CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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209805Orig1s000
209806Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H. Chong
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 209803 NDA 209805 NDA 209806
Applicant	Merck Sharp and Dohme Corp
Date of Submission	December 19, 2016
PDUFA Goal Date	December 19, 2017
Proprietary Name / Non-Proprietary Name	STEGLATRO (ertugliflozin) STEGLUJAN (ertugliflozin and sitagliptin) SEGLUROMET (ertugliflozin and metformin hydrochloride)
Dosage form(s) / Strength(s)	**NDA 209803:** Once daily oral tablet (5 mg and 15 mg) **NDA 209805:** Once daily oral tablet (b) (4) 5 mg/100 mg, 15 mg/100 mg [ertugliflozin/sitagliptin]) **NDA 209806:** Twice daily oral tablet (2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, 7.5 mg/1000 mg [ertugliflozin/metformin hydrochloride])
Applicant Proposed Indication(s)/Population(s)	**NDA 209803:** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus **NDA 209805:** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate **NDA 209806:** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)
Recommendation on Regulatory Action	***NDA 209803****: Approval* ***NDA 209805****: Approval* ***NDA 209806****: Approval*
Recommended Indication(s)/Population(s) (if applicable)	***NDA 209803:*** *adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus* ***NDA 209805:*** *adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate* ***NDA 209806:*** *adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus* (b) (4)

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NDA 209803 (ertugliflozin):

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Drug Product Reviewer	Elise Luong
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NDA 209805 (ertugliflozin and sitagliptin):

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NDA 209806 (ertugliflozin and metformin):

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1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis that leads to chronic hyperglycemia and increases the risk for vascular complications (both microvascular and macrovascular). Therapies for T2DM have focused on improving glycemic control as assessed by change in hemoglobin A1c (HbA1c). While there are multiple drug products approved both as individual drugs and as fixed combination drug products (FCDP), many patients are unable to achieve glucose targets. While reasons for this are likely multi-factorial, one argument that has been made is that there are an insufficient number of available therapies to adequately allow for individualization of therapy.

In these New Drug Applications (NDAs), Merck Sharp and Dohme (hereafter referred to as the applicant) is proposing to market three new antidiabetic drug products: ertugliflozin (a sodium glucose cotransporter-2 [SGLT2] inhibitor), ertugliflozin + sitagliptin (a combination of an SGLT2 inhibitor and a dipeptidyl peptidase-4 [DPP4] inhibitor), and ertugliflozin + immediate-release metformin (a combination of an SGLT2 inhibitor and a biguanide). To support these three NDAs, the applicant has conducted seven phase 3 studies to demonstrate the glycemic lowering effect of ertugliflozin. From these studies, it can be concluded that ertugliflozin is better than placebo for improving glycemic control (as assessed using hemoglobin A1c [HbA1c]). This in turn should result in improved clinical outcomes (i.e., reduced risk for microvascular complications) for patients with T2DM. The fixed combination drug products (FCDPs) have similarly demonstrated the ability to improve glycemic control with each of the components showing a contribution to the glycemic lowering effect.

Safety concerns for ertugliflozin include genital infections, urinary tract infections, hypoglycemia, volume depletion/hypotension, ketoacidosis, acute kidney injury, increases in hematocrit, increases in LDL-C, and lower limb amputations. Aside from lower limb amputations, these safety concerns are consistent with other members of the SGLT2 inhibitor class. One member of the SGLT2 inhibitor class currently includes lower limb amputations as a risk in the prescribing information and includes a Boxed Warning. The basis for that comes from findings of increased risk based on a larger database than is currently available for ertugliflozin. Though there are a limited number of events to consider in the ertugliflozin database, the signal of an increased risk for lower limb amputations that was seen is concerning. This potential risk should be communicated though I do not believe that the current data are sufficient to warrant a Boxed Warning for ertugliflozin. Additional data from the ongoing cardiovascular outcomes trial (CVOT) will inform whether further labeling would be appropriate in the future.

The assessment of cardiovascular safety was performed using a meta-analysis of clinical trial and included interim data from an ongoing cardiovascular outcomes trial (CVOT). Based on this assessment, excess cardiovascular risk as discussed in the 2008 “Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” has been excluded.

The safety profile of the FCDPs reflects the combined safety profiles of the components, and no clear potentiation of identified safety concerns

for the components was seen.

Overall, the data provided in support of these NDAs leads me to conclude that the benefits of improving glycemic control with ertugliflozin outweigh the risks associated with ertugliflozin. The risks associated with ertugliflozin can be adequately communicated through labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis leading to chronic hyperglycemia and an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. The Center for Disease Control estimates that there are over 29 million patients with type 2 diabetes mellitus in the United States.	Type 2 diabetes mellitus is a serious and life threatening condition that if left untreated leads an increased risk for morbidity and mortality.
Current Treatment Options	• Based on the results of the Diabetes Control and Complication Trial and the United Kingdom Prospective Diabetes study, improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes (i.e., reduced microvascular complications). • There are currently 12 classes of medications (generally with multiple members in each class), approved to improve glycemic control in patients with T2DM. Many of these medications are also approved as fixed combination drug products (FCDPs). • There are different safety concerns for each class. Metformin is often considered first-line therapy with the choice of subsequent therapies individualized by prescribers based on the patient. • While all of the approved antidiabetic agents have been shown to improve glycemic control, data on the ability of individual agents to improve clinical outcomes is limited.	Despite the many available treatment options, many patients continue to have difficulty with achieving the desired degree of glycemic control. Further, T2DM is a progressive disorder and patients typically need additional agents added as the course of the disease progresses.
Benefit	• Ertugliflozin has demonstrated an ability to improve glycemic control (as measured using HbA1c). This is in turn expected to result in improved clinical outcomes. • Other findings that might be considered beneficial included changes in blood pressure, and changes in weight. Whether the small	Ertugliflozin has demonstrated the ability to improve glycemic control in adults with T2DM. It has been studied in a variety of use scenarios, and has been found to effective in all of them. Other findings that may be desirable for patients include a reduction in body weight

