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APPLICATION NUMBER:

210874Orig1s000

SUMMARY REVIEW

Division Summary Memo for Regulatory Action and CDTL review

Date	April 29, 2019
From	Patrick Archdeacon, MD Acting Clinical Team Lead Division of Metabolism and Endocrinology Products
NDA # / Sequence #:	NDA 210874 and sNDA 209091/S-002
Applicant	Astra Zeneca
Date of Submission Receipt	July 2, 2018
PDUFA Goal Date	May 2, 2019
Proprietary Name / Established (USAN) names	QTERNMET XR/Dapagliflozin + Saxagliptin + Metformin HCl extended release QTERN/Dapagliflozin + Saxagliptin
Dosage Form(s)	QTERNMET XR: The Applicant is seeking approval of film-coated tablets containing the following dapagliflozin/saxagliptin/metformin extended-release dosage strengths: 2.5 mg/2.5 mg/1000 mg; 5 mg/2.5 mg/1000 mg; 5 mg/5 mg/1000 mg; 10 mg/5 mg/1000 mg QTERN: Film-coated tablets containing 10 mg of dapagliflozin and 5 mg of saxagliptin are currently approved. The Applicant is seeking approval of a 5 mg dapagliflozin /5 mg saxagliptin dosage strength.
Applicant Proposed Indications	QTERNMET XR: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) [redacted (b) (4)]. QTERN: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [redacted (b) (4)]
Recommended Action	Approval
Recommended Indication(s)/Populations(s)	The recommended labeling change for Section 1 of QTERNMET XR and QTERN to include: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended labeling change for Section 2.2 to include: No dose adjustment is needed in patients with an eGFR ≥45 mL/min/1.73 m^2 and to contraindicate use with an eGFR below 45 mL/min/1.73 m^2.

1. Introduction

On July 2, 2018, Astra Zeneca Pharmaceuticals LP (hereafter referred to as the Applicant) submitted original NDA 210874, in support of marketing approval for QTERNMET XR (dapagliflozin/saxagliptin/metformin HCl extended-release], and sNDA 209091-S002, in support of an additional dosage strength of and an expanded indication for QTERN (dapagliflozin/saxagliptin).

The component products of QTERNMET XR are three approved antihyperglycemic agents, each indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D). The submission to NDA 210874 includes manufacturing data, clinical pharmacology data, and clinical trial data. The Applicant proposes that the clinical data demonstrate that the combination of dapagliflozin (an SGLT2 inhibitor), saxagliptin (a DPP-4 inhibitor) and metformin (a biguanide) have complementary mechanisms of action to improve glycemic control. The Applicant has proposed the following as the indication for QTERNMET XR: "An adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4)
QTERNMET XR has been formulated as film-coated tablets available in a variety of dosage strengths: 2.5 mg/2.5 mg/1000 mg; 5 mg/2.5 mg/1000 mg; 5 mg/5 mg/1000 mg; 10 mg/5 mg/1000 mg.

NDA 209091 for QTERN was originally approved on February 27, 2017 with the indication "as an adjunct to diet and exercise to improve glycemic control in adults with T2D who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin." Only one dosage strength is currently marketed: a film-coated tablet containing 10 mg of dapagliflozin and 5 mg of saxagliptin (Dapa 10/Saxa 5). The Applicant has now submitted clinical data to support a conclusion that a 5 mg dose of dapagliflozin in combination with 5 mg of saxagliptin is safe and effective, as well as manufacturing data supporting the quality of the new dosage strength tablets (Dapa 5/Saxa 5). The new dosage strength allows the dosing of dapagliflozin as its starting dose of 5 mg. For that reason, the Applicant has also proposed revising the indication to "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

This memo references the following documents/sources:

Subject	Author	Date
Integrated Quality Assessment (QTERNMET XR)	Ramsharan Mittal, Christopher Galliford, Ted Change, Sarah Ibrahim, Anika Lalmansingh, James Laurenson	March 26, 2019
Integrated Quality Assessment (QTERNMET XR) Addendum	Christopher Galliford	April 24, 2019

CMC Review (QTERN)	Emily Wu	April 18, 2019
Biopharmaceutics Review (QTERN)	Ho-Pi Lin	March 28, 2019
Pharmacology/Toxicology	Jeff Quinn	March 19, 2019
Clinical Pharmacology (QTERNMET XR)	Mohammad Absar	March 27, 2019
Clinical Pharmacology (QTERN)	Mohammad Absar	April 2, 2019
Statistics	Jennifer Clark	March 28, 2019
Clinical	Frank Pucino	April 19, 2019
OSI	Cynthia Kleppinger	March 25, 2019
OPDP	Meera Savani	April 11, 2019
DMPP	Nyedra Booker	April 16, 2019
DMEPA (QTERN)	Stephanie DeGraw	January 25, 2019
DMEPA (QTERNMET XR)	Ariane Conrad	January 23, 2019

