Fed and Fasted Single-dose Assessment of Bioequivalence of Dapagliflozin and Metformin Extended-release Fixed-dose Combination Tablets Relative to Single-component Dapagliflozin and Metformin Extended-release Tablets in Healthy Subjects

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ABSTRACT

Purpose: In patients with type 2 diabetes mellitus, fixed-dose combinations (FDCs) of antihyperglycemic medications may provide complementary efficacy while reducing tablet burden and improving compliance. The aim of this study was to assess the bioequivalence and tolerability of 2 FDCs of dapagliflozin and metformin extended-release (XR) versus their individual component (IC) tablets.

Methods: An open-label, balanced, randomized, 2-way crossover, 4-arm study was conducted in 129 healthy Brazilian subjects (aged 18–55 years). Two oral doses of the FDCs (5 mg dapagliflozin and 500 mg metformin XR, and 10 mg dapagliflozin and 1000 mg metformin XR) were evaluated in fed and fasted states.

Findings: Under fed and fasted conditions the 5 mg dapagliflozin and 500 mg metformin XR FDC showed bioequivalence to its ICs. The 10 mg dapagliflozin and 1000 mg metformin XR FDC was bioequivalent to its ICs in fed subjects. Although AUC for the 10 mg dapagliflozin and 1000 mg metformin XR FDC was bioequivalent in fasted subjects, the C_{max} for metformin was not bioequivalent to its ICs in fasted subjects (upper 90% CI was 127.5%, and thus outside the 80%–125% bioequivalence interval). The small increase in the fasted state is not considered clinically meaningful due to the small magnitude of the difference (9.2%), the lack of metformin C_{max} being associated with efficacy or tolerability concerns, and the fasted state not being the recommended state for dosing of metformin XR. The safety profile and tolerability of the FDCs were similar to those of their ICs and no deaths or serious adverse events were reported.

Implications: Both FDCs of dapagliflozin and metformin XR were bioequivalent to their ICs in fed and fasted subjects, except for the metformin C_{max} from the 10 mg dapagliflozin and 1000 mg metformin XR FDC in fasted subjects. These data support the use of a dapagliflozin and metformin XR FDC in patients with type 2 diabetes mellitus. (*Clin Ther*. 2016;38:99–109)

Key words: bioequivalence, dapagliflozin, fixed-dose combination, metformin extended release, SGLT2 inhibitor, type 2 diabetes mellitus.

INTRODUCTION

Metformin immediate release (IR) and extended release (XR), along with dietary and lifestyle changes, form the basis for first-line treatment of type 2 diabetes mellitus (T2DM).[1] In patients with T2DM, further glycemic control may be needed as β-cell function continues to deteriorate in this chronic, progressive disease. The addition of other anti-diabetes agents as the disease progresses can add to the complexity of the treatment regimen. The differing but

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complementary mechanisms of action of metformin and dapagliflozin as early-administered anti-diabetes agents provide a rationale for a fixed-dose combination (FDC) formulation of dapagliflozin and metformin XR. Metformin acts by reducing hepatic glucose production, lowering glucose absorption from the intestine, and improving insulin sensitivity in the periphery,[2] whereas oral dapagliflozin, a highly selective sodium-glucose co-transporter 2 inhibitor, inhibits renal glucose reuptake, leading to glycosuria, and acts through a non–insulin-dependent mechanism.[3] Data from a drug−drug interaction study in healthy subjects found that coadministration of dapagliflozin and metformin did not affect the pharmacokinetic (PK) parameters of either compound.[4] In clinical trials, dapagliflozin has been shown to reduce hyperglycemia, blood pressure, and body weight with a low risk of hypoglycemia when administered alone or in combination with metformin.[5–15] In combination with metformin, dapagliflozin 5 or 10 mg administered once daily is well tolerated and effective for improving glycemic control in patients with T2DM.[9] An FDC of dapagliflozin and metformin hydrochloride was recently approved for the treatment of patients with T2DM.[16,17]

When developing an FDC, it is necessary to show that the combination is therapeutically equivalent to the individual components (ICs) administered separately. Therapeutic equivalence can be concluded on the basis of a PK parameter evaluation finding that the rate and extent of absorption of each therapeutic entity in the FDC is similar enough to the coadministered respective ICs to be deemed bioequivalent.

The study described here was conducted to support the approval of dapagliflozin and metformin XR FDCs in Brazil using the locally manufactured metformin XR as the IC reference product. While metformin XR and the dapagliflozin and metformin XR FDCs are recommended to be administered with food to improve systemic absorption of metformin, a bioequivalence study performed under both fed and fasted conditions was required by the Brazilian National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária). It is important to note that bioequivalence studies are typically conducted in the fasted state if the formulation being evaluated is to be given in either the fasted state or without regard to meals. If the formulation being evaluated is always to be given with food, then bioequivalence studies are typically conducted in the fed state.

METHODS

Objectives

The primary objective of this study was to assess the bioequivalence of 2 doses of dapagliflozin and metformin XR FDC tablets (5 mg dapagliflozin and 500 mg metformin, and 10 mg dapagliflozin and 1000 mg metformin) after oral administration relative to the same doses of dapagliflozin and glifage XR (metformin XR) tablets administered orally together in both the fed and fasted states.

The secondary objective was to assess the safety profile and tolerability of each FDC relative to the equivalent doses of dapagliflozin and metformin XR administered orally together in fed and fasted subjects.

Study Population

Healthy Brazilian subjects (aged 18−55 years) of both sexes with body mass index $\geq$18.5 kg/m^2 and $\leq$28.5 kg/m^2 were eligible to enter the study. Women must not have been breastfeeding, and those of childbearing age were required to have been using contraception and to have had a negative pregnancy test. Sexually active men were also required to have been using effective birth control.

Key exclusion criteria included any significant chronic or acute medical illness, current or recent gastrointestinal disease or surgery, major surgery within the previous 4 weeks, a recent history of drug or alcohol abuse, and use of tobacco or nicotine-containing products within 6 months before check-in. This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization and Good Clinical Practice and applicable regulatory requirements. The protocol was approved by an Institutional Review Board, and all subjects provided written informed consent before any study-specific activities.

Study Design

An open-label, balanced, 2-way crossover study in which study subjects were randomized into 1 of 4 treatment arms: Arm 1: 5 mg dapagliflozin and 500 mg metformin XR in fasting subjects; Arm 2: 5 mg dapagliflozin and 500 mg metformin XR in fed subjects; Arm 3: 10 mg dapagliflozin and 1000 mg metformin in fasting subjects; and Arm 4: 10 mg dapagliflozin and 1000 mg metformin in fed subjects