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	observed differences are clinically meaningful is unknown.	and in blood pressure.
Risk	• Safety findings for the class that would be considered applicable to ertugliflozin include genital infections, urinary tract infections, hypotension, hypoglycemia, acute kidney injury, and ketoacidosis. • The most common adverse reaction was genital mycotic infections. • An increased risk for amputations has been included in the label for another member of the class. The available data suggest a similar risk with ertugliflozin though there remains some uncertainty due to the small number of events. • Consistent with the 2008 Guidance on evaluating cardiovascular risk with new antidiabetic drugs, excess cardiovascular risk (i.e., the 1.8 upper bound) has been excluded. • There remains uncertainty with regards to exclusion of the 1.3 upper bound.	The safety profile of ertugliflozin is generally consistent with other SGLT2 inhibitors. Genital mycotic infections were seen more frequently in ertugliflozin treated subjects. Other safety concerns include urinary tract infections, hypoglycemia, acute kidney injury, hypotension/volume depletion, ketoacidosis, and lower limb amputations. The increased risk for lower limb amputations is based on a small number of events, but this observation is particularly concerning given the finding of increased risk for these events with another member of the class. Hopefully the ongoing CVOT will be able to provide additional information to consider in evaluating this safety concern.
Risk Management	• The risk associated with ertugliflozin can be adequately managed through labeling. • Labeling for the risk of genital infections, urinary tract infections, ketoacidosis, and hypoglycemia should be similar to other SGLT2 inhibitors. • The findings for a potential increased risk for lower limb amputations should also be included in the prescribing information.	I believe that the risks associated with ertugliflozin can be adequately handled through labeling. Lower limb amputations should be included as a Warning & Precaution for ertugliflozin containing products, though I do not believe the available data are sufficient to warrant a Boxed Warning. This can be addressed in the future once more data are available.

2. Background

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1DM; characterized by autoimmune destruction of pancreatic β-cells and loss of insulin secretion) and type 2 diabetes mellitus (T2DM; characterized by resistance to insulin activity with inadequate insulin production to maintain euglycemia). Chronic hyperglycemia 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.

The development of therapies to treat T2DM has focused on developing agents that can improve glycemic control as assessed by the ability to reduce HbA1c, and this has served as the basis for approval of antidiabetic agents. Recently, studies of some antidiabetic drugs have reported improved clinical outcomes in patients with T2DM. These findings are limited to a few drug products [3, 4] and were conducted in a population with high cardiovascular risk. Whether these findings can be generalized to the entire population of patients with T2DM is unknown.

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.

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 peptidase-4 (DPP4) inhibitors	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin
Glucagon-like peptide-1 (GLP1) receptor agonists	Exenatide (as a twice daily and as a once weekly), Liraglutide, Albiglutide, Dulaglutide, Lixisenatide, Semaglutide
Sodium glucose cotransporter-2 (SGLT2) inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin
Amylin analogs	Pramlintide

[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.
[3] Zinman B, et al. "Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes". NEJM, 2015; 373: 2117-2128.
[4] Marso SP, et al. "Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes". NEJM, 2016; 375: 311-322.

Drug Class	Drug Products
Bile acid sequestrants	Colesevelam
Dopamine agonists	Bromocriptine

Despite the number of available therapies, many patients with T2DM continue to have difficulty in achieving glycemic targets. While reasons for this are likely multifactorial, it has been suggested that more therapeutic options are needed to allow for better individualization of therapy.

Merck Sharp and Dohme (hereafter referred to as the applicant) has submitted three New Drug Applications (NDAs) for three new antidiabetic drug products containing ertugliflozin, a sodium glucose cotransporter-2 (SGLT2) inhibitor. The three drug products consist of ertugliflozin alone (NDA 209803), ertugliflozin + sitagliptin (NDA 209805), and ertugliflozin + immediate-release metformin (NDA 209806).

As an SGLT2 inhibitor, ertugliflozin blocks glucose reabsorption by the kidney. This in turn lowers plasma glucose levels. This approach has been shown to improve glycemic control, and there are already several members of this drug class approved to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

In addition to developing ertugliflozin, the applicant has developed fixed combination drug products (FCDPs) combining ertugliflozin with other antidiabetic drugs.

Ertugliflozin has been combined with sitagliptin, a dipeptidyl peptidase-4 (DPP4) inhibitor. By inhibiting DPP4, sitagliptin prevents the breakdown of endogenous incretin hormones (e.g., glucagon-like peptide-1 [GLP1]). This in turn leads to increased and prolonged levels of these hormones which play a role in glucose homeostasis through enhanced glucose-dependent insulin production and secretion, and reduction of glucagon.

Ertugliflozin has also been combined with immediate-release metformin. The mechanisms by which metformin exerts its antidiabetic effects are not completely understood, but it is believed to decrease hepatic gluconeogenesis and to improve insulin sensitivity.

