In the presence of high concentration of alcohol, the *in vitro* drug dissolution profiles of metformin hydrochloride extended-release oral suspension are very different from the reference profile (0.1 N hydrochloric acid only) (Figure 2.2). 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. For details, refer to biopharmaceutical reviewer Dr. Ibrahim Sarah.

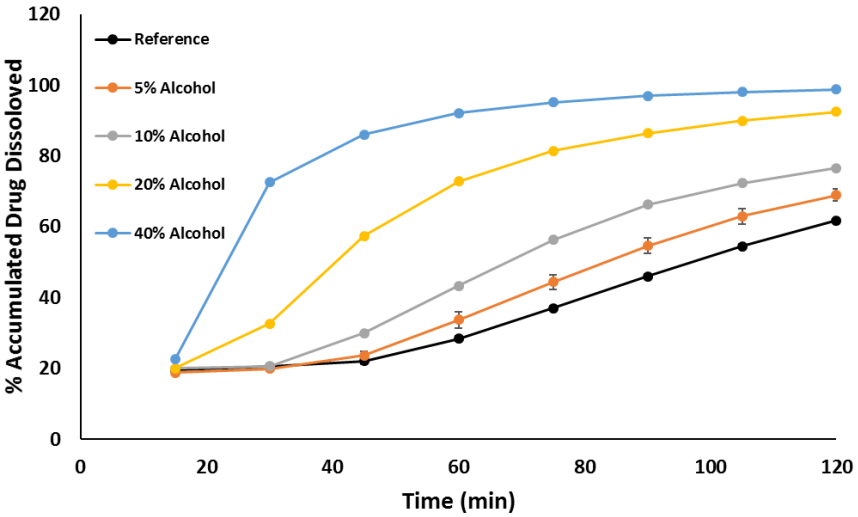


**Figure 2.2** *In vitro* dissolution profile of metformin hydrochloride extended-release oral suspension product. 0.1 N hydrochloric acid solution was used in all the dissolution conditions (Source: summary-biopharm-alcohol-dose-dumping-report.pdf)

The result from the *in vitro* drug dissolution profiles indicates that co-administration metformin hydrochloride extended-release oral suspension with high concentration of alcohol in patients may

substantially accelerate the release of metformin from its extended-release formulation, which will result in a relatively earlier $T_{max}$ with higher $C_{max}$, and a potentially a lower $C_{trough}$. For individuals who routinely take once daily dose of the metformin hydrochloride extended-release oral suspension, the occasional co-administration of high concentration of alcohol may result in a different metformin PK profile temporarily. Theoretically, an occasional higher $C_{max}$ may have potential safety concerns whereas the occasional lower $C_{trough}$ due to may have potential efficacy concerns.

However, the worst-scenario case related to this *in vitro* dose dumping result is that all 2000 mg maximum allowed dose of metformin from the metformin hydrochloride extended-release oral suspension is released as if the product is an immediate-release formulation. This scenario is covered by the approved label of NDA 020357 Glucophage immediate-release tablet:

- Starting dose: 500 mg orally twice a day or 850 mg **once a day**, with meals
- Increase the dose in increments of 500 mg weekly or 850 mg every 2 weeks, up to a maximum dose of 2550 mg per day, given in divided doses (2.1)
- **Doses above 2000 mg** may be better tolerated given 3 times a day with meals

Therefore, the reviewer agrees with the review team that the *in vitro* dose dumping result and its consequence could be regulated by label. The dose dumping results should be listed under section 12.3 of the label. Additional concern of acceleration of the release and absorption of metformin when co-administrated with alcohol (≥ 5% ABV) should be listed under section 7 "DRUG INTETACTIONS" of the label.

### 1.3.5 Pediatric development program

Compared to the listed product NDA 020356 Glucophage® XR extended-release tablet, NDA 212595 metformin hydrochloride extended-release oral suspension changed dosage form (tablet to suspension) under 505(b)(2) pathway. Therefore, this NDA triggers PREA. The sponsor submitted pediatric study plan (PSP) for review during the IND stage and FDA PeRC concurred with the agreed iPSP on 11/28/2017. Under this frame, new pediatric studies are not required for Sun Pharmaceutical seeking for pediatric (10 to <18 years of age) type 2 diabetes mellitus indication. For details, refer to FDA internal meeting minutes dated 11/28/2017.

# 2. QUESTION BASED REVIEW

## 2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

Clinical Pharmacology Study MFM_100S_0381_17 is the only clinical study conducted under this original NDA submission.

## 2.2 General Attributes of the Drug

### 2.2.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Qualitative composition of metformin hydrochloride extended-release oral suspension 100 mg/mL is listed below:

**Table 2.1 Composition of Metformin Hydrochloride Extended-Release Oral Suspension**

| Ingredients | mg/mL | %w/w |
|---|---|---|
| (b) (4) | | (b) (4) |
| (b) (4) | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | (b) (4) |
| Metformin Hydrochloride USP # | | |
| 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) | | |
| | | |
| **Total** | (b) (4) | 100.00 |

Source: pos-drug-product.pdf, page 4

The drug product is presented as following: (b) (4) pellets stored in Drug Pellets Bottle (in 150 cc bottle with 28 mm neck) and (b) (4) in Drug Diluent Bottle (at the bottom/ 600 mL

bottle with 35 mm neck). User needs to unscrew closure from both Drug pellets bottle & Drug diluent bottle by transfer of pellets from Drug pellets bottle to Drug diluent bottle containing the vehicle. Suspension is made upon recommended shaking.

For the acceptability of the drug product presentation, refer to reviewers from CMC and DEMPA.

**2.2.3 What are the proposed mechanism of action and therapeutic indications?**

Refer to the approved label of NDA 020357 Glucophage®,

*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.*

Sponsor of NDA 21595 has proposed following therapeutic indication:

*Metformin hydrochloride for extended-release oral suspension 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* (b) (4) *with type 2 diabetes mellitus*

**2.2.4 What are the proposed dosage(s) and route(s) of administration?**

The proposed dosage(s) are:

- Adult Dosage for metformin hydrochloride for extended-release oral suspension:
  - 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
  - Patients receiving metformin immediate-release treatment may be switched to metformin hydrochloride for extended-release oral suspension once daily at the same total daily dose, up to 2000 mg (20 mL) once daily

- Pediatric Dosage for metformin hydrochloride for extended-release oral suspension:
  - Starting dose: 500 mg (5 mL) orally once daily, with the evening meal
  - Increase dosage in increments of 500 mg (5 mL) weekly up to a maximum of 2000 mg (20 mL) once daily, with the evening meal

- Renal Impairment:
  - Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR)
  - Do not use in patients with eGFR below 30 mL/minute/1.73 $m^2$
  - Initiation is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 $m^2$
  - Assess risk/benefit of continuing metformin hydrochloride for extended-release oral suspension if eGFR falls below 45 mL/minute/1.73 $m^2$

The proposed route is oral administration.

