

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209091Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 24, 2017

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 209091

Product Name and Strength: Qtern (dapagliflozin and saxagliptin), tablets 5 mg/10 mg

Submission Date: February 24, 2017

Applicant/Sponsor Name: AstraZeneca

OSE RCM #: 2016-1009-4

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised commercial container label, professional sample carton labeling, and professional sample blister cards for Qtern (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

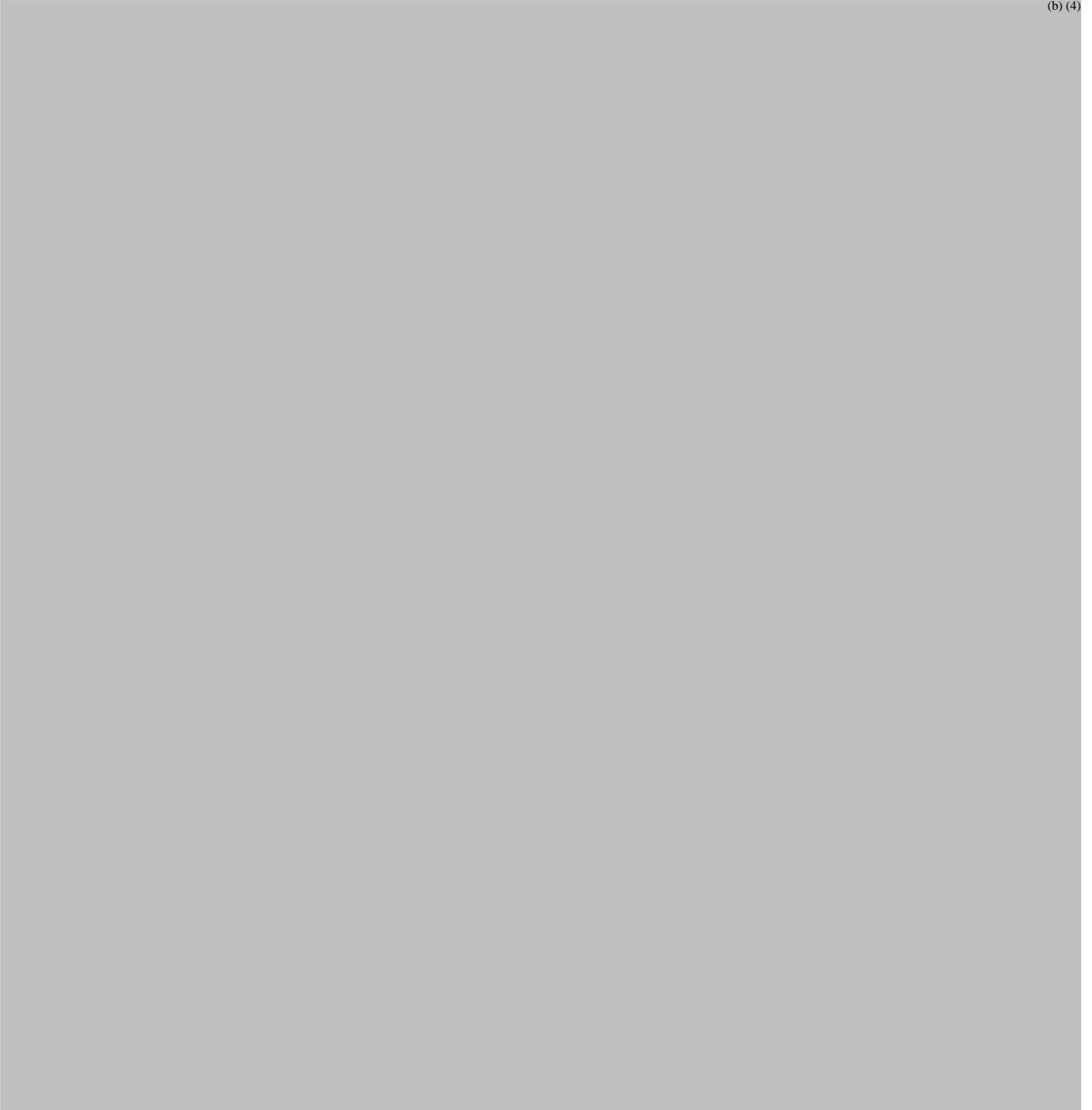
The revised commercial container labels, professional sample carton labeling, and professional sample blister cards for Qtern are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Conrad A. Label and Labeling Review Memo for Qtern (NDA 209091). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Feb 21. 4p. OSE RCM No.: 2016-1009-3.

APPENDIX A. LABEL AND LABELING SUBMITTED ON FEBRUARY 24, 2017

Commercial Container Labels

(b) (4)



Professional Sample Blister Cards

(b) (4)



Professional Sample Carton Labeling

(b) (4)



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/s/

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02/24/2017

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PLLR Labeling Review

Date: February 16, 2017 **Date consulted:** May 2, 2016

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health,
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health,
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: QTERN [dapagliflozin /saxagliptin/ fixed dose combination (FDC) tablet]
for oral use

Class: Sodium glucose cotransporter 2 (SGLT 2) inhibitor/ Dipeptidyl peptidase
4 (DPP 4) inhibitor, respectively, combination product

NDA: 209091

Applicant: AstraZeneca Pharmaceuticals LP (AZ)

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication(s) Qtern is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) [REDACTED] (b) (4)
[REDACTED]

Materials Reviewed:

- August 4, 2016, Labeling Review of Glyxambi (empagliflozin and linagliptin) tablets by Miriam Dinatale, D.O., Medical Officer, which belongs to the same class as Qtern.
- June 2, 2016, applicant's response to IR
- May 17, 2016 Division's Information Request (IR) for a summary of all available published literature and pharmacovigilance database to support the PLLR format of the labeling,
- May 2, 2016, DMEP's request to DPMH-MHT for labeling review
- April 27, 2016 Applicant's submission for New NDA 209091 including labeling in PLLR format
- January 8, 2014, Summary Review for regulatory Action by Jean-Marc Guettier, M.D.C.M., Division Director, DMEP for Farxiga (dapagliflozin)

Consult Question: Assist with Pregnancy and Lactation Labeling

INTRODUCTION

On April 27, 2016, the applicant, AstraZeneca Pharmaceuticals LP (AZ), submitted a New NDA 209091 for Qtern [dapagliflozin 10 mg/ saxagliptin 5 mg fixed dose combination (FDC) tablet] for oral use, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) [REDACTED] (b) (4)

The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on May 2, 2016, to provide input for appropriate labeling of the pregnancy and lactation sections of Qtern labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND**Regulatory History**

Dapagliflozin (Farxiga) NDA 202293, owned by AZ, is a SGLT2 inhibitor approved for the treatment of T2DM on January 8, 2014. Saxagliptin (Onglyza) NDA 022350, also owned by AZ, is a dipeptidyl peptidase 4 (DPP 4) inhibitor and was approved on July 31, 2009.