The applicant has proposed the following indications for these NDAs:

- **NDA 209803 (ertugliflozin):** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

- **NDA 209805 (ertugliflozin and sitagliptin):** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate

- **NDA 209806 (ertugliflozin and immediate-release metformin):** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

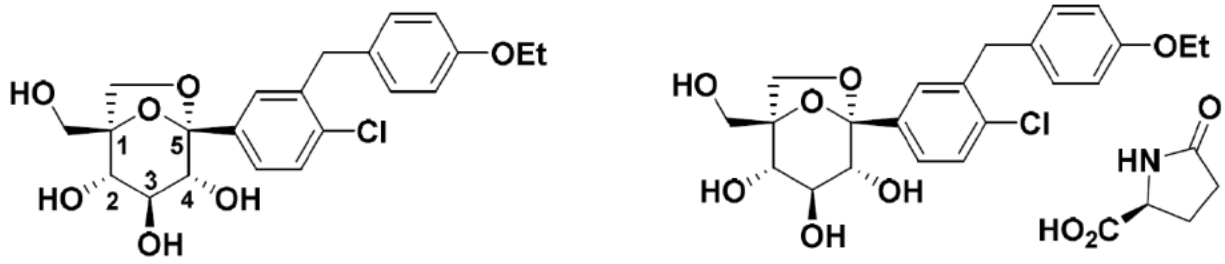
3. Product Quality

a. Drug Substance

The focus in the discussion of drug substances will be on ertugliflozin. Details on the chemistry, manufacturing, and controls (CMC) information for the other components of the FCDPs (i.e., sitagliptin and metformin) can be found in the previous NDA reviews and approved prescribing information for these drug products.

Ertugliflozin is an unstable amorphous material. The active ertugliflozin moiety is manufactured in a co-crystal form with L-pyroglutamic acid (L-PGA) to achieve better physical and chemical properties including stability (Figure 1).

Figure 1: Structure of ertugliflozin and ertugliflozin L-PGA co-crystal



Ertugliflozin **Ertugliflozin L-PGA**

Source: Excerpted from Figure 2.3.S.1-1 of the General Information provided in module 2.3.S of NDA 209803

The ertugliflozin L-PGA [redacted] (b) (4) is manufactured as a white to off-white powder. (b) (4) [redacted]

The commercial manufacturing process is the same as that used for the phase 3 clinical batches and the primary stability batches. The to-be-marketed drug substance will be manufactured by Pfizer Ireland Pharmaceuticals.

b. Drug Products

NDA 209803 (ertugliflozin):

The ertugliflozin drug product will be manufactured as a 5 mg or 15 mg immediate release oral tablet. There are no novel excipients or human/animal-derived excipients. (b) (4) [redacted] The manufacturing process and evaluation of drug product

specifications, degradants and stability data were found to be adequate and supportive of the proposed 24 month shelf-life at room temperature.

NDA 209805 (ertugliflozin and sitagliptin):

The ertugliflozin and sitagliptin drug product will be manufactured as an immediate-release, film-coated oral tablet in four dosage strengths (mg of ertugliflozin/mg of sitagliptin: (b) (4) (b) (4) 5 mg/100 mg, and 15 mg/100 mg). (b) (4) The manufacturing process and evaluation of drug product specifications, degradants and stability data were found to be adequate and supportive of the proposed 24 month shelf-life at room temperature.

NDA 209806 (ertugliflozin and metformin hydrochloride):

The ertugliflozin and metformin hydrochloride drug product will be manufactured as an immediate-release, film-coated oral tablet in four dosage strengths (mg of ertugliflozin/mg of metformin: 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5 mg/1000 mg). (b) (4) The manufacturing process and evaluation of drug product specifications, degradants and stability data were found to be adequate and supportive of the proposed 24 month shelf-life at room temperature.

4. Nonclinical Pharmacology/Toxicology

The discussion here will focus on the nonclinical data for ertugliflozin. Sitagliptin and metformin are both approved drug products and the nonclinical data for these components of the fixed combination drug products has been discussed in other reviews and is described in the currently approved labeling of those products.

In vitro studies of ertugliflozin demonstrate that it is a potent and selective inhibitor of SGLT2 with a low probability of sodium glucose co-transporter-1 (SGLT1) inhibition at clinical exposures. Metabolism of ertugliflozin is primarily through glucuronidation, and there are two main metabolites (M5a and M5c). Neither metabolite is likely to inhibit SGLT2 or SGLT1 at clinical exposures, and the nonclinical program has adequately qualified these metabolites (i.e., no significant toxicological concern at clinical exposures).

In the nonclinical studies, adverse findings were observed in the kidney and urinary tract. These findings included renal pelvic and tubule dilatation, mineral deposits, and hypertrophy/hyperplasia of the organs of the urinary tract. These findings were felt to be secondary to the pharmacodynamic effects of SGLT2 inhibition (i.e., glucosuria).

Adverse findings were also observed in the digestive tract. These included GI dilatation, stomach erosions/ulcers, and increased intestinal villi height. These findings were felt to be secondary to SGLT1 inhibition.

Hypercalciuria was observed in the nonclinical studies, and this was accompanied by decreases in parathyroid hormone and calcium levels as well as with increases in trabecular bone and hyperostosis.

All of these findings were seen at large multiples of the clinical exposure.

Carcinogenicity studies showed a drug-related increase in adrenal medulla pheochromocytoma. This was observed in male rats at a dosage of 15 mg/kg/day (safety margin of 18x maximum recommended human dose).

Juvenile rats exposed to ertugliflozin during the period of renal development had adverse renal findings similar to that seen in adult animals. Reversibility was not assessed. Other findings (e.g., decreased weights, decreased growth) were felt to be secondary to the glucosuric effect and subsequent caloric loss.

In reproductive toxicity studies, adverse fetal effects were attributed to maternal toxicity.

Studies of ertugliflozin in combination with sitagliptin and in combination with metformin did not raise any concerns for significant toxicities. Combination therapy was generally well tolerated and the safety margins were felt to be adequate.

