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APPLICATION NUMBER:

210913Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	210874
Submission Date	07/02/2018
Brand Name	QTERNMET XR
Generic Name	Dapagliflozin, Saxagliptin and Metformin Hydrochloride
Reviewer	Mohammad Absar, Ph.D.
Team Leader (Acting)	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Division of Metabolic and Endocrine Products
Applicant	AstraZeneca
Formulation; Strength	Extended release oral tablet; four strengths- Dapagliflozin/Saxagliptin/Metformin HCL 10/5/1000 mg Dapagliflozin/Saxagliptin/Metformin HCL 5/5/1000 mg Dapagliflozin/Saxagliptin/Metformin HCL 2.5/2.5/1000 mg Dapagliflozin/Saxagliptin/Metformin HCL 5/2.5/1000 mg
Dosage Regimen (proposed)	For patients not currently taking dapagliflozin, the recommended starting total daily dose of QTERNMET XR is dapagliflozin/saxagliptin/Metformin HCl 5/5/1000 or 2000 mg taken orally, once daily in the morning with food
Relevant IND/NDA	IND 131385
Indication	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM (b) (4) [redacted]

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1. EXECUTIVE SUMMARY

AstraZeneca (Applicant) has submitted NDA 210874 under the 505(b)(1) pathway seeking marketing approval for dapagliflozin/saxagliptin/metformin hydrochloride (HCL) (Dapa/Saxa/Met) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (b) (4) The drug product is an extended release oral tablet with four strengths: Dapa/Saxa/Met 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg. The proposed starting total daily dose for patients not currently taking dapagliflozin is Dapa/Saxa/Met 5/5/1000 or 2000 mg taken orally, once daily in the morning with food.

The clinical pharmacology program included a single Phase 1 comparative pharmacokinetic (PK)/food effect study (D168AC00001) in which the systemic exposure of dapagliflozin, saxagliptin and metformin following administration of single oral dose of the triple combination product – Dapa/Saxa/Met 5/2.5/1000 mg – were compared with that from administration of single oral dose of saxagliptin 2.5 mg (ONGLYZA) + dapagliflozin/metformin HCL 5/1000 mg (XIGDUO XR) in healthy subjects under fed condition (Cohort

1). Similar comparison was also performed following single oral dose administration of triple combination product – Dapa/Saxa/Met 10/5/1000 mg with that following single oral administration of Saxagliptin 5 mg (ONGLYZA) + dapagliflozin/metformin HCl 10/1000 mg (XIGDUO XR) in healthy subjects (Cohort 2).

In addition, the effect of food on the triple combination product was evaluated in each cohort. This study was conducted to bridge the data generated in the two pivotal Phase 3 studies in T2DM patients (Studies D1683C00005 and CV181169) that used monocomponents of dapagliflozin, saxagliptin and metformin HCl.[1] The Applicant requested biowaiver for the other two strengths – Dapa/Saxa/Met 2.5/2.5/1000 mg and 5/5/1000 mg. The following are the major findings from the current review –

1. Following single dose administration of Dapa/Saxa/Met 5/2.5/1000 mg in healthy subjects under fed condition, the mean peak concentration (C_{max}) and total systemic exposure (AUC_{inf}) of dapagliflozin were 42.3 ng/mL and 239.9 ng.hr/mL, respectively, of saxagliptin were 10.6 ng/mL and 51.6 ng.hr/mL, respectively, and of metformin were 1098 ng/mL and 10930 ng.hr/mL, respectively (Cohort 1, Study D168AC00001).
2. In the same study (Cohort 2), following single dose administration of Dapa/Saxa/Met 10/5/1000 mg, the C_{max} and AUC_{inf} dapagliflozin were 75.7 ng/mL and 463.6 ng.hr/mL, respectively, of saxagliptin were 20.9 ng/mL and 102.6 ng.hr/mL, respectively, and of metformin were 1057 ng/mL and 10470 ng.hr/mL, respectively.
3. The geometric mean ratio (GMR) of C_{max} and AUC_{inf} of dapagliflozin, saxagliptin and metformin were, in general, comparable between Dapa/Saxa/Met triple combination products (i.e., 5/2.5/1000 mg and 10/5/1000 mg) and their respective reference arms (i.e., single dose administration of ONGLYZA+XIGDUO XR) under fed condition.
4. There was no clinically meaningful effect of food on the systemic exposure of dapagliflozin, saxagliptin and metformin from the triple combination product. Under fed condition, the C_{max} and AUC_{inf} of saxagliptin and metformin were comparable to that under fasting condition for both strengths – Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg. While AUC_{inf} of dapagliflozin was comparable, C_{max} was reduced by approximately 38% under fed condition. This reduction in C_{max} is consistent with previous findings of dapagliflozin and is not considered clinically meaningful.[2]

1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the clinical pharmacology data submitted under NDA 210874 and finds the data acceptable to support approval.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The clinical program for Dapa/Saxa/Met triple combination product includes two pivotal Phase 3 efficacy/safety studies (D1683C00005 and CV181169) that utilized a dual add-on strategy to evaluate the combination of dapagliflozin and saxagliptin when added to metformin in adults with T2DM who had inadequate glycemic control. Both the Phase 3 studies were conducted using monoproducts of dapagliflozin, saxagliptin and metformin HCl; refer to the Clinical Review by Dr. Frank Pucino for additional detail.