On October 15, 2015, AZ had submitted NDA [REDACTED] (b) (4) which received a complete response (CR) because [REDACTED] (b) (4)

On April 27, 2016, the applicant, AZ, submitted a New NDA 209091 including labeling in PLLR format for Qtern [dapagliflozin/ saxagliptin fixed dose combination (FDC) tablet] for oral use.

The current submission does not address the deficiencies outlined in the CR letter; therefore, the applicant in agreement with the Division was required to submit a new NDA 209091. (b) (4)

During the clinical trials, the primary safety assessment of the combined use of dapagliflozin and saxagliptin in adults with T2DM was based on pooled data from 3 Phase 3, randomized, double-blind, active/placebo-controlled, parallel group, multicenter clinical studies.

- Study CV181168: This Phase 3 clinical study compared the addition of saxagliptin 5 mg versus placebo when administered sequentially to metformin \geq 1500 mg and dapagliflozin 10 mg in adults with T2DM who had inadequate glycemic control on metformin plus dapagliflozin therapy. It was a 24-week, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study.
- Study MB102129: This Phase 3 clinical study compared the addition of dapagliflozin 10 mg versus placebo when administered sequentially to metformin \geq 1500 mg and saxagliptin 5 mg in adults with T2DM who had inadequate glycemic control on metformin plus saxagliptin therapy. It was a 24-week, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study.
- Study CV181169: This Phase 3 clinical study compared the addition of saxagliptin 5 mg plus dapagliflozin 10 mg versus placebo plus saxagliptin 5 mg and versus placebo plus dapagliflozin 10 mg when administered concomitantly with metformin \geq 1500 mg in adults with T2DM who had inadequate glycemic control on a stable dose of metformin monotherapy. It was a 24-week, 3-arm, randomized, double-blind, active-controlled, parallel-group study

Three pregnancies were reported during the CV181169 study. No cases of pregnancy were reported in Studies CV181168 and MB102129.

During the observational study MB102242 for dapagliflozin, a case series analysis of foreign and domestic spontaneously reported events of pregnancy outcomes from January 8, 2015 through January 7, 2016, 5 pregnancies were reported, one premature delivery, one congenital anomaly and 3 unknown outcomes.

Drug's Characteristics

Dapagliflozin (Farxiga)

SGLT2 inhibitors reduce hyperglycemia by targeting the kidney to promote urinary glucose excretion. Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. SGLT2 is expressed in the proximal renal tubules, and it is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin has a molecular weight of 502.98 Daltons. The mean

plasma terminal half-life ($t_{1/2}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of Farxiga 10 mg.

Saxagliptin (Onglyza)

DPP4 inhibitor class of antihyperglycemic agents targets the incretin defect in T2DM by improving the β -cell sensitivity to glucose, increasing insulin secretion, and decreasing glucagon secretion. The DPP4 inhibitors are associated with a low intrinsic risk of hypoglycemia and are neutral on patient's weight. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus. It has a molecular weight of 333.43 Daltons. Following a single oral dose of Onglyza 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Background on Current Treatments

In 2015, the American Diabetes Association (ADA)¹ and the European Association for the Study of Diabetes (EASD) issued an update to their joint position statement including SGLT2 inhibitors use among the options for second-line therapy after metformin.² Balancing the benefits of glycemic control with its potential risks, taking into account the adverse effects of glucose-lowering medications (particularly hypoglycemia) is a cornerstone of diabetes treatment. Initial combination therapy with metformin plus a second agent may allow patients to achieve HbA1c targets more quickly than sequential therapy. While the SGLT2 inhibitors are approved as monotherapy, they are mainly used in combination with metformin and/or other agents.³ When compared with most standard oral agents, they appear to be as efficacious with regard to initial HbA1c lowering.^{4,5}

Similar to most combinations, efficacy may be less than additive when SGLT2 inhibitors are used in combination with DPP-4 inhibitors.⁶ DPP4 inhibitors are associated with a low intrinsic risk of hypoglycemia.

There are no data available on the use of SGLT2 inhibitors in conjunction with GLP-1 receptor agonists.

¹ Diabetes Care. Standards of Medical Care in Diabetes—2015, Position Statement. The J of Clinical and Applied Research and Education. Jan 2015;38(S1)1-93

² Inzucchi SE, Bergenstal RM, Buse JB, et al: Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015 Jan; 38(1): 140-149.

³ Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014;16:457-466

⁴ Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941-950

⁵ Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 2011;34:2015-2022

⁶ Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. Diabetes Obes Metab 2011;13:1088-1096

As noted in the original position statement by ADA and EASD in 2012⁷, initial combination therapy with metformin plus a second agent may allow patients to achieve HbA1c targets more quickly than sequential therapy. SGLT2 and DPP4 are complementary to each other in reducing hyperglycemia.

Disease Background

Diabetes Mellitus and Pregnancy

Adverse outcomes of diabetes during pregnancy relate to the onset of diabetes, its duration, and the degree of vasculopathy. Women with pregnancies complicated by diabetes mellitus may be separated into one of two groups:

- Gestational diabetes (GDM): women with carbohydrate intolerance of variable severity, with onset or first recognition during the present pregnancy. This means that the glucose intolerance may have antedated the pregnancy but was not recognized by the patient or the physician.
- Pregestational diabetes (PGD): women known to have diabetes before pregnancy.

Ninety percent of all pregnant diabetic women have gestational diabetes mellitus (GDM), whereas type 1 (insulin-dependent diabetes) and type 2 (non-insulin dependent diabetes) account for the remaining 10%.⁸

Gestational Diabetes

The incidence of GDM varies in different study populations and is estimated to occur in 3–5% of all pregnant women in the United States. The likelihood of developing GDM is significantly increased among certain subgroups, and these include women with a family history of type 2 diabetes, advancing maternal age, obesity, and nonwhite ethnicity. Infants born to women diagnosed with GDM do not have an increased risk of congenital anomalies when compared to infants born to women without GDM. GDM usually is diagnosed later in pregnancy when the risk of MCM has passed. PGD that is well under control is not associated with an increased risk either, however, infants of women with poorly controlled PGD have an increased risk of MCM.

Pregestational Diabetes

Poorly controlled PGD during pregnancy increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, polyhydramnios, stillbirth and cesarean section due to fetal macrosomia. In addition, poorly controlled DM during pregnancy increases the risk for fetal malformations, including neural tube defects (anencephaly, open spina bifida, and holoprosencephaly), cardiovascular anomalies (ventricular septal defects and transposition of the great vessels), oral clefts, genitourinary abnormalities (absent kidneys, polycystic kidney, and double ureter), and sacral agenesis or caudal regression. Fetal complications include pyelonephritis, hypertensive disorders and macrosomia-related injuries (brachial plexus injury, hypoxia). Also directly related to metabolic control are fetal hyperglycemia and neonatal hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia.

