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APPLICATION NUMBER:

209483Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H. Chong, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 209091 NDA 022350, Suppl 18 NDA 200678, Suppl 18
Applicant	AstraZeneca
Date of Submission	April 27, 2016
PDUFA Goal Date	February 27, 2017
Proprietary Name / Established (USAN) names	**NDA 209091:** QTERN (dapagliflozin and saxagliptin) **NDA 022350:** ONGLYZA (saxagliptin) **NDA 200678:** KOMBIGLYZE XR (saxagliptin and metformin hydrochloride extended release
Dosage forms / Strength	**NDA 209091:** 10 mg/5 mg (dapagliflozin/saxagliptin) tablets **NDA 022350:** 5 mg and 2.5 mg tablets (saxagliptin) **NDA 200678:** 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg (saxagliptin/metformin HCl extended release) tablets
Proposed Indication(s)	**NDA 20901:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) **NDA 022350:** Not applicable **NDA 200678:** Not applicable
Recommended Indication(s)	**NDA 209091:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who have inadequate glycemic control on dapagliflozin or who are already treated with dapagliflozin and saxagliptin **NDA 022350:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus **NDA 200678:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.
Recommendation:	*Approval*

1. Introduction

AstraZeneca (hereafter referred to as the applicant) submitted a new drug application (NDA) for a fixed combination drug product (FCDP) that combines saxagliptin, a dipeptidyl peptidase4 (DPP4) inhibitor, with dapagliflozin, a sodium glucose cotransporter2 (SGLT2) inhibitor for use in adult patients with type 2 diabetes mellitus (T2DM). The applicant has previously submitted an NDA (b) (4) for this FCDP, but a Complete Response was issued for that application citing a need for more data (b) (4) Rather, the applicant has submitted a new NDA with a different study to support use of this FDCP. This Cross-Discipline Team Leader (CDTL) review will summarize the relevant information from the involved review disciplines and their recommendations. I will discuss the efficacy data and the relevance to the indication as well as safety findings focusing on the additional available data on muscle injury.

2. Background

Type 2 diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia which in turn leads to an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. Based on the results of the Diabetes Control and Complication Trial (DCCT) [1] and the United Kingdom Prospective Diabetes study (UKPDS) [2], improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes.

Many patients with T2DM require multiple antidiabetic drugs to achieve the desired degree of glycemic control, and most patients require intensification of therapy (i.e., addition of antidiabetic drugs) as the duration of disease progresses. There are currently 11 classes of antidiabetic drugs with most classes having multiple members (Table 1). Many of these drug products are also available as FCDPs. The FDA has also approved combinations of basal insulin with a GLP1 receptor agonist.

[1] The Diabetes Control and Complications Trial Research Group. "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus". NEJM, 1993; 329 (14): 977-986.
[2] UK Prospective Study Group. "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)". Lancet, 1998; 352 (9131): 837-853.

Table 1: Summary of FDA approved drugs to improve glycemic control in diabetes

Drug Class	Drug Products
Insulin and insulin analogs	Multiple products including basal, prandial, and mixed insulin products
Biguanides	Metformin (as an immediate release and an extended release formulation)
Sulfonylureas	Chlorpropamide, Glimepiride, Glipizide, Glyburide
Thiazolidinediones	Rosiglitazone, Pioglitazone
Meglitinides	Repaglinide, Nateglinide
Alpha glucosidase inhibitors	Acarbose, Miglitol
Dipeptidyl peptidase4 (DPP4) inhibitors	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin
Glucagonlike peptide1 (GLP1) receptor agonists	Exenatide (as a twice daily and as a once weekly), Liraglutide, Albiglutide, Dulaglutide, Lixisenatide
Sodium glucose cotransporter2 (SGLT2) inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin
Amylin analogs	Pramlintide
Bile acid sequestrants	Colesevelam
Dopamine agonists	Bromocriptine
Basal insulin and GLP1 receptor agonist combinations	Insulin glargine and lixisenatide, insulin degludec and liraglutide

The applicant is now proposing to market an FCDP that combines saxagliptin (a DPP4 inhibitor) with dapagliflozin (an SGLT2 inhibitor). The DPP4 inhibitors prolong the circulation of endogenous incretin hormones by preventing DPP4 mediated degradation. This in turn is believed to increase insulin secretion in response to a glucose load and decrease glucagon secretion. The SGLT2 inhibitors block glucose reabsorption in the kidney, thus resulting in an insulin independent reduction in plasma glucose levels. The applicant believes that this FCDP offers patients with T2DM a way to combine two drugs which improve glycemic control through different mechanisms of action in a manner that will be convenient and that may improve compliance.

An NDA for this FCDP was previously submitted (NDA (b) (4)), but a Complete Response was issued for that NDA (b) (4) (see Complete Response Letter issued on October 15, 2015 under NDA (b) (4)). Following receipt of the Complete Response Letter, an End of Review meeting was held on December 17, 2015 to discuss potential paths forward for the FCDP. Options included (b) (4) or submitting a new NDA with data from a study of adding saxagliptin to patients with inadequate glycemic control on dapagliflozin (see Meeting Minutes issued on January 14, 2016). The applicant has opted to do the latter (b) (4)

3. CMC/Device

There is no new Chemistry, Manufacturing, and Controls (CMC) data for NDA 022350 or NDA 200678. For the CMC information of these two drug products, see the currently approved prescribing information. This section will discuss data relevant to NDA 209091.

The Chemistry, Manufacturing, and Controls (CMC) review of the FCDP was previously completed during review of NDA (b) (4) The drug substance and drug product review was completed by John Amartey, the manufacturing process and microbiology review was completed by Daniel Peng, the manufacturing facilities review was completed by Vipul Dholakia, and the biopharmaceutics review was completed by Peng Duan.

The reviewers from the Office of Product Quality recommended Approval of the NDA during review of NDA (b) (4) In the current submission, the applicant has made only minor changes to the CMC information. (b) (4) These changes have been reviewed by the CMC reviewers and were found to be acceptable. The Office of Product Quality recommends Approval for NDA 209091.

For detailed discussion of the CMC findings, see the completed Quality Review from NDA (b) (4) and the Dr. Amartey's Memorandum for NDA 209091. A brief summary of the CMC data is included below.

The saxagliptin and dapagliflozin FCDP is manufactured as a film coated tablet (b) (4) (see Figure 1).

Figure 1: Saxagliptin and dapagliflozin tablet

(b) (4)

Source: Excerpted from page 11 of the Quality Review for NDA (b) (4)

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