### 2.2.5 What drugs (substances, products) indicated for the same indication are approved in the US?

There are 34 metformin products approved in the US, including 8 extended-release tablet products. However, NDA 21595 is the first extended-release oral suspension product.

## 2.3 General Clinical Pharmacology

### 2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Clinical Pharmacology Study MFM_100S_0508_17 was an open-labeled, randomized, single-dose, three-treatment, three-period, crossover study comparing the bioavailability of metformin systemic exposure following 750 mg extended-release oral suspension and 750 mg Glucophage® XR extended-release tablet in healthy adults.

The primary objective is to assess the effect of food on bioavailability of extended-release oral suspension and to assess the bioequivalence between metformin hydrochloride extended-release oral suspension and Glucophage® XR extended-release tablet in healthy adult human subjects under fed condition

### 2.3.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Metformin plasma concentration is measured by an ultra-high performance liquid chromatography tandem mass spectrometric method.

## 2.4 Exposure Response

No dose-response or exposure-response relationship was evaluated for metformin in this submission.

## 2.5 PK Characteristics of the Drug

### 2.5.1 What are the single and multiple dose PK parameters of parent drug in healthy adults?

Following 750 mg metformin hydrochloride single dose oral administration of extended-release suspension under fed condition, the arithmetic mean $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ of metformin in healthy subjects is 815.4 ± 180.2 ng/mL, 7694 ± 1692.1 ng•h/mL, and 7894.0 ± 1707.9 ng•h/mL, respectively (Table 2.2). The median $T_{max}$ is reached at 4.5 (2.5 to 16) hours post dose. The mean terminal elimination of metformin half-life is 4.2 ± 1.0 hours.

**Table 2.2 Arithmetic Mean (±SD) Metformin PK Parameters following 750 mg Single Dose Oral Administration of ER-Suspension under Fed Condition (PK Set, N=52)**

| Parameter | Fed Condition |
|---|---|
| $C_{max}$ (ng/mL) | 815.4 (180.2) |
| $AUC_{0-t}$ (ng·h/mL) | 7694.8 (1692.1) |
| $AUC_{0-inf}$ (ng·h/mL) | 7894.0 (1707.9) |
| $T_{max}$ (hour)* | 5.5 (3.5, 10) |
| $t_{1/2}$ (hour) | 4.19 (1.04) |

* Median (min, max)
Source: from Table 4.4

**2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?**

Refer to the approved label of NDA 020357 Glucophage®, metformin systemic exposure is slightly higher in adults with diabetic mellitus compared to healthy, nondiabetic adults (Table 2.3).

**2.5.3. What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**

Upon ANOVA analysis, metformin intra-subject variability (CV%) of $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ is 12.2%, 11.2%, and 11.4%, respectively. Metformin inter-subject variability (CV%) of $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ is 18.4%, 20.6%, and 20.3%, respectively.

**2.5.4 What are the characteristics of drug absorption?**

Refer to the approved label of NDA 020357 Glucophage® XR:

*The absolute bioavailability of a GLUCOPHAGE 500 mg tablet given under fasting conditions is approximately 50% to 60%.*

*Following a single oral dose of GLUCOPHAGE XR……, peak plasma levels are approximately 20% lower compared to the same dose of GLUCOPHAGE the extent of absorption (as measured by AUC) is comparable to GLUCOPHAGE.*

**2.5.5 What are the characteristics of drug distribution?**

According to reviewer's analysis, following 750 mg single dose oral administration of extended-release oral suspension metformin, the mean apparent volume of distribution (Vz/F) was 597 ± 173 L in healthy males.

**2.5.6 What are the characteristics of drug metabolism?**

Refer to the approved label of NDA 020357 Glucophage®:

*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.*

**2.5.7 What are the characteristics of drug elimination?**

Refer to the approved label of NDA 020357 Glucophage®:

*Renal clearance 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.*

**2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?**

Only one dose was studied in this submission.

**2.5.9 How do the PK parameters change with time following chronic dosing?**

Only single dose was studied in this submission.

**2.6 Intrinsic Factors**

**2.6.1 Does body weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?**

Refer to the approved label of NDA 020357 Glucophage®:

- ***Geriatrics***
  *Limited data from controlled pharmacokinetic studies of GLUCOPHAGE in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and $C_{max}$ is increased, compared to healthy young subjects. It appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (Table 2.3)*

- ***Pediatrics***
  *After administration of a single oral GLUCOPHAGE 500 mg tablet with food, geometric mean metformin $C_{max}$ and AUC differed less than 5% between pediatric type 2 diabetic patients (12-16 years of age) and gender-and weight-matched healthy adults (20-45 years of age), all with normal renal function.*

- ***Gender***

*Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender (males=19, females=16).*

- ***Race***
  *No studies of metformin pharmacokinetic parameters according to race have been performed.*

### 2.6.2 Renal Impairment

Refer to the approved label of NDA 020357 Glucophage®:

*In patients with decreased renal function the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (Table 2.3)*

**Table 2.3 Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of GLUCOPHAGE**

| Subject Groups: GLUCOPHAGE dose[a] (number of subjects) | $C_{max}$[b] (mcg/mL) | $T_{max}$[c] (hrs) | Renal Clearance (mL/min) |
|---|---|---|---|
| **Healthy, nondiabetic adults:** | | | |
| 500 mg single dose (24) | 1.03 (±0.33) | 2.75 (±0.81) | 600 (±132) |
| 850 mg single dose (74)[d] | 1.60 (±0.38) | 2.64 (±0.82) | 552 (±139) |
| 850 mg three times daily for 19 doses[e] (9) | 2.01 (±0.42) | 1.79 (±0.94) | 642 (±173) |
| **Adults with type 2 diabetes mellitus:** | | | |
| 850 mg single dose (23) | 1.48 (±0.5) | 3.32 (±1.08) | 491 (±138) |
| 850 mg three times daily for 19 doses[e] (9) | 1.90 (±0.62) | 2.01 (±1.22) | 550 (±160) |
| **Elderly[f], healthy nondiabetic adults:** | | | |
| 850 mg single dose (12) | 2.45 (±0.70) | 2.71 (±1.05) | 412 (±98) |
| **Renal-impaired adults:** | | | |
| **850 mg single dose** | | | |
| **Mild** ($CL_{cr}$[g] 61-90 mL/min) (5) | 1.86 (±0.52) | 3.20 (±0.45) | 384 (±122) |
| **Moderate** ($CL_{cr}$ 31-60 mL/min) (4) | 4.12 (±1.83) | 3.75 (±0.50) | 108 (±57) |
| **Severe** ($CL_{cr}$ 10-30 mL/min) (6) | 3.93 (±0.92) | 4.01 (±1.10) | 130 (±90) |

