CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209091Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	*Stamp Date*
From	Jean-Marc Guettier, MDCM
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 209091 NDA 022350/Supplement 18 NDA 200678/Supplement 18
Applicant Name	AstraZeneca Pharmaceuticals LP
Date of Submission	April 27, 2016
PDUFA Goal Date	February 27, 2017
Proprietary Name / Established (USAN) Name	QTERN (dapagliflozin and saxagliptin)
Dosage Forms / Strength	Tablets, for oral use / 10 mg dapagliflozin and 5 mg saxagliptin
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (b) (4)
Approved Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin
Action/Recommended Action for NME:	*Approval*

1. Introduction

Astra Zeneca Inc., submitted a new drug application pursuant to Section 505(b)(1) of the Food Drug and Cosmetic Act for QTERN. QTERN is a fixed combination drug product combining two approved oral antidiabetic drugs used for the treatment of adults with type 2 diabetes mellitus; Dapagliflozin approved on 08 January 2014 (NDA# 202293) and Saxagliptin approved on 31 July 2009 (NDA# 22350).

The proposed adult indication is; *"as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)* (b) (4) ".

Reference ID: 4062120

2. Background

Drs. Chong and Pucino have summarized the regulatory background for the application. See these reviews for full details. QTERN has been previously reviewed under NDA (b) (4) The application received a complete response letter on 15 October 2015 (b) (4)

An end of review meeting was held on 17 December 2015 to review deficiencies listed in the complete response letter and discuss possible paths forward. The Division agreed that new data from an ongoing pivotal study (CV181168) along with supportive data could be used establish the safety and effectiveness of a dapagliflozin 10 mg/saxagliptin 5 mg strength (b) (4)

3. CMC/Device

No CMC deficiencies to preclude approval were identified. CMC data were previously reviewed. For a detailed discussion of CMC findings refer to primary reviews by Drs. Amartey, Peng, Duan and Dholakia filed for NDA (b) (4) Refer to Dr. Chong's memorandum for a summary of the issues.

4. Nonclinical Pharmacology/Toxicology

Refer to reviews by Drs. Alavi and Quinn. No nonclinical pharmacology/toxicology deficiencies to preclude approval were identified.

5. Clinical Pharmacology/Biopharmaceutics

No nonclinical pharmacology/toxicology deficiencies to preclude approval were identified. The clinical pharmacology/biopharmaceutics data were reviewed by Drs. Lau and Deng and summarized in Dr. Chong's memorandum, see these reviews for details.

6. Clinical/Statistical-Efficacy

Efficacy was reviewed by Drs. Kettermann and Pucino and summarized in Dr. Chong's CDTL memorandum. A single trial is used to inform the new indication (study CV181168). Two other studies provide information on dapagliflozin/saxaglitpin combination use when the maximum strength of each component is used (studies MB102129 and CV181169 (b) (4)

Reference ID: 4062120

(b) (4) the studies provide supportive efficacy and safety data.

Study CV181168 was a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, multi-national study. In the trial, 315 adult subjects with type 2 diabetes, inadequately controlled (HbA1c > 7%) on maximally effective doses of metformin (>1500 mg per day) and dapagliflozin (i.e., 10 mg per day) were randomized 1:1 to 5 mg of saxagliptin (N=153) or placebo (N=162). The primary objective of the trial was to compare the change in HbA1c from baseline to Week 24 between subjects randomized to saxagliptin and subjects randomized to placebo. Dr. Kettermann noted that 6.5% (n=10) of subjects randomized to saxagliptin and 3.1% (n=5) randomized to placebo arm did not have HbA1c data at week 24.

At the end of 24 weeks, subjects randomized to saxagliptin were observed to have greater reduction in HbA1c compared to patients randomized to placebo. Drs. Chong and Kettermann reviewed the validity of the clinical and statistical assumptions made in the analytical methods used by the applicant to handle missing 24 week data. The conclusion of superiority was not sensitive to varying the assumptions made in the handling missing HbA1c data. Secondary analyses examining HbA1c responders and other glucose lowering endpoints (e.g., fasting plasma glucose) were directionally consistent with mean HbA1c results (i.e., greater improvement in subjects randomized to saxagliptin). Examination of HbA1c effects based on subgroups defined by age, sex, race and geographical regions were qualitatively similar. The result of the primary analysis based on Dr. Kettermann' s multiple imputation model using all available 24 week HbA1c data is shown below.