⁷ ADA-EASD Position Statement: Management of Hyperglycemia in T2DM: A Patient-Centered Approach. Diabetes Care, Diabetologia. April 19, 2012

⁸ Reece, EA, Hobbins, JC: Clinical Obstetrics, Third Edition, Chapter 38: Diabetes Mellitus in Pregnancy, pp: 292-305, Jan 14, 2008

Infants of diabetic mothers in unsatisfactory glycemic control often develop hypoglycemia during the first few hours of life. The reported incidence ranges from 25% to 40% of infants of diabetic mothers. Poor glycemic control during pregnancy and high maternal plasma glucose levels at the time of delivery increase the risk of hypoglycemia in the infant. Clinical studies suggest that euglycemia during organogenesis in pregestational pregnant diabetics is critical in the prevention of congenital anomalies.³ Achieving and maintaining maternal euglycemia prior to conception and throughout pregnancy decreases the risk of adverse outcomes for both the mother and the infant.^{9,10,11}

Poorly controlled pre-gestational Diabetes Mellitus (PGD) (before conception) and in the first trimester is associated with Major Congenital Malformation (MCM) (5-10%) and spontaneous abortion (15-20%).¹² The higher the fasting serum glucose level is at diagnosis, the higher the incidence of MCM.¹³

The Micromedex database states that pregestational diabetes mellitus in pregnant women with poor control during organogenesis is associated with a 3-fold increase in congenital anomalies that include cardiac malformations, lumbosacral agenesis, hyperbilirubinemia, polycythemia, and renal vein thrombosis. Offspring of mothers with poorly controlled PGD during pregnancy have a mortality rate that is 5 times greater than that of non-diabetic mothers; the mortality rate is higher at all gestational ages.¹⁴

The American College of Obstetricians and Gynecologists (ACOG) in a statement issued in 2005 and reaffirmed in 2012 for PGD, states that HbA1c of 5-6% is associated with a fetal malformation rate close to what is seen in normal pregnancies. An HbA1c near 10% is associated with a fetal malformation rate of 20-25%.¹⁵ Major malformations include: Hydrocephalus, meningomyelocele (lumbar), anencephaly, cleft palate, atresia of pulmonary valve, caudal regression syndrome, agenesis of a kidney, supernumerary toe, anomalous lumbar spine, aplasia of left diaphragm with hypoplasia of left lung, and omphalocele.¹⁶

PLLR

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect.¹⁷ The PLLR requirements

⁹ Mills JL. Malformations in infants of diabetic mothers. *Teratology*.1982;25:385-94

¹⁰ Persson, M. and Fadi, H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes- a population-based study. *Diabetes Med*. 2014; 31(9): 1047-54.

¹¹ www.cdc.gov. Problems of Diabetes in Pregnancy. Accessed 12/30/2015.

¹² Ornoy, et al. Effect of Maternal Diabetes on the Embryo, Fetus, and Children: Congenital Anomalies, Genetic and Epigenetic Changes and Developmental Outcomes. *Birth Defects Research, Part C: Embryo Today: Reviews*. 2015; 105(1): 53-72.

¹³ Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am J Obstet Gynecol*. 1997;177:1165–1171.

¹⁴ The Behrman RE, Kleigman RM, Nelson WE, et al: *Nelson Textbook of Pediatrics*, 14th. WB Saunders Company, Philadelphia, PA, 1992.

¹⁵ ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. 2005; 60:675-685.

¹⁶ Ylinen K, Aula P, Stenman UH, et. al. Risk of minor and major fetal malformations in diabetics with high haemoglobin A1c values in early pregnancy. *British Med. J*.1984;289:345-6

include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

Current Labeling

The current labeling for Onglyza (saxagliptin) states¹⁸:

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD.

Co-administration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the MRHD (saxagliptin 5 mg and metformin 2000 mg), respectively, in rats; and 249 and 1.1 times the MRHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of wavy ribs; associated maternal toxicity was limited to weight decrements of 11% to 17% over the course of the study, and related reductions in maternal food consumption. In rabbits, co-administration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures \geq 1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

¹⁷ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

¹⁸ Onglyza labeling, updated January 18, 2017

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

The current labeling for Farxiga (dapagliflozin) states¹⁹:

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Farxiga in pregnant women. Based on results of reproductive and developmental toxicity studies in animals, dapagliflozin may affect renal development and maturation. In a juvenile rat study, increased incidence and/or severity of renal pelvic and tubular dilatations were evident at the lowest tested dose which was approximately 15 times clinical exposure from a 10 mg dose.

These outcomes occurred with drug exposures during periods of animal development that correlate with the late second and third trimesters of human pregnancy. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. Farxiga should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and renal pelvic and tubular dilatations were reported at all levels. Exposure at the lowest tested dose was 15 times the maximum clinical dose, based on AUC. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a prenatal and postnatal development study, maternal rats were dosed from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed in utero and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415 times and 137 times, respectively, the human values at the clinical dose). Dose-related reductions in pup body weights were observed at doses ≥ 1 mg/kg/day (approximately ≥ 19 times the clinical dose). No adverse effects on developmental endpoints were noted at 1 mg/kg/day, or approximately 19 times the clinical dose.

In embryo-fetal development studies in rats and rabbits, dapagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested. In rats, dapagliflozin was neither embryo-lethal nor teratogenic at doses up to 75 mg/kg/day or 1441 times the maximum clinical dose of 10 mg. At higher doses in rats, malformations of blood vessels, ribs, vertebra, manubria, and skeletal variations in fetuses at ≥ 150 mg/kg or 2344 times the 10 mg clinical dose were observed.

PREGNANCY

Animal Data

¹⁹ Farxiga labeling, updated August 12, 2016

The applicant states that no new animal data for the use of mono-components dapagliflozin and saxagliptin are available. No animal studies were performed with the combined use of dapagliflozin and saxagliptin. In animal studies, adverse renal pelvic and tubular dilatations, that were not fully reversible, were observed in juvenile rats when dapagliflozin (a component of Qtern) was administered at an exposure 15-times the exposure at the 10 mg clinical dose, during a period of renal development and corresponding to the late second and third trimesters of human pregnancy. No adverse developmental effects were observed when saxagliptin was administered to pregnant rats and rabbits.

For nonclinical experience of the mono-components dapagliflozin and saxagliptin, the reader is referred to the corresponding updated labelings.