[a] All doses given fasting except the first 18 doses of the multiple dose studies
[b] Peak plasma concentration
[c] Time to peak plasma concentration
[d] Combined results (average means) of five studies: mean age 32 years (range 23-59 years)
[e] Kinetic study done following dose 19, given fasting
[f] Elderly subjects, mean age 71 years (range 65-81 years)
[g] CLcr = creatinine clearance normalized to body surface area of 1.73 m2
Source: NDA 020357 approved Drug Label, page 16

## 2.7 Extrinsic Factors

### 2.7.1 What extrinsic factors (drugs herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

The above extrinsic factors were not evaluated in this submission.

### 2.7.2 Drug-drug interactions (DDI)

Refer to the approved label of NDA 020357 Glucophage®, the effects of concomitant drugs on metformin systemic exposure are listed in Table 2.4.

**Table 2.4 Effect of Co-Administered Drug on Plasma Metformin Systemic Exposure**

| Coadministered Drug | Dose of Coadministered Drug* | Dose of Metformin* | Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00 | | |
|---|---|---|---|---|---|
| | | | | AUC† | $C_{max}$ |
| **No dosing adjustments required for the following:** | | | | | |
| Glyburide | 5 mg | 850 mg | metformin | 0.91‡ | 0.93‡ |
| Furosemide | 40 mg | 850 mg | metformin | 1.09‡ | 1.22‡ |
| Nifedipine | 10 mg | 850 mg | metformin | 1.16 | 1.21 |
| Propranolol | 40 mg | 850 mg | metformin | 0.90 | 0.94 |
| Ibuprofen | 400 mg | 850 mg | metformin | 1.05‡ | 1.07‡ |
| **Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination** [See *Warnings and Precautions (5.9)* and *Drug Interactions (7.2).*] | | | | | |
| Cimetidine | 400 mg | 850 mg | metformin | 1.40 | 1.61 |
| **Carbonic anhydrase inhibitors may cause metabolic acidosis** [See *Warnings and Precautions (5.1)* and *Drug Interactions (7.1).*] | | | | | |
| Topiramate | 100 mg§ | 500 mg§ | metformin | 1.25§ | 1.17 |

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF)
‡ Ratio of arithmetic means § At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0-12h
Source: NDA 020357 approved Drug Label, page 17

Refer to the approved label of NDA 020357 Glucophage®, the clinically significant drug interactions with Glucophage are listed in Table 2.5.

**Table 2.5 Clinically Significant Drug Interactions with GLUCOPHAGE/GLUCOPHAGE XR**

| | |
|---|---|
| **Carbonic Anhydrase Inhibitors** | |
| *Clinical Impact:* | Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with GLUCOPHAGE/GLUCOPHAGE XR may increase the risk for lactic acidosis. |
| *Intervention:* | Consider more frequent monitoring of these patients. |
| *Examples:* | Topiramate, zonisamide, acetazolamide or dichlorphenamide. |
| **Drugs that Reduce GLUCOPHAGE/GLUCOPHAGE XR Clearance** | |
| *Clinical Impact:* | Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*. |
| *Intervention:* | Consider the benefits and risks of concomitant use with GLUCOPHAGE/GLUCOPHAGE XR. |
| *Examples:* | Ranolazine, vandetanib, dolutegravir, and cimetidine. |
| **Alcohol** | |
| *Clinical Impact:* | Alcohol is known to potentiate the effect of metformin on lactate metabolism. |
| *Intervention:* | Warn patients against excessive alcohol intake while receiving GLUCOPHAGE/GLUCOPHAGE XR. |
| **Insulin Secretagogues or Insulin** | |
| *Clinical Impact:* | Coadministration of GLUCOPHAGE/GLUCOPHAGE XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia. |
| *Intervention:* | Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin. |
| **Drugs Affecting Glycemic Control** | |
| *Clinical Impact:* | Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. |
| *Intervention:* | When such drugs are administered to a patient receiving GLUCOPHAGE/GLUCOPHAGE XR, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUCOPHAGE/GLUCOPHAGE XR, observe the patient closely for hypoglycemia. |
| *Examples:* | Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. |

Source: NDA 020357 approved Drug Label, page 10

## 2.8 General Biopharmaceutics

### 2.8.1 How is the proposed to-be-marketed formulation linked to the clinical development formulation?

The proposed to-be-marketed formulation of metformin hydrochloride extended-release oral solution was used in clinical pharmacology pivotal Study MFM_100S_0508_17.

**2.8.2 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

The 90% CI of geometric mean ratios of metformin primary PK endpoints were all within the range of the pre-defined 80%-125% bounds.

**2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?**

Following 750 mg single-dose administration of extended-release oral suspension in healthy adults under fed and fasted conditions, metformin AUCs are comparable between fed and fasting conditions as the 90% CI of geometric mean ratios (fed/fasting) of $AUC_{0-t}$ and $AUC_{0-inf}$ are all within the range of 0.80 and 1.25 (Table 1.2). Metformin $C_{max}$ is about 20% less in fed condition compared to fasting condition. The lower boundary of 90% CI of geometric mean ratio (fed/fasting) of $C_{max}$ is lower than 0.80. The median $T_{max}$ in fed condition is 4.5 hours post-dose, which is about 1 hour earlier than in fasting condition (Table 2.6).