Table 1: Change in HbA1c from Baseline to Week 24 observed in Study CV181168

Trial/ Treatment Group	**Number of subjects**	**Baseline HbA1c Mean (SD)**	**Mean (SD) Change from Baseline**	**Adjusted[1] Mean Difference**	**95% CI**	**P-value**
Placebo	162	7.9 (0.9)	-0.5 (0.8)	---	---	---
Saxagliptin	153	8.0 (0.8)	-0.2 (0.8)	-0.4	(-0.5, -0.2)	<0.0001

7. Safety

The safety findings for combination use have been previously reviewed under NDA 202293. Dr. Pucino has reviewed the safety data in this submission in detail and Dr. Chong has summarized the salient safety findings. In the previous NDA, a potential signal for muscle related injury with combination use was identified from the examination of creatine kinase outlier data. In the Complete Response Letter, the applicant was asked to provide updated

[1] Analysis of Covariance model with treatment and baseline HbA1c as covariates and all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputations to model washout of the treatment effect using placebo data for all subjects having missing week 24 data.

Reference ID: 4062120

clinical trial data (b) (4)

Safety information on an additional ~ 100 patient-year of exposure is available from the updated dapagliflozin/saxagliptin combination use pooled clinical trial dataset. No additional cases of elevated creatine kinase were identified with the additional exposure. Dr. Pucino provides narrative and graphical summaries for the previously reviewed cases of rhabdomyolysis and markedly elevated CK in the integrated clinical trial dataset (refer to Appendix 13.7 of his review). The majority of cases were confounded by the presence of acute co-morbid conditions around the time of the event, antecedent CK abnormalities, and concomitant medications (i.e., statins). Cases resolved despite continued use of dapagliflozin and saxagliptin and otherwise lacked a clear temporal association with combination treatment onset. These data do not support the existence of a clear causal relationship between combination use and muscle injury. Dr. Pucino also compared occurrence of incident musculoskeletal adverse events across the pooled safety dataset informing combination use. This analysis was unrevealing. Finally, a search of FDA's adverse Event Reporting System database for events of rhabdomyolysis associated with saxagliptin and dapagliflozin use was conducted. Eleven cases were identified but were often insufficiently detailed to fully evaluate the event or the presence of an association with one or more drug (refer to Appendix 13.8 in Dr. Pucino's review for details). The data and re-analysis do not neither support the presence of a strong association between muscle related injury and combination treatment nor completely exclude it. The review team recommends labeling the observed CK imbalance in Section 6 of the full prescribing information. I concur with this plan.

8. Advisory Committee Meeting

No efficacy or safety issues requiring the input from an advisory panel was needed for this application. Therefore no advisory committee was convened.

9. Pediatrics

Refer to Dr. Chong's memorandum for details.

10. Other Relevant Regulatory Issues

No other relevant regulatory issues were identified.

11. Labeling

Dr. Chong has summarized labeling discussions. The data in the application support the following indication; *"As an adjunct to diet and exercise to improve glycemic control in adults*

Reference ID: 4062120

with type 2 diabetes mellitus (T2DM) who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin"

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend approval.

- Risk Benefit Assessment

I agree with all review disciplines and Dr. William Chong, cross-discipline team leader for the application, who recommends approval. The applicant has shown that adding saxagliptin to dapagliflozin and metformin improves glucose control at Week 24 in adult subjects with type 2 diabetes inadequately controlled on these agents at baseline. Inadequate glycemic control over years results in microvascular complications in some patients which can lead to loss of vision and loss of nerve and kidney function. Landmark trials in type 1 and type 2 diabetes have shown that reduction in ambient glucose levels over years reduces the risk of microvascular disease complications. In the current regulatory paradigm, HbA1c reduction over six months is accepted as a substitute for reduction in microvascular disease risk.

In the safety evaluation for this application, adverse drug related risks associated with combination use were found to be additive and not synergistic and were expected based on the known side effect profiles of individual components. In the study, the risks of adding saxagliptin to a regimen of metformin and dapagliflozin in patients whose glucose was not adequately controlled were not found to outweigh the benefits attributed to glucose lowering. Risks that were identified can be monitored, are reversible with drug discontinuation and can be adequately mitigated through labeling.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None are recommended at this time.

- Recommendation for other Postmarketing Requirements and Commitments

None are recommended at this time.

Reference ID: 4062120

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
02/27/2017