The observed adverse findings are consistent with effects seen with other SGLT2 inhibitors and they generally occur at high multiples of the clinical exposure. Similar to other SGLT2 inhibitors, Dr. Hawes has concerns with respect to the use of ertugliflozin in the 2nd and 3rd trimester due to adverse renal effects in the developing kidney.

Based on review of the nonclinical data, Dr. Hawes recommends approval of ertugliflozin and of the ertugliflozin fixed combination drug products.

5. Clinical Pharmacology

The discussion here will focus on the clinical pharmacology data for ertugliflozin. Sitagliptin and metformin are both approved drug products and the clinical pharmacology data for these components of the fixed combination drug products has been discussed in other reviews and is described in the currently approved labeling of those products.

Following oral administration of ertugliflozin tablets in the fasted condition, there is rapid absorption of ertugliflozin with nearly 100% bioavailability. The time to maximum concentration (T_{max}) was 1 hour. Administration of ertugliflozin with a high-fat and high-calorie meal reduced the maximum concentration (C_{max}) by 29% and prolonged the T_{max} by 1 hour. The area under the curve (AUC), however, remained unchanged. Thus, the observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant.

Based on a population PK analysis, the elimination half-life of ertugliflozin in patients with T2DM and normal renal function is approximately 16.6 hours.

No meaningful differences in the pharmacokinetic findings for ertugliflozin were seen when ertugliflozin was co-administered with metformin or sitagliptin.

In patients with renal impairment, mean increases in AUC of ertugliflozin were 1.6x, 1.7x, and 1.6x (mild, moderate, and severe, respectively) that of patients with normal renal impairment. Exposure to ertugliflozin was not increased in patients with moderate hepatic impairment. The AUC and C_{max} of ertugliflozin decreased by ~13% and ~ 21%, respectively, compared to patients with normal hepatic function. Neither of these findings was felt to be clinically meaningful.

In a thorough QT study, no significant prolongation of the QTc was seen with ertugliflozin 100 mg.

Additional clinical pharmacology studies were conducted to support the final formulation of ertugliflozin and the two FCDPs.

In the phase 3 clinical trials, patients randomized to ertugliflozin 15 mg were administered one 10 mg tablet and one 5 mg tablet. The to-be-marketed product consists of a 5 mg dosage strength and a 15 mg dosage strength. To support the 15 mg dosage strength, the applicant has compared the pharmacokinetic profile of the 15 mg tablet with that of administration of one 10 mg tablet and one 5 mg tablets. No meaningful difference was seen.

To support the ertugliflozin + sitagliptin FCDP (NDA 209805), the applicant conducted single-dose bioequivalence studies to bridge the to-be-marketed tablets to co-administration of the individual components. The geometric mean ratios for C_{max}, AUC_{o-t}, and $AUC_{0-\infty}$ were all within the 80-125% range used to demonstrate bioequivalence. No clinically meaningful drug-drug interaction was observed with co-administration of ertugliflozin and sitagliptin.

To support the ertugliflozin + metformin FCDP (NDA 209806), the applicant conducted bridging studies to bridge once daily dosing of ertugliflozin with split/twice daily dosing of ertugliflozin. At steady-state (i.e., after 6 days of administration), exposure to ertugliflozin was similar between once daily and twice daily administration (as measured by AUC_{0-24h}). The pharmacodynamic effect ((i.e., UGE_{0-24h}) was also similar. Thus, split/twice daily dosing is expected to yield a clinical response similar to once daily dosing. Additional bioequivalence studies were conducted to bridge the to-be-marketed FDCP with co-administration of the individual components. These studies indicate that exposure with the FDCP is similar to that of co-administration of the individual components. No clinically meaningful drug-drug interaction was observed with co-administration of ertugliflozin and metformin.

Based on the review of the submitted data, the reviewers from the Office of Clinical Pharmacology recommend approval of ertugliflozin, the ertugliflozin + sitagliptin FDCP, and the ertugliflozin + metformin FDCP. The clinical pharmacology reviewers recommend approval of both the 5 mg and the 15 mg dose of ertugliflozin.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The statistical assessment of the efficacy of ertugliflozin and the ertugliflozin fixed combination drug products (FCDPs) was reviewed by Dr. Alexander Cambon. I will summarize findings from the statistical review in this section. For a detailed discussion, see Dr. Cambon's statistical review.

In support of the ertugliflozin NDAs, the applicant conducted seven phase 3 studies. Features of these studies are briefly summarized in Table 2.

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Table 2: Summary Description of Phase 3 Studies