**Table 2.6 Arithmetic Mean (±SD) Metformin PK Parameters following 750 mg Single Dose Oral Administration of ER-Suspension under Fasting and Fed Condition (PK Set, N=52)**

| Parameter | Fasting Condition | Fed Condition |
|---|---|---|
| $C_{max}$ (ng/mL) | 1067.6 (377.1) | 815.4 (180.2) |
| $AUC_{0-t}$ (ng·h/mL) | 7472.0 (1946.1) | 7694.8 (1692.1) |
| $AUC_{0-inf}$ (ng·h/mL) | 7662.9 (1964.6) | 7894.0 (1707.9) |
| $T_{max}$ (hour)* | 4.5 (3.5, 6.5) | 5.5 (3.5, 10) |
| $t_{1/2}$ (hour) | 4.64 (1.98) | 4.19 (1.04) |

* Median (min, max)
Source: from Table 4.4

**2.8.4 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so were they bioequivalent or not?**

Only the highest dosing strength (750 mg) of the listed product (Glucophage XR®) is used in clinical pharmacology pivotal Study MFM_100S_0508_17. This approach is acceptable regarding Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products.

**2.9 Analytical Section**

**2.9.1 What was the bioanalytical method used to assess metformin plasma concentrations?**

Metformin plasma concentration is measured by an ultra-high performance liquid chromatography tandem mass spectrometric method. Metformin-d6 is used as internal standard. The method was developed and validated at the Department of Clinical Pharmacology and Pharmacokinetics, Sun Pharmaceutical Industries Ltd.

**2.9.2 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?**

Parameters of bioanalytical method validation are listed in Table 2.7. The validated bioanalytical method used for measuring metformin plasma concentration is acceptable.

**Table 2.7 Parameters of Somatropin Bioanalytical Method Validation**

| Validation Parameters | Value |
|---|---|
| LLOQ | 15.0 ng/mL |
| ULOQ | 3511.1 ng/mL |
| Calibrated Range | 15.0 to 3504.8 ng/mL |
| Dilution Linearity Accuracy (bias%) | -4.37% to 4.50% up to 1:4 dilution |
| Dilution Linearity Precision | 1.11% to 2.92% up to 1:4 dilution |
| Intra-assay Accuracy (bias%, 4 runs) | -4.87% to 4.50% |
| Intra-assay Precision (4 runs) | 1.11% to 6.49% |
| Inter-assay Accuracy (bias%, 4 runs) | -1.90% to -0.75% |
| Inter-assay Precision (4 runs) | 1.66% to 4.50% |
| Matrix Selectivity Accuracy (bias%, n=10) | -1.03% to -0.33% |
| Concomitant Medication Selectivity Precision (bias%, n=6) | 0% to 1.50% |
| Freeze and Thaw Stability | 3 freeze (-50°C)-thaw cycles |
| Bench-top Stability in Matrix | 6.28 hours under low light condition in ice cold water bath |
| Short-term Stability | 16.37 hours under low light condition at room temperature |
| Long-term Stability | 216 days at -50°C |

Source: distilled from study-mfm-100s-0508-17-ar-mv-rep.pdf

- Calibration curve

  The standard curve consisted of 8 non-zero calibration standard samples of metformin (15.0, 41.7, 126.4, 351.1, 702.2, 1404.4, 2808.8, 3511.1 ng/mL) in pooled normal human plasma. The LLOQ (15 ng/mL) and ULOQ (3511.1 ng/mL) samples standard sample were provided in duplicates. The acceptance of the calibration standards is at least 75% of non-zero standards meet the following criterion, including at least one LOQ and ULOQ standard:

  Accuracy of the LOQ standard in the calibration curve should be within ± 20% of the nominal value and within ±15% for other calibration standards.

  According to this criterion, 14 runs [V657/CC1, 2, 3, 4, 7, 8, 10, 11, V657/CC(ST)1, V657/CC(STP)1, V657/CC(2STP)1, V657/CC(FS)1, V657/CC(ST051)1, and V657/CC(STP060)1] met the criteria and the results from 2 runs (V657/CC 5 and 6) were rejected.

- QC samples

  QC samples consisted of 6 concentration levels of metformin [15.1 (LOQ-QC), 42.2 (LQC), 1405.4 (MQC), 2810.8 (HQC), 5967.8 with 1:1 dilution (D2QC), and 5967.8 ng/mL with 1:4 dilution (D4QC)] in pooled normal human plasma. Each QC sample was measured in 6 wells and average calculated concentrations were used for sequence acceptance. At least 67% of total QC samples including at least 50% at each concentration should meet following acceptance criteria:

  - LQC, MQC, HQC, D2QC and D4QC samples should be within ±15% of their respective nominal values and LOQQC samples should be within ±20% of their respective nominal values.

- Precision: the % CV at LQC, MQC, HQC, D2QC and D4QC concentrations should be ≤ 15% and at LOQQC concentration should be ≤ 20%.
- Accuracy: the mean concentrations should be within ± 15% of the nominal concentrations at LQC, MQC, HQC, D2QC and D4QC level and should not deviate by more than ± 20% at the LOQQC level.

According to this criterion, results of QC samples from run V657/CC2 did meet the criteria due to failure of one (1/6) LQC sample and one (1/6) HQC sample.

- Acceptance of Matrix Effect

The matrix effect was tested in LOQQC and HQC samples. The mean concentration had to be within ±20% of the nominal concentrations at LOQQC level and within ± 15 % of the nominal concentrations at HQC level. The %CV should be ≤ 20% at LOQQC level and ≤ 15% at HQC level.

LLOQC and HQC samples were tested in 10 individual human plasma (including 2 hemolyzed matrix and 2 lipemic matrix). The accuracy (bias%) was within ±1.03% of the nominal value and the %CV was ≤3.80% (run V657/CC10).

- Acceptance of Dilution Linearity

Dilution linearity results was mostly coming from the diluted QC samples [D2QC (1:2) and D4QC (1:4)]. The intra-assay accuracy (bias%) of D4QC sample ranged from -4.37% to 4.50% of the nominal values. The intra-assay precision of D4QC sample ranged from 1.11% to 2.92% (runs V657/CC1, 3, 8, and 9). According to the PK results from Study MFM_100S_0508_17 was 2323 ng/mL, which was lower than HQC concentration and therefore no PK sample was diluted.

- Acceptance of Intra- and inter-Assay Precision and Accuracy

The acceptance criteria for intra-assay and inter-assay precision and accuracy are:

- Precision: the % C.V. at LQC, MQC, HQC, D2QC and D4QC concentrations should be ≤ 15% and at LOQ QC concentration should be ≤ 20%.
- Accuracy: the mean concentrations should be within ± 15% of the nominal concentrations at LQC, MQC, HQC, D2QC and D4QC level and should not deviate by ± 20% at the LOQ QC level.