Summary

The nonclinical data on dapagliflozin /saxagliptin (Qtern) have been previously reviewed and remain unchanged. Based on animal reproduction studies, there may be risks to the fetus from exposure to dapagliflozin during pregnancy.

Review of Literature

Applicant's Review

Onglyza

A literature search of Embase, Medline and (b) (4) database up to September 16, 2015, was performed by the applicant. The following search parameters were used “(saxagliptin or KOMBIGLYZE XR)” and (pregnancy* OR lactation* OR “breast milk”). The following criteria were used for the (b) (4) search: (SAXAGLIPTIN OR "BMS 477118" OR "BMS 512148" OR "BMS477118" OR "BMS-477118" OR "Onglyza") AND (PREGNANT OR "maternal" OR "pregnancy" OR LACTATE OR LACTATION OR "breast feeding" OR LACTATING OR "BREAST MILK" OR "BREAST FEEDING"). No new and/or relevant studies of saxagliptin exposure and pregnancy were found upon review of the literature. No adequate and well-controlled studies of saxagliptin in pregnant women have been conducted. Overall, this search did not reveal any relevant literature articles regarding potential use of saxagliptin in pregnancy.

Farxiga

Similarly, a literature search of Embase, Medline and (b) (4) database up to May 19, 2016, was performed with search parameters: “(dapagliflozin or 'bms 512148' or Edistride or FARXIGA or FORXIGA)” and (pregnancy* OR lactation* OR 'breast milk'). The following criteria was used for the (b) (4) search: (dapagliflozin or "bms 512148" or "Farxiga" or "Forxiga") AND (“pregnant” OR "maternal" OR "pregnancy" OR “lactate” OR “lactation” OR "breast feeding" OR lactating OR "breast milk" OR "breast feeding”). No new and/or relevant studies of dapagliflozin exposure and pregnancy were found upon review of the literature. No adequate and well-controlled trials of dapagliflozin in pregnant women have been conducted. This search did not reveal any relevant literature articles regarding potential use of dapagliflozin in pregnancy and lactation.

DPMH Review

In addition to the search of published literature performed by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases²⁰ for

dapagliflozin/saxagliptin and use in pregnancy. No publications were identified discussing use of dapagliflozin/saxagliptin in pregnancy or lactation.

Experience with other drugs in the class include Glyxambi (empagliflozin and linagliptin) tablets FDC of a SGLT2 and a DPP4 inhibitor approved on January 30, 2015. As per Dr. M. Dinatale review of August 4, 2016, there was no relevant information that discussed the use of linagliptin or empagliflozin or the combination of the two in the literature in pregnancy. Empagliflozin, a SGLT2 inhibitor, use during pregnancy raises concerns for the developing kidney in the fetus based on juvenile animal studies similar to dapagliflozin.

Review of Pharmacovigilance

The applicant's Global Patient Safety database (SAPPHIRE) search included any report of pregnancy using dapagliflozin/ saxagliptin FDC, or combined use of the mono-components dapagliflozin and saxagliptin through May 18, 2016.

Dapagliflozin

From the clinical trials, a 39-year-old White female randomized to the dapagliflozin + metformin group, received study medication from [REDACTED] (b) (6) until the positive pregnancy test on [REDACTED] (b) (6). The baby was born on [REDACTED] (b) (6). The infant was seen by a cardiac specialist in [REDACTED] (b) (6) for a congenital cardiac anomaly. The birth defect was deemed not related to study treatment.

A cumulative review of the Global Patient Safety database (SAPPHIRE) through May 20, 2016 of all reports for Farxiga (dapagliflozin) associated with pregnancy yielded 24 reports. See Table 1 below.

²⁰ TERIS and ReproTox databases, Truven Health Analytics, Micromedex Solutions, 2016.

Table 1: Cumulative Pregnancy Outcomes Reported for Farxiga maternal use

| Pregnancy Outcome | # of Events | Exposure time | Infant Outcome |
|---|--------------------|--|--|
| Premature delivery | 1 | For 5 weeks in 1 st trimester | Healthy baby |
| Baby with serious diabetic fetopathy, hypoglycemia and hyperbilirubinemia. | 1 | For 4 weeks in 1 st trimester | At 9 months child reported no problems |
| Male baby born with birth defect of right aortic arch (congenital aortic anomaly) | 1 | For 46 days prior and 18 days after conception (1 st trimester) | Baby in good health |
| Fetal encephalocele | 1 | Up to diagnosis of pregnancy | Infant died |
| Severe congenital hydrocephalus | 1 | Unknown/Dapagliflozin was discontinued | Unknown |
| Miscarriage | 1 | For 2 weeks in 1 st trimester | |
| Elective abortion | 1 | For 107 days (pregnancy date confirmation not reported) | No anomaly |
| Ectopic pregnancies | 1 1 | Unknown For 173 days, of which 44 days after last menstrual period | |
| Not reported | 3 | Unknown | |
| Unknown AEs or outcomes | 9 | Unknown | |
| Normal deliveries | 3 | Unknown | Normal infants |

Applicant's response to IR, June 2, 2016

Saxagliptin

From the clinical trials, a 36-year-old female partner of a 36-year-old White male randomized to the saxagliptin + metformin group, had a positive pregnancy test on (b) (6) (paternal drug exposure). She had a miscarriage/spontaneous abortion on (b) (6)

Dapagliflozin /Saxagliptin FDC

Qtern (dapagliflozin /saxagliptin FDC) is not currently marketed anywhere in the world. No reports of pregnancy associated with use of Qtern (dapagliflozin /saxagliptin FDC) were identified. However, 1 pregnancy report was identified with the combined use of the mono-components dapagliflozin and saxagliptin in the integrated phase 3 trial evaluating the safety and efficacy of the combined use of saxagliptin 5 mg and dapagliflozin 10 mg in the first trimester. When the pregnancy was identified, the subject discontinued from the study and declined follow-up. The subject, a 41-year-old White female, randomized to the saxagliptin + dapagliflozin + metformin group, received study medication on (b) (6). The subject reported the pregnancy on (b) (6) and discontinued from the study on (b) (6). She withdrew consent and declined follow-up. The site contacted the subject on (b) (6), after the expected due date of (b) (6), and the subject declined follow-up.

Conclusion

The reported cases do not identify a trend. The current safety information does not warrant changes in the existing safety profile of Farxiga or Qtern. The single case reported in the applicant's pharmacovigilance database on saxagliptin is not sufficient to inform a risk of miscarriage.

Summary

Overall, there are limited reports from exposure to the FDC during the clinical trials use during pregnancy to inform on any potential risk of major malformation or miscarriage. Given the limited human data regarding FDC and dapagliflozin (no data on saxagliptin) and use during pregnancy and the concerns to the developing kidney in the fetus based on juvenile animal studies, DPMH recommends maintaining current pregnancy recommendations and restructuring labeling to the PLLR format.