To bridge clinical data generated in the two pivotal Phase 3 studies with the proposed fixed dose triple combination product, the Applicant conducted a Phase 1 comparative pharmacokinetic (PK)/food effect

[1] Studies D1683C00005 and CV181169 were also submitted as an efficacy supplement under NDA 209091 (QTERN).
[2] Prescribing information of XIGDUO XR (dated 02/22/2019)

study (D168AC00001) in which healthy subjects received a single oral dose of Dapa/Saxa/Met 5/2.5/1000 mg under fasted and fed condition or saxagliptin 2.5 mg (ONGLYZA) + dapagliflozin/metformin HCL 5/1000 mg ((XIGDUO XR) under fed condition in a crossover fashion (Cohort 1). In Cohort 2, healthy subjects received the highest strength of the triple combination product, Dapa/Saxa/Met 10/5/1000 mg, under fasted and fed condition, or saxagliptin 5 mg (ONGLYZA) + dapagliflozin/metformin HCl 10/1000 mg (XIGDUO XR) under fed condition in a crossover fashion.

The results from this study demonstrated that the geometric mean ratio (GMR) of C_{max} of dapagliflozin following single dose administration of Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg to that of the respective reference arm (i.e., single dose administration of ONGLYZA + XIGDUO XR) under fed condition were 1.14 and 0.93, respectively, while that of AUC_{inf} were 1.03 and 0.98, respectively. The GMR of C_{max} of saxagliptin following single dose administration of Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg to that of the respective reference arm were 1.00 and 0.94, respectively, while that of AUC_{inf} were 1.00 and 1.01, respectively. The GMR of C_{max} of metformin following single dose administration of Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg to that of the reference arm were 1.05 and 0.96, respectively, while that of AUC_{inf} were 0.99 and 0.94, respectively.

The comparison in PK parameters from this study is summarized in Table 1.

Table 1: Comparison of PK parameters of dapagliflozin, saxagliptin and metformin following single dose administration in healthy subjects

	PK parameter	GMR (90% CI) Dapa/Saxa/Met 5/2.5/1000 vs ONGLYZA 2.5 + XIGDUO XR 5/1000	GMR (90% CI) Dapa/Saxa/Met 10/5/1000 vs ONGLYZA 5 + XIGDUO XR 10/1000
Dapagliflozin	C_{max}	1.14 (1.01 – 1.28)	0.93 (0.83 – 1.03)
	AUC_t	1.03 (0.94 – 1.12)	0.98 (0.90 – 1.07)
	AUC	1.03 (0.94 – 1.12)	0.98 (0.90 – 1.07)
Saxagliptin	C_{max}	1.00 (0.85 – 1.17)	0.94 (0.83 – 1.06)
	AUC_t	1.00 (0.88 – 1.15)	1.01 (0.91 – 1.11)
	AUC	1.00 (0.88 – 1.14)	1.01 (0.91 – 1.11)
Metformin	C_{max}	1.05 (0.95 – 1.17)	0.96 (0.86 – 1.07)
	AUC_t	0.99 (0.88 – 1.10)	0.96 (0.86 – 1.06)
	AUC	0.99 (0.88 – 1.12)	0.94 (0.84 – 1.06)

Source: NDA 210874, Module 2.7; Summary of Biopharmaceutic Studies

In general, PK of dapagliflozin, saxagliptin and metformin were comparable between the triple combination and ONGLYZA+XIGDUO XR. The 90% CI for GMR of C_{max}, AUC_t and AUC_{inf} of saxagliptin and metformin were within the prespecified bioequivalence margin of 0.8 – 1.25 for both strengths. The upper bound of 90% CI for GMR of C_{max} of dapagliflozin for the lower strength was 1.28, outside of the prespecified bioequivalence margin. However, the 90% CI for GMR of dapagliflozin AUC_t and AUC_{inf} both were within the margin of 0.8 – 1.25. In addition, for the highest strength product, the GMR of all three PK parameters (i.e., C_{max}, AUC_t and AUC_{inf}) for dapagliflozin were within 0.8 – 1.25. Since this deviation is for peak exposures for one of the component of the FDC, not consistently observed for both strengths, and difference being on the higher side with regards to the relative exposure to reference single components, there are no efficacy related concerns due to assurance of total exposure being comparable by the bioequivalence criteria; the observed marginally higher C_{max} from the lower strength does not appear to

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