From 4 runs (runs V657/CC1, 3, 8, and 9), the intra-assay precision ranged from 1.11% to 6.49%; the intra-assay accuracy (bias%) was within ± 4.97% of the normal values. From 5 runs (runs V657/CC1, 2, 3, 8, and 9), the inter-assay precision ranged from 1.74% to 4.38%; the intra-assay accuracy (bias%) was within ± 1.87% of the normal values. Sponsor excluded two QC samples from run V657/CC2 to calculate the inter-assay precision and accuracy.

The inter-assay precision ranged from 1.66% to 4.50% after exclusion results from run V657/CC2. The intra-assay accuracy (bias%) was within ± 1.90% of the normal values after exclusion results from run V657/CC2.

- Acceptance of Assay Selectivity in the Presence of Concomitant Medication

Selectivity of metformin and metformin-d6 (ISTD) in six normal blank matrix lots and six LOQ samples was evaluated in presence of six different drugs (acetaminophen ~ 25 µg/mL, diclofenac ~ 2 µg/mL, amoxicillin ~ 10 µg/mL, clavulanic acid ~ 2 µg/mL, caffeine ~ 10 µg/mL and nicotine ~ 16 ng/mL).

Acceptance criteria for selectivity:

- %CV should be ≤ 20% for both analyte(s) peak area and ISTD(s) peak area in the extracted LOQ samples.
- If above acceptance criteria for %CV are met for both analyte(s) and ISTD(s), then only evaluate following acceptance criteria for selectivity:
  - Peak area response at the RT of analyte(s) in all blank matrix lots must be less than 20% of the mean peak area response of the analyte(s) in the extracted LOQ samples.
  - Peak area response at the RT of ISTD(s) in all blank matrix lots must be less than 5% of the mean peak area response of the ISTD(s) in the extracted LOQ samples.

Results showed that precision (%CV) was 2.07% for analyte peak area and 1.12% for ISTD peak area. The % area of blank matrix spiked with concomitant medication with respect to mean peak area response of analyte and ISTD in extracted LOQ was ≤ 1.50% and ≤0.04, respectively.

- Acceptance of Stability

Stability of metformin was assessed in QC samples. The acceptance criteria of stability are:

- The % CV of peak area of analyte should be ≤ 15%.
- The % CV of peak area of ISTD should be ≤15%.
- The stability is deemed acceptable if % stability is within the range of 90-110%.

For stability samples experienced three cycles of freeze (-50°C) and thaw, the precision was 0.61% and 2.86% for HQC samples (N=4) and LQC samples (N=4), respectively. The accuracy was 0.59% and 3.33% for HQC samples and LQC samples, respectively.

For ben-top stability samples under low light condition in ice cold water bath for 6.28 hours, the precision was 1.43% and 0.93% for HQC samples (N=4) and LQC samples, respectively. The accuracy (bias%) was -1.20% and 4.02% for HQC samples and LQC samples, respectively.

For short-term stability samples under low light condition at room temperature for 16.37 hours, the precision was 1.07% and 2.47% for HQC samples (N=6) and LQC samples, respectively. The accuracy (bias%) was -3.99% and -2.07% for HQC samples and LQC samples, respectively.

For long-term stability samples stored at -50°C for 216 days, the precision was 3.76% and 1.76% for HQC samples (N=4) and LQC samples (N=4), respectively. The accuracy (bias%) was 0.62% and 2.82% for HQC samples and LQC samples, respectively.

## 3.0 SUMMARY of LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

- The listed product (Glucophage® XR tablet) should not be listed in the label.
- The *in vitro* dose dumping result should be included in the label.
- Although the metformin labels already contain a warning for concomitant consumption of alcohol for its effects on lactate metabolism. The label should provide additional concerns that consuming alcohol greater or equal to 5% ABV (alcohol by volume) with this metformin hydrochloride extended-release oral suspension can substantially accelerate the release and absorption of metformin and acceleration will be greater with increased alcohol content.

## 4. Appendix– Individual Study Review

**Study MFM_100S_0508_17**

**Study Type:** Phase 1 single dose crossover BE study in healthy adults
**Study Date:** 04/23/2018-05/08/2018

**Title:**
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 extended-release tablets 750 mg in healthy adult human subjects under fed condition

**Objective:**

- Primary objective is to assess the effect of food on bioavailability of metformin hydrochloride extended release oral suspension (ER-suspension) and to assess the bioequivalence between ER-suspension and Glucophage® XR extended-release tablets (ER-tablet) in healthy adult human subjects under fed condition.

- Secondary objective is to assess the safety of ER-suspension and ER-tablet in healthy adult human subjects

**PK Endpoints:**
$AUC_{0-t}$, $AUC_{0-inf}$, $C_{max}$, $AUC_{\% Extrap}$, $T_{max}$, $K_{el}$, and $t_{1/2}$ were estimated in plasma for metformin. Arithmetic means, standard deviations and coefficients of variation were calculated for all of these parameters.

**Statistical Plan:**
The log-transformed pharmacokinetic parameters ($C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$) were analyzed using Type III sum of squares with sequence, period and formulation as fixed effects and subjects nested within sequence as random effects.

Assuming a geometric ratio (suspension/tablet) of ~88% and intra-subject CV of approximately 18%, 45 subjects may yield a power of 80% to show bioequivalence under bioequivalence assumptions. However, to be conservative and allow for possible dropouts and/or withdrawals, 60 subjects were considered for this study.

**Study Design and Method:**
This study was an open-labeled, randomized, single-dose, three-treatment, three-period, six-sequence, crossover study comparing the bioavailability of metformin systemic exposure following 750 mg ER-suspension and 750 mg ER-tablet in healthy adults. In total, 60 subjects were planned. All periods were separated by washout period of 6 days. The treatments were:

- Treatment A: single dose of 750 mg/7.5 mL ER-suspension oral co-administration with 240 mL 20% glucose solution after 10-hour overnight fasting.

- Treatment B: single dose of 750 mg/7.5 mL ER-suspension oral co-administration with 240 mL 20% glucose solution, 30 minutes after the start of high-fat high-calorie breakfast. The breakfast was after 10-hour overnight fasting.