Study ID	Population	Design	Duration	Treatment Arms
p001/1016 [1]	Adults with T2DM and stage 3 CKD (eGFR 30 to 60 ml/min/1.73 m^2) treated with antidiabetic drugs	Randomized, double-blind, placebo-controlled	26 weeks	• Ertugliflozin 5 mg once daily • Ertugliflozin 15 mg once daily • Placebo once daily
p002/1013 [1, 2]	Adults with T2DM treated with metformin	Randomized, double-blind, active-controlled	52 weeks	• Ertugliflozin 5 mg once daily • Ertugliflozin 15 mg once daily • Glimepiride titrated to maximum approved (6 or 8 mg) or maximum tolerated dose
p003/1022 [1]	Adults with T2DM not treated with antidiabetic drugs	Randomized, double-blind, placebo-controlled	26 weeks	• Ertugliflozin 5 mg once daily • Ertugliflozin 15 mg once daily • Placebo once daily
p005/1019 [1, 2, 3]	Adults with T2DM treated with metformin	Randomized, double-blind, active-controlled	26 weeks	• Ertugliflozin 5 mg once daily • Ertugliflozin 15 mg once daily • Sitagliptin 100 mg once daily • Ertugliflozin 5 mg + sitagliptin 100 mg once daily • Ertugliflozin 15 mg + sitagliptin 100 mg once daily
p006/1015 [1, 2, 3]	Adults with T2DM treated with metformin and sitagliptin	Randomized, double-blind, placebo-controlled	26 weeks	• Ertugliflozin 5 mg once daily • Ertugliflozin 15 mg once daily • Placebo once daily
p007/1017 [1, 2]	Adults with T2DM treated with metformin	Randomized, double-blind, placebo-controlled	26 weeks	• Ertugliflozin 5 mg once daily • Ertugliflozin 15 mg once daily • Placebo once daily
p017/1047 [1, 3]	Adults with T2DM not treated with antidiabetic drugs	Randomized, double-blind, placebo-controlled	26 weeks	• Ertugliflozin 5 mg + sitagliptin 100 mg once daily • Ertugliflozin 10 mg + sitagliptin 100 mg once daily • Placebo

[1] relevant to NDA 209803 (ertugliflozin); [2] relevant to NDA 209806 (ertugliflozin and metformin); [3] relevant to NDA 209805 (ertugliflozin and sitagliptin)
T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; LAR = long-acting release
Source: Adapted from the submitted "Tabular Listing of All Clinical Studies" in module 5.2 of NDA 209803

Baseline demographics were balanced across treatment arms in all the studies (see Tables 4, 5, 6, 7, 8, 9, and 10 of Dr. Cambon's statistical review, not shown here).

The primary endpoint in all of the phase 3 trials was change from baseline in HbA1c. Both doses were compared to placebo or active-comparator. Most of the studies were designed to demonstrate superiority of the treatment (i.e., ertugliflozin or ertugliflozin + sitagliptin). In one study (study p002, ertugliflozin vs. glimepiride) the objective was demonstration of non-inferiority using a non-inferiority margin of 0.3%. Statistical testing used a hierarchical testing strategy to control type 1 error at a one-sided $\alpha \leq 0.025$ (or two-sided $\alpha \leq 0.05$).

The applicant's statistical approach used all randomized subjects who had received at least one dose of study drug and had a baseline or post-randomization measurement after at least one dose of study drug. A constrained longitudinal data analysis (cLDA) model was used. Measurements obtained after discontinuation of study drug were excluded from the analysis, and observations obtained after initiation of rescue medication were considered as missing.

Dr. Cambon has noted some concerns with the applicant's statistical approach.

One concern is the analysis population. Dr. Cambon believes that the analysis population should include all randomized subjects with a baseline measurement and who have been exposed to study drug, rather than all randomized subjects who received at least one dose of study drug and had an endpoint measurement after at least one dose of study drug. Additionally, Dr. Cambon favors including all measurements obtained after randomization in the analysis (e.g., should include measurements obtained after initiation of rescue medication). This is in contrast to the applicant's approach where data after rescue were considered missing. Subjects who initiate rescue medication may not be the same as those who do not initiate rescue medication, thus excluding this data may not preserve randomization.

Another concern that Dr. Cambon raises is that few patients that discontinued treatment early were followed after discontinuing study drug. As a result, there is sparse data to conduct a retrieved dropout analysis (Dr. Cambon's preferred approach to imputing missing data). Dr. Cambon had to consider alternative imputation methods to model what might have happened to those patients. Dr. Cambon has conducted analyses using both a jump to reference (J2R) and a return to baseline (RTB) imputation method. The J2R approach assumes that subjects with missing final assessments take on the profile of subjects in the comparator arm. The RTB approach assumes that patients with missing data revert to their baseline status. The J2R approach may be appropriate when subjects have missing data due to treatment discontinuation and these subjects are given alternative therapy. The RTB approach may be appropriate when subjects have missing data due to treatment discontinuation and the effect of alternative therapy (or continued background therapy) is only expected to prevent deterioration from baseline.

As a result of these concerns, Dr. Cambon does not agree with the applicant's cLDA analysis. He does not believe that it adequately addresses missing data, and he does not agree with the choice to exclude data after rescue medication. As such, Dr. Cambon prefers the results based

on RTB analysis as he believes this approach best addresses the issue of missing data. Additionally, Dr. Cambon has included all available data, including data after discontinuation and data after glycemic rescue, in his analyses.

Regardless of statistical method, ertugliflozin was shown to be statistically significantly superior to placebo and ertugliflozin 15 mg was non-inferior to glimepiride in terms of reducing HbA1c (Table 3). Additionally, simultaneous initiation of ertugliflozin and sitagliptin was statistically significantly superior to either of the individual components, as well as to placebo. I agree with Dr. Cambon that the effectiveness of ertugliflozin to improve glycemic control has been adequately demonstrated.