LACTATION

Animal Data

Dapagliflozin and saxagliptin are present in the milk of lactating rats. Dapagliflozin was present at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.¹⁴ Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations.¹³

Review of Literature

No publications were identified by either the applicant or by this reviewer upon search of the literature for lactation or breastfeeding in patients treated with saxagliptin and dapagliflozin. There are no reports in Medication's and Mother's Milk by Thomas Hale or LactMed. Lactation studies have not been conducted to assess the presence of saxagliptin and dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production.

Review of Pharmacovigilance

There are no reports of lactation/breastfeeding in the applicant's pharmacovigilance database. No information regarding potential adverse effects of saxagliptin and dapagliflozin on the infants/neonates was provided.

Summary

Dapagliflozin and saxagliptin are present in rat milk. Dapagliflozin and saxagliptin characteristics (low molecular weight <500 Daltons, and long half-life up to 13 hours) may increase the likelihood that the drug is transferred into breast milk. However, physicochemical characteristics alone are not sufficient to determine the transfer of a drug into breastmilk.²¹ Because of the potential risk to the newborn's kidneys from dapagliflozin, DPMH recommends not to breastfeed.

²¹ Labeling Review of Glyxambi (empagliflozin and linagliptin) tablets by Miriam Dinatale, D.O., August 4, 2016

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Animal data

No animal studies have been conducted with the combined products in Qtern to evaluate impairment of fertility. The following data are based on findings in studies with dapagliflozin and saxagliptin individually.

Saxagliptin

Saxagliptin had no effect on the ability of rats to mate and sire or maintain a litter up to exposures at 603-times and 776-times the 5 mg clinical dose (based on AUC) in males and females, respectively. Higher doses elicited maternal toxicity and increased fetal resorptions (approximately 2069- and 6138-times the MRHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at approximately 6138-times the MRHD.

Dapagliflozin

Dapagliflozin had no effect on the ability of rats to mate and sire, maintain a litter or early embryonic development at exposure multiples less than or equal to 1707- and 998-times the maximum recommended human dose of 10 mg/day (based on AUC) in males and females, respectively.

Review of Literature

There are no reports of Qtern or its components for effects on the fertility of females and males of reproductive potential neither in the published literature (identified by either the applicant or this reviewer) nor in the applicant's pharmacovigilance database.

Summary

There is no human or animal information regarding infertility in females and males of reproductive potential. As discussed above in pregnancy, in animal studies, adverse renal pelvic and tubular dilatations, that were not fully reversible, were observed in juvenile rats when dapagliflozin (a component of Qtern) was administered during a period of renal development and corresponding to the late second and third trimesters of human pregnancy. The potential for fetal harm from use of dapagliflozin is mainly during the second and third trimesters; therefore, contraception and pregnancy testing are not recommended. Section 8.3, Females and Males of Reproductive Potential will be omitted from labeling because there is nothing to be reported.

CONCLUSIONS

Qtern (dapagliflozin and saxagliptin) labeling has been updated to comply with the PLLR. The limited reports from the pharmacovigilance database on saxagliptin and dapagliflozin use are not sufficient to inform of any new drug-associated risk of adverse pregnancy and lactation related outcomes. No new safety information about any major congenital malformations or pregnancy related complications was identified during the current review.

The Pregnancy and Lactation sections of Qtern labeling were structured to be consistent with the PLLR as follows:

- Pregnancy, Section 8.1
The "Pregnancy" section of Qtern labeling was formatted in the PLLR format to include: "Risk Summary", "Clinical Considerations" and "Data" sections.
- Lactation, Section 8.2

The “Lactation” section of Qtern labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” sections.

- Females and Males of Reproductive Potential, Section 8.3
Females and Males of Reproductive Potential, Section 8.3 is omitted because there is nothing to be reported. There is no data to be found on Qtern and its effects on fertility. Contraception and pregnancy testing are not recommended.
- Patient Counseling Information, Section 17
The “Patient Counseling Information” section of labeling was updated to correspond with sections 8.1 and 8.2 of labeling. .

RECOMMENDATIONS

The below recommendations include DPMH revised sections 8.1, 8.2, and 17 of Qtern labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling.

PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION USE IN SPECIFIC POPULATIONS

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters
- Lactation: QTERN is not recommended when breastfeeding.

FULL PRESCRIBING INFORMATION 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, from dapagliflozin, QTERN is not recommended during the second and third trimesters of pregnancy. Limited data with QTERN or its components (saxagliptin and dapagliflozin) in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

In animal studies, adverse renal pelvic and tubular dilatations, that were not fully reversible, were observed in juvenile rats when dapagliflozin (a component of QTERN) was administered at an exposure 15-times the exposure at the 10 mg clinical dose during a period of renal development corresponding to the late second and third trimesters of human pregnancy. No adverse developmental effects were observed when saxagliptin was administered to pregnant rats and rabbits [see *Data*].

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with an HbA1c greater than 7 and has been reported to be as high as 20 to 25% in women with an HbA1c greater than 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

*Dapagliflozin*¹

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all doses. Exposure at the lowest dose was 15-times the 10 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal

development. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In a prenatal and postnatal development study, maternal rats were dosed from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed in utero and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at exposures greater than or equal to 19-times the 10 mg clinical dose, based on AUC. No adverse effects on developmental endpoints were noted at 1 mg/kg/day, or approximately 19-times the 10 mg clinical dose, based on AUC. In embryo-fetal development studies, dapagliflozin was administered to pregnant rats and rabbits during the period of organogenesis, corresponding to the first trimester of human pregnancy. No adverse developmental effects were observed in either species at exposures 1441-times the clinical dose of 10 mg, based on AUC.

Saxagliptinⁱⁱ

In embryo-fetal development studies, saxagliptin was administered to pregnant rats and rabbits during the period of organogenesis, corresponding to the first trimester of human pregnancy. No adverse developmental effects were observed in either species at exposures 1503- and 152-times the 5 mg clinical dose in rats and rabbits, respectively, based on AUC. Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

In a prenatal and postnatal development study, no adverse developmental effects were observed in maternal rats administered saxagliptin from gestation day 6 through lactation day 21 at exposures up to 470-times the 5 mg clinical dose, based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of QTERN or its components (saxagliptin and dapagliflozin) in human milk, the effects on the breastfed infant, or the effects on milk production. Saxagliptin and dapagliflozin are present in the milk of lactating rats. (b) (4)

Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of QTERN is not recommended while breastfeeding.

Data

Dapagliflozinⁱⁱⁱ

Dapagliflozin was present at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Saxagliptin^{iv}

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations.