- Treatment R: single dose of one 750 mg ER-tablet oral co-administration with 240 mL 20% glucose solution, 30 minutes after the start of high-fat high-calorie breakfast. The breakfast was after 10-hour overnight fasting.

60 mL of the 20% w/v glucose solution was administered every 15 minutes for up to 4 hours after dosing.

The content of the breakfast menu for fed condition is listed in Table 4.1.

**Table 4.1 Breakfast Menu in Study MFM_100S_0508_17**

| S. No. | Food Stuff | Quantity (gm/ml) | Energy (cal) | Carbohydrate (g) | Proteins (g) | Fat (g) |
|---|---|---|---|---|---|---|
| 01 | Chicken | 60 | 146 | - | 14 | 10 |
| 02 | Whole milk | 240 | 152 | 12 | 8 | 8 |
| 03 | Hash Brown Potatoes | 120 | 162 | 15 | 3 | 10 |
| 04 | Eggs fried in butter | 2 med | 267 | - | 15 | 23 |
| 05 | a) Bread slices | 2 large | 160 | 35.5 | 4.5 | - |
| | b) Butter | 10 | 90 | - | - | 10 |
| | **Total** | | **977** | **62.5** | **44.5** | **61** |
| | | | **Kcal.** | **250** | **178** | **549** |
| | | | **%** | **26** | **18** | **56** |

Source: study-mfm-100s-0508-17-body.pdf, page 235

A total of 93, 1-mL blood samples (including pre-dose duplicate sample), were collected from each subject in $K_3$EDTA vacutainers, during the course of the study. The blood samples were collected at pre-dose (duplicate) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 14, 16, 20, 24, 36 and 48 hours post dose in each period. All blood samples were collected under low light condition.

**Analytical Method:**
Metformin plasma concentration is measured by an ultra-high performance liquid chromatography tandem mass spectrometric method. The LOQ of this method is 15.1 ng/mL.

**Noteworthy Inclusion Criteria:**
Subjects included

- were in the age range of 18-45 years.
- were neither overweight nor underweight for his height as per the Life Insurance Corporation of India height/weight chart for non-medical cases.
- were of normal health as determined by medical history and physical examination of the subjects performed within 28 days prior to the commencement of the study.
- had hemoglobin level: ≥12.0 g/dL.
- were non-vegetarian.

**Noteworthy Exclusion Criteria:**

- Subject had history of hypersensitivity to Metformin or to any other drug.
- Subject had history of lactic acidosis.
- Subject had history of nausea, vomiting and/or diarrhea in the week preceding the study.
- Subject had eGFR< 90mL/min/1.73m$^2$
- Subject had liver function (total Bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase) > 20 % above upper limit of laboratory reference range.
- Subject had history of drug induced rash and/or pruritus.
- Subject had any evidence of organ dysfunction or any clinically significant deviation from the normal in physical or clinical determinations
- Investigations with urine samples of the subject showed clinically abnormal chemical and microscopic examination of urine defined as presence of RBC (>2 /HPF), WBC (>4 /HPF), glucose (Positive) or Protein (+, ++, +++, ++++)
- Subject had history of drug dependence or excessive alcohol intake on a habitual basis or had difficulty in abstaining or found positive in alcohol breath test before admission.
- Consumption of alcohol for 48 hours prior to admission.
- Consumption of grapefruit juice and or grape fruit supplements containing products for 48 hours prior to admission.

**Subjects Disposition:**

75 subjects were screened and 60 male subjects were enrolled (safety set). 52 subjects completed study.

- Subjects # (b) (6) withdrew from the study in Period1 because not consuming the breakfast. It appears that this subject was not administered with metformin.

- Subjects # (b) (6) withdrew from the study in Period 2 due to positive alcohol result. The subject was administered with ER-tablet during Period 1.

- Subjects # (b) (6) withdrew from the study in Period 2 due to positive alcohol result. The subject was administered with ER-suspension under fasting condition during Period 1.

- Subjects # (b) (6) withdrew from the study in Period 2 due to positive cannabinoids result. The subject was administered with ER-suspension under fasting condition during Period 1.

- Subjects # (b) (6) lost contact after Period 1. The subject was administered with ER-suspension under fasting condition during Period 1.

- Subjects # (b) (6) lost contact after Period 1. The subject was administered with ER-tablet during Period 1.

- Subjects # (b) (6) lost contact after Period 2. The subject was administered with ER-tablet during Period 1 and ER-suspension under fasting condition during Period 2.

- Subjects # (b) (6) lost contact after Period 2. The subject was administered with ER-suspension under fasting condition during Period 1 and ER-tablet during Period 2.

All 52 subjects were included in PK set and statistical evaluation was performed on PK set.

Following PK samples were missing from completed subjects:

**Table 4.2 Missing PK Samples by Time Points in 52 Subjects completed Study**


Source: study-mfm-100s-0508-17-body.pdf, page 40

**Demographics:**

The demographic summary is summarized in Table 4.3. Only male subjects were enrolled. The mean body weight was 59.7 ± 7.3 kg.

**Table 4.3 Demographic Characteristics (Safety set)**

| | Subjects enrolled in the study (N = 60) |
|---|---|
| **Age (years)** | |
| **Mean ± SD** | 28.65± 6.69 |
| **Range** | 18 - 41 |
| **Groups** | |
| **< 18** | 0 % |
| **18 – 40** | 59 (98.33%) |
| **41 – 64** | 01 (1.67%) |
| **65 – 75** | 0 % |
| **> 75** | 0 % |
| **Sex** | |
| **Female** | 0 % |
| **Male** | 60 (100 %) |
| **Race** | |
| **Asian** | 60 (100 %) |
| **Black** | 0 % |
| **Caucasian** | 0 % |
| **Hispanic** | 0% |
| **Others** | 0 % |
| **Height (cm)** | |
| **Mean ± SD** | 165.10± 5.37 |
| **Range** | 152.4–180.3 |
| **Weight (kg)** | |
| **Mean ± SD** | 59.66 ± 7.34 |
| **Range** | 46.1– 74.2 |
| **Smokers** | |
| **Yes** | 04 (6.67%) |
| **No** | 56 (93.33%) |

Source: study-mfm-100s-0508-17-body.pdf, page 52

**Results:**

- PK Results

The statistical summary of metformin PK parameters by treatment is listed in Table 4.4.