Table 3: Summary of findings for change from baseline in HbA1c in the ertugliflozin development program

Study p003 – no background antidiabetic therapy			
cLDA excluding rescue	P	E5	E15
• Change from baseline	0.2	-0.79	-0.96
• Difference from placebo (95% CI)		-0.99 (-1.22, -0.76)	-1.16 (-1.39, -0.93)
RTB including rescue			
• Change from baseline	-0.17	-0.75	-0.84
• Difference from placebo (95% CI)		-0.58 (-0.8, -0.36)	-0.67 (-0.89, -0.44)
J2R including rescue			
• Change from baseline	-0.16	-0.79	-1.06
• Difference from placebo (95% CI)		-0.67 (-0.91, -0.44)	-0.76 (-1.02, -0.51)
Study p007 - add-on to metformin			
cLDA excluding rescue	P	E5	E15
• Change from baseline	-0.03	-0.73	-0.91
• Difference from placebo (95% CI)		-0.7 (-0.87, -0.53)	-0.88 (-1.05, -0.71)
RTB including rescue			
• Change from baseline	-0.17	-0.72	-0.86
• Difference from placebo (95% CI)		-0.55 (-0.71, -0.39)	-0.69 (-0.86, -0.53)
J2R including rescue			
• Change from baseline	-0.23	-0.74	-0.95
• Difference from placebo (95% CI)		-0.55 (-0.71, -0.38)	-0.67 (-0.83, -0.5)

Study p002 - add-on to metformin vs. glimepiride			
cLDA excluding rescue	G	E5	E15
• Change from baseline	-0.74	-0.56	-0.64
• Difference from glimepiride (95% CI)		0.18 (0.06, 0.3)	0.1 (-0.02, 0.22)
RTB including rescue			
• Change from baseline	-0.63	-0.46	-0.53
• Difference from glimepiride (95% CI)		0.17 (0.04, 0.3)	0.1 (-0.02, 0.23)
J2R including rescue			
• Change from baseline	-0.62	-0.67	-0.76
• Difference from glimepiride (95% CI)		0.17 (0.05, 0.3)	0.11 (-0.01, 0.23)
Study p006 - add-on to metformin and sitagliptin			
cLDA excluding rescue	P	E5	E15
• Change from baseline	-0.09	-0.78	-0.86
• Difference from placebo (95% CI)		-0.69 (-0.87, -0.5)	-0.76 (-0.95, -0.58)
RTB including rescue			
• Change from baseline	-0.21	-0.69	-0.79
• Difference from placebo (95% CI)		-0.48 (-0.66, -0.3)	-0.58 (-0.76, -0.4)
J2R including rescue			
• Change from baseline	-0.27	-0.81	-0.86
• Difference from placebo (95% CI)		-0.49 (-0.67, -0.3)	-0.58 (-0.77, -0.39)
Study p017 - no background antidiabetic therapy			
cLDA excluding rescue	P	E5+S100	E15+S100
• Change from baseline	-0.44	-1.6	-1.68
• Difference from placebo (95% CI)		-1.16 (-1.49, -0.84)	-1.24 (-1.57, -0.91)
RTB including rescue			
• Change from baseline	-0.58	-1.56	-1.52
• Difference from placebo (95% CI)		-0.97 (-1.28, -0.66)	-0.94 (-1.28, -0.62)
J2R including rescue			
• Change from baseline	-0.72	-1.64	-1.69
• Difference from placebo (95% CI)		-0.97 (-1.28, -0.66)	-0.94 (-1.26, -0.62)

Study p005 - add-on to metformin					
cLDA excluding rescue	S100	E5	E15	E5+S100	E15+S100
• Change from baseline	-1.05	-1.02	-1.08	-1.49	-1.52
• Difference from sitagliptin (95% CI)				-0.43 (-0.6, -0.27)	-0.47 (-0.63, -0.3)
• Difference from ertugliflozin[2] (95% CI)				-0.46 (-0.63, -0.3)	-0.49 (-0.66, -0.33)
RTB including rescue					
• Change from baseline	-1.02	-1.04	-1.01	-1.4	-1.39
• Difference from sitagliptin (95% CI)				-0.37 (-0.55, -0.19)	-0.37 (-0.55, -0.19)
• Difference from ertugliflozin[2] (95% CI)				-0.36 (-0.54, -0.18)	-0.38 (-0.56, -0.21)
J2R including rescue					
• Change from baseline	-1.12	-1.13	-1.13	-1.53	-1.56
• Difference from sitagliptin (95% CI)				-0.35 (-0.52, -0.19)	-0.36 (-0.53, -0.19)
• Difference from ertugliflozin[2] (95% CI)				-0.39 (-0.55, -0.24)	-0.41 (-0.57,-0.24)

[1] pre-specified non-inferiority margin of 0.3; [2] compared to respective dose of ertugliflozin
cLDA = constrained longitudinal data analysis; RTB = return to baseline; J2R = jump to reference; P = placebo; E5 = ertugliflozin 5 mg; E15 = ertugliflozin 15 mg; G = glimepiride; S100 = sitagliptin 100 mg
Source: Adapted from Table 9 of Dr. Pucino's clinical review and Supplemental Efficacy Analyses for p003, p005, p006, p007, and p017 submitted to NDA 209803 on July 21, 2017 and Supplemental Efficacy Analyses for p002 submitted to NDA 209803 on August 9, 2017

Notable in comparing the different analytical approaches is that the magnitude of the treatment difference is generally smaller with the analyses that included data after rescue. This appears primarily to be due to differences in the estimated change from baseline in the comparator arm. The estimated change from baseline in the ertugliflozin treatment arms does not markedly change with the different statistical approaches. The observed differences are likely due to the different approaches to handling missing data, data after discontinuation, and data after glycemic rescue, and the differential proportion of subjects with missing data or that received rescue medication (see Table 3 of Dr. Cambon's review, excerpted below).

Table 3: Descriptive statistics for patients having primary efficacy data, and patients discontinuing treatment.