2. Background

In addition to the CMC data, the Applicant submitted data from nine studies (see Table 1): D1683C00005 and CV181169 are new pivotal Phase 3 trials intended to support the approval of QTERNMET XR and the expanded indication for QTERN; CV181168 is the pivotal Phase 3 trial (previously submitted and reviewed) that served as the basis of the original approval of QTERN; one new trial intended (CV181365) and one previously submitted and reviewed trial (CV181369) intended to support efficacy and safety; three new trials intended primarily to support safety (CV181363, MB102129, and D168C00014); and a biopharmaceutical study (D168AC00001) to support a conclusion of bioequivalence between two QTERNMET XR dose formulations and equivalent doses of dapagliflozin, saxagliptin, and metformin HCl. In addition to the biopharmaceutical study, the Applicant submitted biowaivers for demonstrating the bioequivalence of additional QTERNMET XR and QTERN dose formulations to monocomponents based on dissolution, compositional similarity, and physiochemical and pharmacokinetic (PK) bridges to dose formulations directly shown bioequivalent to monocomponents (either in D168AC00001 or biopharmaceutical trials previously submitted to NDA 209091). Importantly, D1683C00005 and CV181169 were conducted with the monocomponents rather than the fixed combined drug products (FCDPs). The Applicant proposes that the results of D168AC00001, in conjunction with the biowaivers, provide a bridge between the clinical data generated in the two pivotal Phase 3 trials and the FCDPs.

Table 1: Clinical Trials Submitted to NDA 210874 and sNDA 209091/S-002

Trial Identifier	Trial Design	Regimen/ Schedule/ Route	No. of Subjects Randomized/ Completed
Pivotal Efficacy and Safety Trials			
D1683C00005 (Efficacy and Safety)	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 5 mg + Saxa 5 mg + OL Met ≥1500 mg • Saxa 5 mg + Met ≥1500 mg • Dapa 5 mg + OL Met ≥1500 mg	883/832
CV181169 (Efficacy and Safety)	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter efficacy and safety trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + Saxa 5 mg + OL Met XR ≥1500 mg • Saxa 5 mg + OL Met XR ≥1500 mg • Dapa 10 mg + OL Met XR ≥1500 mg	534/490
Supporting Efficacy and Safety Trials			
CV181168 (Efficacy and Safety)	Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter efficacy and safety trial – Sequential add-on to Met (inadequate control on Dapa + Met)	• Saxa 5 mg + OL Dapa 10 mg + OL Met IR ≥1500 mg • Placebo + OL Dapa 10 mg + OL Met IR ≥1500 mg	ST: 315/298 ST+LT: 297/280
CV181365 (Efficacy and Safety)	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + Saxa 5 mg + OL Met ≥1500 mg • Glim 1-6 mg + OL Met ≥1500 mg	444/385
CV181369 (Efficacy and Safety)	Phase 3, randomized, OL, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + Saxa 5 mg + Met XR ≥1500 mg ± SU • Insulin glargine + OL Met XR ≥1500 mg ± SU	650/584
Supporting Safety Trials			
MB102129 (Efficacy and Safety)	Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter efficacy and safety trial – Sequential add-on to Saxa + Met (inadequate control on Saxa + Met)	• Dapa 10 mg + OL Saxa 5 mg + OL Met IR ≥1500 mg • Placebo + OL Saxa 5 mg + OL Met IR ≥1500 mg	ST: 320/301 ST+LT: 294/281
D1689C00014 (Efficacy and Safety)	Phase 4, randomized, double-blind, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + OL Met IR ≥1500 mg • Dapa 10 mg + Saxa 5 mg + OL Met IR ≥1500 mg • Glim 1-6 mg + OL Met ≥1500 mg	939/867
CV181363 (Efficacy and Safety)	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + Saxa 5 mg + OL Met ≥1500 • Sita 100 mg + OL Met ≥1500 mg	461/411
Biopharmaceutics Study			
D168AC00001 (Pivotal BE Study)	Phase 1, OL, randomized, 2 parallel cohorts, 3-treatment, 3-period, crossover BE study	Cohort 1 • Saxa + (Dapa+Met XR) 2.5/5/1000 mg; Fed • Dapa+Saxa+Met XR 5/2.5/1000 mg; Fed • Daxa+Saxa+Met XR 5/2.5/1000 mg; Fasted Cohort 2 • Saxa + (Dapa+Met XR) 5/10/1000 mg; Fed	84/81

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