**Table 4.4 Arithmetic Mean (±SD) Metformin PK Parameters following 750 mg Single Dose Oral Administration (PK Set)**

| Parameter | Treatment A (N=52) | Treatment B (N=52) | Treatment R (N=52) |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 1067.6 (377.1) | 815.4 (180.2) | 766.5 (150.6) |
| $AUC_{0-t}$ (ng·h/mL) | 7472.0 (1946.1) | 7694.8 (1692.1) | 8932.3 (2106.3) |
| $AUC_{0-inf}$ (ng·h/mL) | 7662.9 (1964.6) | 7894.0 (1707.9) | 9252.3 (2179.9) |
| $AUC_{\% Extrap}$ (ng·h/mL) | 2.58% (1.01%) | 2.58% (0.81%) | 3.43% (1.44%) |
| $T_{max}$ (hour)* | 4.5 (3.5, 6.5) | 5.5 (3.5, 10) | 8 (4, 9.5) |
| $K_{el}$ ($hour^{-1}$) | 0.161 (0.0333) | 0.172 (0.0289) | 0.178 (0.0246) |
| $t_{1/2}$ (hour) | 4.64 (1.98) | 4.19 (1.04) | 3.99 (;0.68) |

* median (range)
Source: study-mfm-100s-0508-17-body.pdf, page 62-64

Metformin plasma concentration-time profiles by treatments are depicted in Figure 4.1

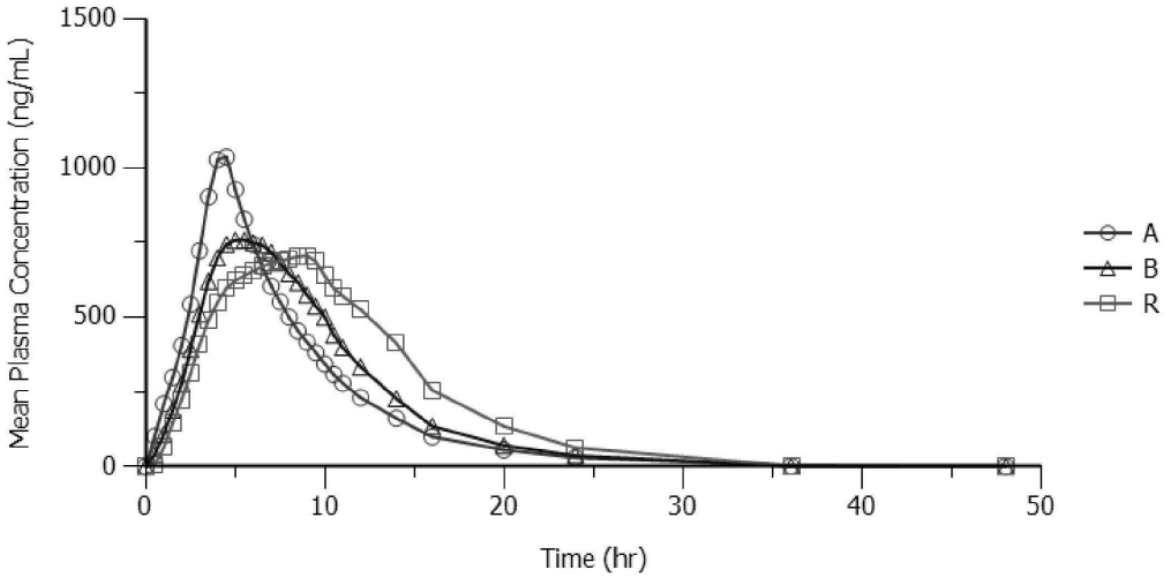


**Figure 4.1** Mean metformin plasma concentration (ng/mL)-time profile by treatment (N=52) (Source: study-mfm-100s-0508-17-body.pdf, page 58, Figure 1)

The statistical comparison of metformin systemic exposure between ER-suspension and ER-tablet under fed condition is presented in Table 4.5. 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 0.80 and 1.25.

**Table 4.5 Statistical Comparison of Metformin PK Parameters following 750 mg Single Dose Administration of ER-Suspension and ER-Tablet (PK Set, N=52)**

| 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% |

Source: study-mfm-100s-0508-17-body.pdf, page 61

The statistical comparison of metformin systemic exposure between ER-suspension under fed condition and ER-suspension under fasting condition is presented in Table 4.6. The 90% CI of geometric mean ratios (fed/fasting) of $AUC_{0-t}$ and $AUC_{0-inf}$ were all within the range of 0.80 and 1.25. The lower limit of 90% CI of geometric mean ratio (fed/fasting) of $C_{max}$ was <0.80.

**Table 4.6 Statistical Comparison of Metformin PK Parameters following 750 mg Single Dose Administration of ER-Suspension under Fed Condition and Fasting Condition (PK Set, N=52)**

| Parameter | Fed Condition | Fasting Condition | Ratio (Fed/Fasting) | 90% CI | Intra-Subject Variation |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 796.6 | 1002.0 | 0.795 | 0.747 – 0.846 | 19.1% |
| $AUC_{0-t}$ (ng·h/mL) | 7506.8 | 7178.8 | 1.046 | 1.006 – 1.087 | 11.9% |
| $AUC_{0-24h}$ (ng·h/mL) | 7706.4 | 7370.2 | 1.046 | 1.006 – 1.086 | 11.6% |

Source: study-mfm-100s-0508-17-body.pdf, page 61

- Safety Results

There were no serious and significant adverse events or deaths during the conduct of the study.

- One adverse event of headache (Subject (b) (6)) was reported on Treatment A in period II. The event was judged to have possible relationship with study drug and the subject recovered without sequelae. The event was moderate and not serious in nature.

- One laboratory abnormality adverse event of increased AST (135 U/L) (Subject (b) (6)) was reported in Treatment R at the end of the study. The event was judged to have no relationship with study drug and the subject recovered without sequelae. The event was mild and not serious in nature.

- One laboratory abnormality adverse event of increased eosinophils (Subject (b) (6)) was reported in Treatment A at the end of the study safety follow-up. The event was judged to have no relationship with study drug and was mild and not serious in nature.

**Conclusions:**

- Metformin PK comparison between ER-suspension and ER-tablet following single dose of 750 mg oral administration under fed condition

The bioequivalence between ER-suspension and ER-tablet is established under fed condition as 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 0.80 and 1.25. The median $T_{max}$ following administration of ER-suspension is 2.5 hours earlier than ER-tablet.