17 PATIENT COUNSELING INFORMATION

Pregnancy and Lactating Mothers *[See (8.1) and (8.2)]*

- Advise pregnant patients of the potential risk to a fetus with treatment with QTERN
.Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant.
 - Advise patients that use of QTERN is not recommended while breastfeeding.
-

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/s/

CHRISTOS MASTROYANNIS
02/16/2017

TAMARA N JOHNSON
02/21/2017

LYNNE P YAO
02/22/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 21, 2017

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 209091

Product Name and Strength: Qtern (dapagliflozin and saxagliptin), tablets 5 mg/10 mg

Submission Date: February 17, 2017

Applicant/Sponsor Name: AstraZeneca

OSE RCM #: 2016-1009-3

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised commercial container label, professional sample carton labeling, and professional sample blister cards for Qtern (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to labeling recommendations from DMEP to change the established name from “saxagliptin and dapagliflozin” to “dapagliflozin and saxagliptin”.^a

2 CONCLUSION

Our review of the revised commercial container label, professional sample carton labeling, and professional sample blister cards for Qtern identified deficiencies; thus, we recommend additional modifications to the revised labels and labeling to minimize the risk for medication errors with this product.

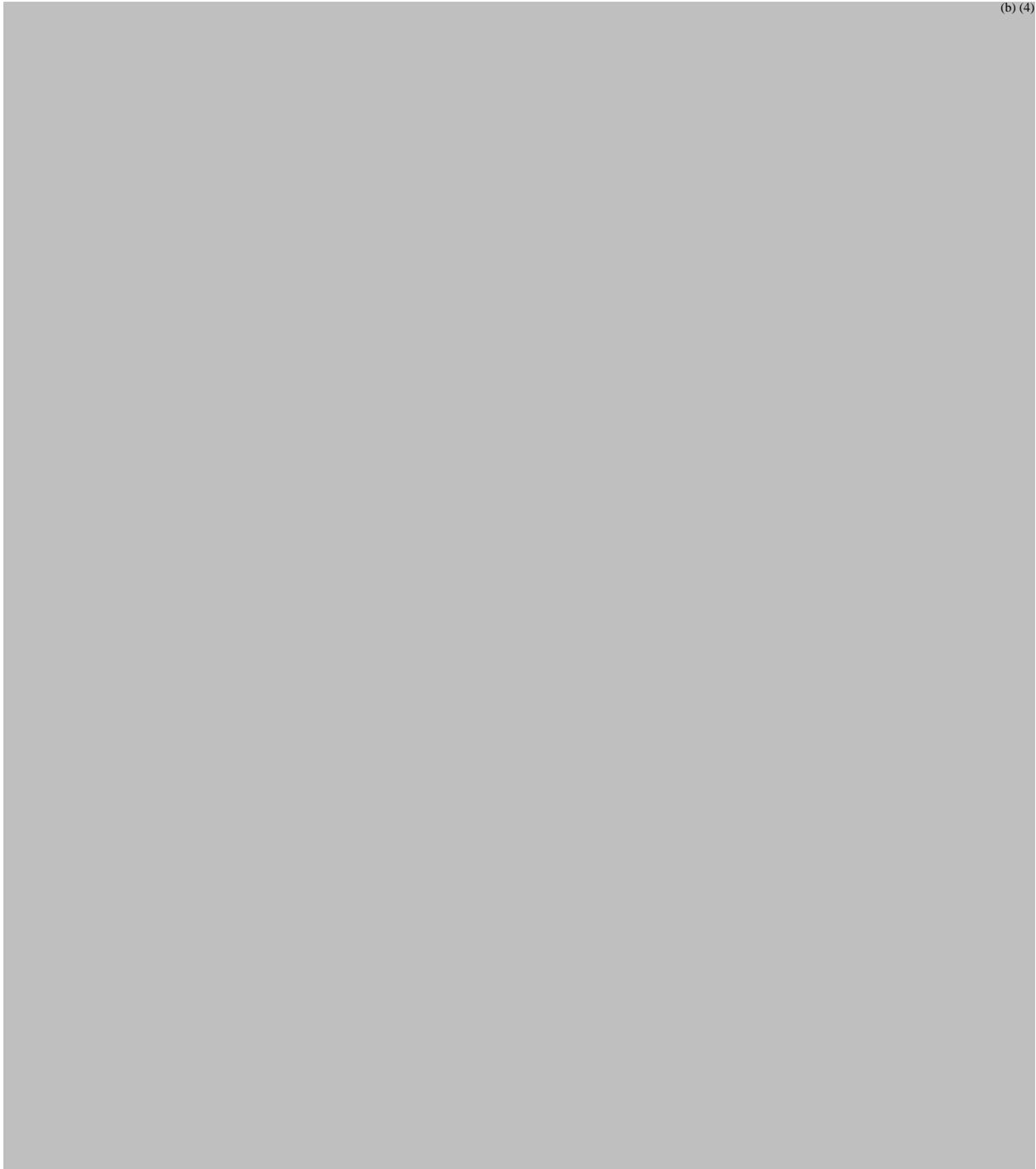
^a Adeolu A. General Advice Letter (COR-NDAIR-10) for Invokamet XR. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs, Division of Metabolism and Endocrinology Products (US); 2017 Jan 31. NDA 209091.

3 RECOMMENDATIONS FOR ASTRAZENECA

We recommend that you revise the presentation of the established name on the commercial labels, professional sample carton labeling, and professional sample blister cards to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: Remove the “/” and replace with “and” to read as “(dapagliflozin and saxagliptin)”.