Study	Group	All Patients Random.	Treated, With BL	Missing*	(%)	Had Primary Efficacy Data in Final Ass. Window	(%)	Disc. Treatment Early**	(%)	Started Rescue Med. Before Final Assess. Window***	(%)
P002	E5	448	447	88	19.7%	359	80.3%	76	17.0%	23	5.1%
P002	E15	441	440	71	16.1%	369	83.9%	64	14.5%	13	3.0%
P002	Glim.	437	437	66	15.1%	371	84.9%	60	13.7%	10	2.3%
P005	E5	250	244	18	7.4%	226	92.6%	16	6.6%	15	6.1%
P005	E15	248	247	26	10.5%	221	89.5%	19	7.7%	7	2.8%
P005	S100	247	242	27	11.2%	215	88.8%	22	9.1%	13	5.4%
P005	E5+S100	243	237	20	8.4%	217	91.6%	17	7.2%	5	2.1%
P005	E15+S100	245	241	26	10.8%	215	89.2%	20	8.3%	0	0.0%
P006	Placebo	153	152	14	9.2%	138	90.8%	11	7.2%	20	13.2%
P006	E5	156	155	16	10.3%	139	89.7%	12	7.7%	2	1.3%
P006	E15	154	152	11	7.2%	141	92.8%	10	6.6%	3	2.0%
P007	Placebo	209	207	23	11.1%	184	88.9%	17	8.2%	33	15.9%
P007	E5	207	205	11	5.4%	194	94.6%	6	2.9%	6	2.9%
P007	E15	205	201	14	7.0%	187	93.0%	14	7.0%	3	1.5%
P017	Placebo	97	96	20	20.8%	76	79.2%	21	21.9%	30	31.3%
P017	E5+S100	98	98	7	7.1%	91	92.9%	7	7.1%	6	6.1%
P017	E15+S100	96	96	10	10.4%	86	89.6%	8	8.3%	0	0.0%
P003	Placebo	153	153	35	22.9%	118	77.1%	33	21.6%	37	24.2%
P003	E5	156	155	16	10.3%	139	89.7%	22	14.2%	3	1.9%
P003	E15	152	151	24	15.9%	127	84.1%	23	15.2%	4	2.6%
P001	Placebo	154	152	27	17.8%	125	82.2%	14	9.2%	9	5.9%
P001	E5	158	154	21	13.6%	133	86.4%	16	10.4%	13	8.4%
P001	E15	156	151	25	16.6%	126	83.4%	14	9.3%	5	3.3%

*The final assessment for a subject was considered missing if they had no assessment within 26 +/- 4 weeks for the 26 week studies, and within 52 +/- 8 weeks for the non-inferiority study.** For 52-Week study (P002), number (%) discontinuing treatment is defined as at < 44 weeks after randomization. For all other studies, treatment discontinuation is defined as < 22 weeks.; *** Assessment window is defined previously - +/- 4 weeks for 26 week studies and 52 +/- 8 weeks for non-inferiority study;
Abbreviations: Glim. – glimepiride. E5- ertugliflozin 5mg; E15- ertugliflozin 15mg; S100- sitagliptin 100 mg; Ass. – Assessment; Rand. – Randomized; Disc. – Discontinued; Med.-Medication

I agree with Dr. Cambon's recommendation to include data after glycemic rescue. While the inclusion of data after rescue may impact the assessment of the treatment difference, including that information most accurately reflects the findings from the study as designed since rescue medication was part of the design. Further, treating data after glycemic rescue as missing may no longer preserve randomization. As randomization is intended to minimize bias, preserving randomization is critical in considering the results.

Acknowledging that this approach may impact the treatment difference (particularly in study p003), inclusion of additional information (such as proportion of patients with missing data, proportion of patients that received rescue medication) may provide context for understanding the results of the clinical trial.

8. Safety

The review of overall safety was completed by Dr. Frank Pucino. The focus of Dr. Pucino's review was on the non-cardiovascular safety findings. For the assessment of cardiovascular risk, the applicant performed a meta-analysis of phase 2 and phase 3 trials in combination with interim data from an ongoing blinded cardiovascular outcomes trial (CVOT). Dr. Elande Baro from the Division of Biostatistics-7 completed the statistical review for cardiovascular safety.

The overall safety assessment and the cardiovascular risk are discussed separately. Findings from Dr. Pucino's safety review make up the overall safety assessment and are summarized below. Findings from Dr. Baro's cardiovascular risk assessment are briefly discussed separately.

Safety Assessment:

The overall safety assessment was conducted using two main pools (Table 4).. The first was a placebo-controlled pool (referred to as the "Placebo Pool" in Dr. Pucino's review) which consisted of three studies. A second pool (referred to as the "Broad Pool" in Dr. Pucino's review) consisted of seven phase 3 studies.

Table 4: Summary of size and exposure of safety pools

Safety Pool - Included Trials	Ertu 5 mg N (mean exp)	Ertu 15 mg N (mean exp)	All Ertu N (mean exp)	Comparator[1] N (mean exp)
Placebo Pool - p003/1022; p006/1015; p007/1017	519 (174.8)	510 (172.6)	1029 (173.7)	515 (170.2)
Broad Pool[2] - p001/1016; p002/1013; p003/1022; p005/1019; p006/1015; p007/1017; p017/1047	1716 (391.5)	1693 (391)	3409 (391.2)	1450 (396)

Ertu = ertugliflozin; N = number of subjects; mean exp = mean duration of exposure in days
[1] Comparator for Placebo Pool was placebo. Comparator for Broad Pool included placebo, glimepiride, sitagliptin (+/- ertugliflozin); [2] Broad Pool based on information provided at 120 day safety update
Source: Adapted from Table 2.7.4: 4 of the Summary of Clinical Safety submitted with the initial NDA submission (NDA 209803, SD-3, submitted December 19, 2016) and from Table 2.7.4: 4 of the Summary of Clinical Safety submitted in the 120 day safety update (NDA 209803, SD-17, April 20, 2017)

For NDA 209805 (ertugliflozin + sitagliptin), the sponsor conducted three trials relevant to the FCDP (p005/1019 [ertugliflozin vs. sitagliptin vs. ertugliflozin + sitagliptin in patients on metformin]; p006/1015 [ertugliflozin vs. placebo in patients on metformin and sitagliptin]; p017/1047 [ertugliflozin + sitagliptin vs. placebo in patients on metformin]) which were also submitted to the ertugliflozin monotherapy NDA. Exposure to study drug in this pool was generally similar between treatment arms, with mean exposure for the active drug arms being 170.9 to 174 days. Due to design differences, the safety data from these trials were considered separately rather than in a pool.