- Food effect on metformin ER-suspension following single dose of 750 mg oral administration

  The AUCs of metformin following 750 mg single dose administration of ER-suspension under fed condition is comparable to the AUCs obtained under fasting condition. Metformin $C_{max}$ under fed condition is about 25% lower than the $C_{max}$ obtained under fasting condition. The median $T_{max}$ under fed condition is 1 hour later than $T_{max}$ under fasting condition.

- Safety

Both metformin ER-suspension and ER-tablet (Glucophage XR tablet) were well tolerated by the subjects in Study MFM_100S_0508_17.

**Reviewer's analysis:**
*Reviewer's independent analysis by Phoenix 64 showed same results, which agrees with the Sponsor's conclusions:*

*Since there were only 52 subjects (PK set) having their PK results available from both ER-suspension (treatment B) and ER-tablet (Treatment R) under fed condition, the reviewer also used PK set to do the analysis. Reviewer's analysis showed that following 750 mg single dose oral administration under fed condition, bioequivalence is established between ER-suspension and ER-tablet. The 90% CI of geometric mean ratios (suspension/tablet) of $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ are all within the range of 0.80 and 1.25 (Table 4.7).*

**Table 4.7 Statistical Comparison of Metformin PK Parameters following 750 mg Single Dose Administration of ER-Suspension and ER-Tablet (PK Set, N=52)**

| 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.

*The geometric mean concentration-time profiles (PK set) of metformin following 750 mg single dose of ER-suspension and ER-tablet are summarized in Figure 4.2.*

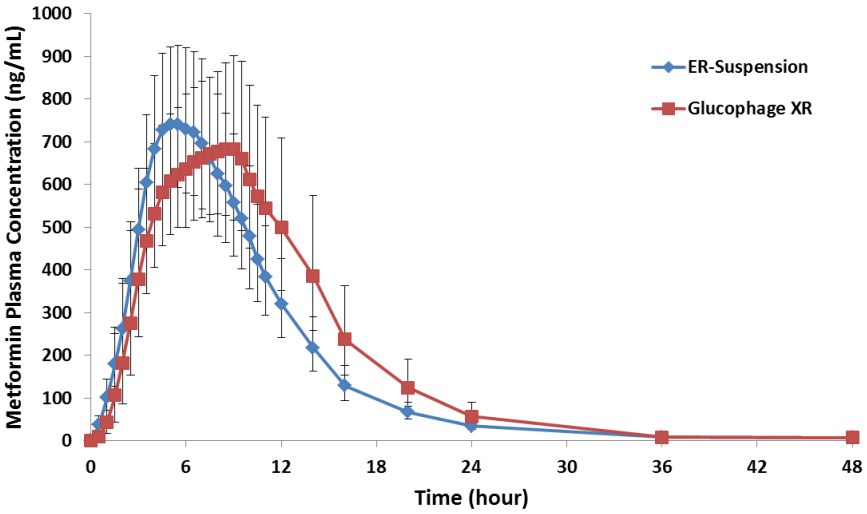


**Figure 4.2** Geometric mean (± SD) metformin plasma concentration-time profiles (PK set, N=52) following 750 mg single dose of ER-suspension (blue) and ER-tablet (red). BLQ samples were imputed with 1/2 LLOQ values (7.55 ng/mL).

*When using PK set (N=52), following 750 mg single dose ER-suspension oral administration, the 90% CI of geometric mean ratios (fed/fasting) of $AUC_{0-t}$ and $AUC_{0-inf}$ are all within the range of 0.80 and 1.25 (Table 4.8). The lower boundary of 90% CI of geometric mean ratio (fed/fasting) of $C_{max}$ is lower than 0.80.*

**Table 4.8 Statistical Comparison of Metformin PK Parameters following 750 mg Single Dose Administration of ER-Suspension under Fed Condition and Fasting Condition (PK Set, N=52)**

| Parameter | Fed Condition | Fasting Condition | Ratio (Fed/Fasting) | 90% CI | Intra-Subject Variation |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL)* | 796.6 | 1002.0 | 0.795 | 0.747 – 0.846 | 19.1% |
| $AUC_{0-t}$ (ng·h/mL)* | 7506.8 | 7178.8 | 1.046 | 1.006 – 1.087 | 11.9% |
| $AUC_{0-24h}$ (ng·h/mL)* | 7706.4 | 7370.2 | 1.046 | 1.006 – 1.086 | 11.6% |

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

*The geometric mean concentration-time profiles (PK set) of metformin following 750 mg single dose of ER-suspension under fed and fasting conditions are summarized in Figure 4.3.*

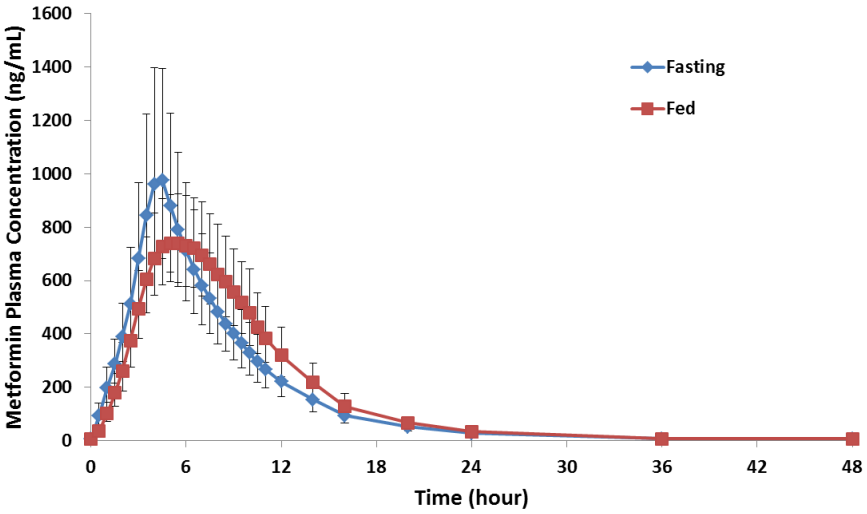


**Figure 4.3** Geometric mean (± SD) metformin plasma concentration-time profiles (PK set, N=52) following 750 mg single dose of ER-suspension under fasting condition (blue) and fed condition (red). BLQ samples were imputed with 1/2 LLOQ values (7.55 ng/mL).

---

**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/

---

YUNZHAO REN
07/29/2019 11:49:37 AM

MANOJ KHURANA
07/29/2019 01:52:00 PM