APPENDIX A. LABEL AND LABELING SUBMITTED ON FEBRUARY 17, 2017

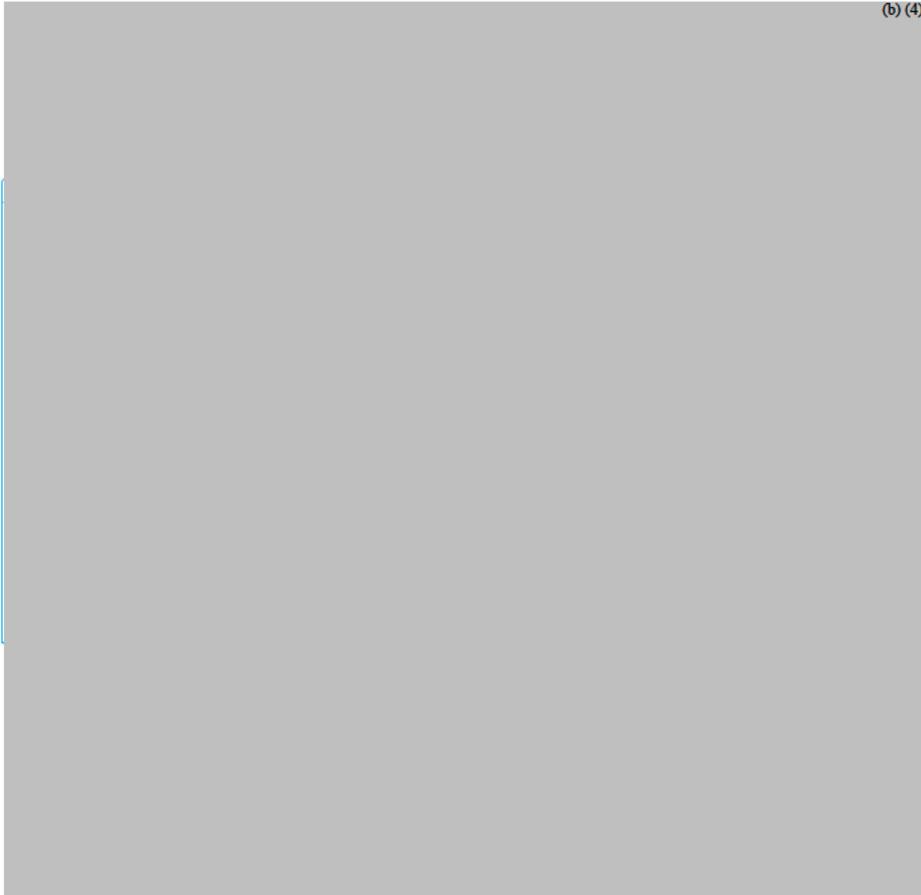
Commercial Container Labels



Professional Sample Blister Cards



Professional Sample Carton Labeling



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/s/

ARIANE O CONRAD
02/21/2017

HINA S MEHTA
02/22/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 10, 2017

To: Abolade Adeolu., Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 209091
QTERN[®] (saxagliptin and dapagliflozin) tablets, for oral use

On May 2, 2016, OPDP received a consult request from DMEP for a subsequent review of the proposed draft Prescribing Information (PI) and Medication Guide for QTERN[®] (saxagliptin and dapagliflozin) tablets, for oral use (Qtern), following issuance of a Complete Response (CR) letter on October 15, 2015. OPDP's review of the proposed draft PI is based on the version provided below, sent via email by Abolade Adeolu on February 6, 2017. We have no comments on the proposed labeling at this time.

Additionally, OPDP worked collaboratively with DMPP to provide comments on the Medication Guide under a separate cover.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
02/10/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 10, 2017

To: Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Charuni Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): QTERN (dapafloglozin and saxagliptin)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 209091

Applicant: AstraZeneca Pharmaceuticals LP

1 INTRODUCTION

On April 27, 2016, AstraZeneca Pharmaceuticals LP submitted for the Agency's review a new drug application (NDA) for QTERN (dapagliflozin and saxagliptin) tablets, for oral use. QTERN (dapagliflozin and saxagliptin) tablets for oral use are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) [REDACTED] (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on May 2, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for QTERN (dapagliflozin and saxagliptin) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft QTERN (dapagliflozin and saxagliptin) tablets, for oral use MG received on April 27, 2016, and received by DMPP on February 6, 2017.
- Draft QTERN (dapagliflozin and saxagliptin) tablets, for oral use MG received on April 27, 2016, and received by OPDP on February 9, 2017.
- Draft QTERN (dapagliflozin and saxagliptin) tablets, for oral use Prescribing Information (PI) received on April 27, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on February 6, 2017.
- Draft QTERN (dapagliflozin and saxagliptin) Prescribing Information (PI) received on April 27, 2016, revised by the Review Division throughout the review cycle, and received by OPDP on February 6, 2017.
- Approved comparator labeling FARXIGA (dapagliflozin) tablets for oral use dated August 17, 2016 and ONGLYZA (saxagliptin) tablets, for oral use dated January 18, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labelings where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
02/10/2017

CHARUNI P SHAH
02/10/2017

MARCIA B WILLIAMS
02/10/2017

LASHAWN M GRIFFITHS
02/10/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 17, 2017

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 209091

Product Name and Strength: Qtern (saxagliptin and dapagliflozin), tablets, 5 mg/10 mg

Submission Date: January 13, 2017

Applicant/Sponsor Name: AstraZeneca

OSE RCM #: 2016-1009-2

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised commercial container label, professional sample carton labeling, and professional sample blister cards for Qtern (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised commercial container label, professional sample carton labeling, and professional sample blister cards for Qtern are acceptable from a medication error perspective. We have no further recommendations at this time.

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^a Conrad A. Review of Revised Label and Labeling Memorandum for Qtern (NDA 209091). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Jan 4. 6 p. OSE RCM No.: 2016-1009-1.

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/s/

ARIANE O CONRAD
01/17/2017

HINA S MEHTA
01/17/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 4, 2016
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 209091
Product Name and Strength: Qtern (saxagliptin and dapagliflozin), tablets, 5 mg/10 mg
Submission Date: December 16, 2016
Applicant/Sponsor Name: AstraZeneca
OSE RCM #: 2016-1009-1
DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised commercial container label, professional sample carton labeling, and professional sample blister cards for Qtern (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised professional sample blister card for Qtern is acceptable from a medication error perspective. However, we are still unclear regarding the intended formatting of the lot number and expiration date on the commercial container label and the sample carton labeling as noted in our previous review.

^a Conrad A. Label and Labeling Review for Qtern (NDA 209091). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Dec 2. 10 p. OSE RCM No.: 2016-1009.

3 RECOMMENDATIONS FOR ASTRAZENECA

We continue to recommend that you indicate the intended location for the lot number and expiration date on the commercial container label and professional sample carton labeling so that we are able to determine if these numbers will be visible on the label and that these numbers will be clearly differentiated for user understanding. We noted that there is an area labeled (b) (4) on each label. Please confirm if the lot number and expiration date will be noted in that space.

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/s/

ARIANE O CONRAD
01/04/2017

HINA S MEHTA
01/04/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

| | |
|---------------------------------------|--|
| Date of This Review: | December 2, 2016 |
| Requesting Office or Division: | Division of Metabolism and Endocrinology Products (DMEP) |
| Application Type and Number: | NDA 209091 |
| Product Name and Strength: | Qtern (saxagliptin and dapagliflozin), tablets, 5 mg/10 mg |
| Product Type: | Multi-ingredient |
| Rx or OTC: | Rx |
| Applicant/Sponsor Name: | AstraZeneca |
| Submission Date: | April 27, 2016 and October 7, 2016 |
| OSE RCM #: | 2016-1009 |
| DMEPA Primary Reviewer: | Ariane O. Conrad, PharmD, BCACP, CDE |
| DMEPA Team Leader: | Hina Mehta, PharmD |

1 REASON FOR REVIEW

AstraZeneca submitted NDA 209091 for Qtern (saxagliptin and dapagliflozin) on April 27, 2016. The Division of Metabolism and Endocrinology Products (DMEP) requested that we evaluate the container labels, carton labeling, prescribing information, and medication guide for vulnerabilities that could lead to medication errors.

1.1 REGULATORY HISTORY

AstraZeneca submitted NDA (b) (4) for saxagliptin/dapagliflozin (b) (4) but that submission received a Complete Response (CR) on October 15, 2015. The Division of Metabolism and Endocrinology Products (DMEP) met with the sponsor on December 17, 2015 to discuss the sponsor's plan to submit under a new NDA (b) (4). They were required to submit this product under a separate NDA because this submission does not address the deficiencies outlined for the CR under NDA (b) (4). Therefore, the sponsor has submitted saxagliptin/dapagliflozin under NDA 209091 for approval.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |
| Labels and Labeling | C |

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, professional sample blister cards and carton labeling, prescribing information, and medication guide for Qtern (saxagliptin/dapagliflozin) to identify deficiencies that may lead to medication errors and other areas of improvement. Our review identified deficiencies in the labels and labeling. We provide recommendations in sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.

4 CONCLUSION & RECOMMENDATIONS

We recommend that AstraZeneca increase the readability and prominence of important information in the proposed labeling to clarify information and mitigate any confusion that may interfere with the safe use of Qtern.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Highlights of Prescribing Information: Dosage and Administration
 - a. We recommend the instructions listed under the Dosage and Administration section be separated out into bullets for ease of readability.
 - b. Add a bullet stating “Tablet should be swallowed whole and not to be split or cut” so this important information is not overlooked and to maintain consistency with the full prescribing information.
2. Full Prescribing Information: Section 16 How Supplied/Storage and Handling
 - a. In the tablet strength column, we recommend revising the statement as follows: “5 mg saxagliptin/10 mg dapagliflozin”.

B. Medication Guide

1. Revise the presentation of the established name to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: (b) (4) Also, remove the word (b) (4)

4.2 RECOMMENDATIONS FOR ASTRAZENECA

We recommend the following be implemented prior to approval of this NDA:

A. Commercial Container Label

1. Revise the presentation of the established name to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: (b) (4) Also, remove the word (b) (4) so this statement reads as follows: (b) (4)
2. Revise the usual dosage information on the side panel to include the recommended dose as follows as per 21 CFR 201.55: “Usual Dosage: 1 tablet once daily in the morning.”.
3. A space holder for the lot number and expiration date is not indicated on the label so it was not possible to determine if these numbers will be visible on the label and that these numbers will be clearly differentiated for user understanding.

B. Professional Sample Carton Labeling

1. See comments A1-A3 under section 4.2.

C. Professional Sample Blister Cards

1. Revise the presentation of the established name to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: [REDACTED] (b) (4)
2. Revise the statement [REDACTED] (b) (4) to read as follows for improved clarity: [REDACTED] (b) (4)
3. Revise the dosage information to include the recommended dose: "Dosage: 1 tablet once daily in the morning."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Qtern that AstraZeneca submitted on October 7, 2016.

| Table 2. Relevant Product Information for Qtern | |
|--|---|
| Initial Approval Date | N/A |
| Active Ingredient | saxagliptin and dapagliflozin |
| Indication | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [REDACTED] (b) (4) |
| Route of Administration | Oral |
| Dosage Form | Tablets |
| Strength | 5 mg saxagliptin and 10 mg dapagliflozin |
| Dose and Frequency | Once daily in the morning with or without food |
| How Supplied | Bottles of 30, 90, or 500 tablets |
| Storage | Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] |

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 9, 2016, we searched the L:drive and AIMS using the terms, “saxagliptin dapagliflozin” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review^a, and we confirmed that our previous recommendations were implemented.

a

(b) (4)

APPENDIX C. LABELS AND LABELING

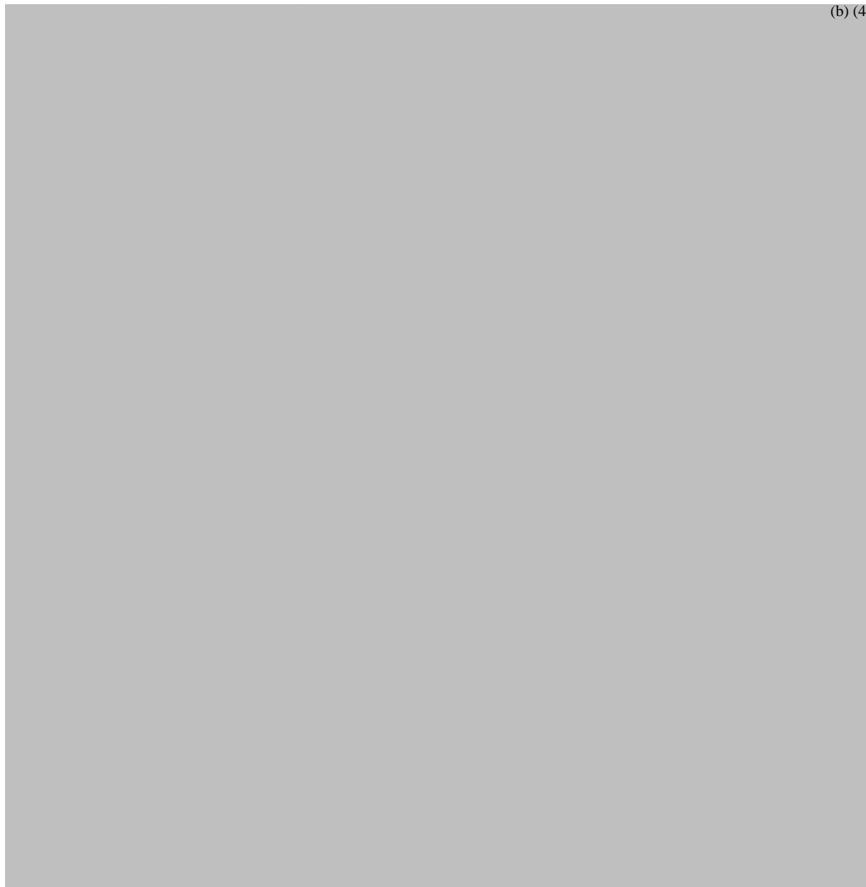
C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Qtern labels and labeling submitted by AstraZeneca on April 27, 2016.

- Commercial Container label
- Professional Sample Blister Cards
- Professional Sample Carton Labeling
- Medication Guide

C.2 Label and Labeling Images

Commercial Container label



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



Professional Sample Blister Cards



Professional Sample Carton Labeling



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

/s/

ARIANE O CONRAD
12/02/2016

HINA S MEHTA
12/02/2016