For NDA 209806 (ertugliflozin + metformin), the sponsor conducted four trials relevant to the FCDP (p002/1013 [ertugliflozin vs. glimepiride in patients on metformin]; p005/1019 [ertugliflozin vs. ertugliflozin + sitagliptin vs. sitagliptin in patients on metformin]; p006/1015 [ertugliflozin vs. placebo in patients on metformin and sitagliptin]; p007/1017 [ertugliflozin

vs. placebo in patients on metformin]). Due to design differences, safety analyses for the ertugliflozin + metformin FDCP were based on a pool of the two placebo-controlled studies (i.e., p006 and p007).

It should be noted that, in order to preserve the integrity of that ongoing trial, no safety data from the ongoing cardiovascular outcomes trial (CVOT) were included in these assessments.

Discussion of Safety Findings:

Dr. Pucino has conducted a review of the overall safety of ertugliflozin. From his review, he did not identify any concerning imbalances in deaths, serious adverse events, or adverse events leading to discontinuation.

In general, the safety findings for ertugliflozin are similar to those of the currently approved SGLT2 inhibitors. An increased incidence for genital infections and increased urination was seen in the ertugliflozin treated patients vs. comparator. Ertugliflozin treated patients were more likely to have increases in hemoglobin, increases in serum phosphate, and increases in LDL-C. The clinical relevance of these laboratory changes is unclear. Based on the mechanism of action and experience with other members of the class, it is expected that treatment with ertugliflozin incurs an increased risk for hypotension, genital infections, acute kidney injury, serious urinary tract infections, hypoglycemia (particularly when used in combination with insulin or insulin secretagogues), and ketoacidosis. For detailed discussion of the safety findings, see Dr. Pucino's clinical review.

For the fixed combination drug products, Dr. Pucino has not identified any new safety concerns. The safety profiles of the FCDPs appears to be consistent with what might be expected given the safety profiles of the individual components.

For this review, I will focus my discussion on the findings for amputations as this is a new safety concern identified with another member of the class.

- Lower Limb Amputations

A risk for non-traumatic lower limb amputations was observed in a cardiovascular outcomes trial for another SGLT2 inhibitor. In considering that finding, the applicant was asked to conduct a search of their safety database for cases of non-traumatic limb amputations. To identify cases, a custom MedDRA query (CMQ) was used and the comment field for serious adverse events was searched for mention of 'amputation'.

Based on this search strategy, more events were identified in ertugliflozin treated patients than in comparator treated patients. Including data from the 120-day safety update, 1 (0.1%), 3 (0.2%), and 8 (0.5%) subjects were identified as having a non-traumatic lower limb amputation with comparator, ertugliflozin 5 mg, or ertugliflozin 15 mg (Table 5).

While the limited number of events does raise questions as to whether the observation could be due to chance, the observed imbalance is concerning. This concern was expressed to the

applicant who noted that there are additional events in the ongoing CVOT, and that this data may be informative in considering this safety signal.

At the Division's request, the applicant provided the unblinded data on events of amputation that have occurred thus far in the CVOT. This was done via the dedicated, firewalled team so as to not impact the integrity of this ongoing trial. An additional 61 subjects have experienced at least one amputation event. Again, a higher incidence was seen with ertugliflozin than with comparator.

Table 5: Summary of amputation events in the ertugliflozin development program

	Ertu 5 mg	Ertu 15 mg	Comparator
Broad Pool [1]			
• n/N (%)	3/1716 (0.2)	8/1693 (0.5)	1/1450 (0.1)
• Event per 1000 patient-years exposed [2]	1.6	4.4	0.6
Interim CVOT Data			
• n/N (%)	26/2746(0.9)	19/2747 (0.7)	16/2744 (0.6)
• Event per 1000 patient-years exposed	6.8	5	4.3

Ertu = ertugliflozin; n = number of subjects with event; N = number of subjects per treatment arm; CVOT = cardiovascular outcomes trial
[1] does not include events from ongoing CVOT; [2] estimated based on [number of events / (number of subjects x mean exposure in days from Table 4 / 365)] x 1000
Source: Adapted from section 8.5.14 and Table 38 of Dr. Pucino's clinical review

In Dr. Pucino's review, he has considered the findings from both sources of safety data and believes that the data are sufficiently concerning to include this risk in the prescribing information for ertugliflozin. His concern is based on the increased incidence of events and the higher event rate seen in the ertugliflozin treated subjects. This was seen in both the Broad Pool (which excludes data from the CVOT), and in the interim data from the CVOT.

I agree with Dr. Pucino that this finding is concerning and should be included in the prescribing information.

The reason for the observed increased risk for amputations seen with canagliflozin is not known. Whether this represents a drug class concern or if it is a drug-specific safety issue is also unclear at this time. A similar signal has not been seen with the other two SGLT2 inhibitors, though the dapagliflozin database does not include data from a CVOT. The data from the EMPA-REG OUTCOME trial was searched extensively to ascertain whether a signal of risk could be found. No such signal was identified. In this context, it seems most appropriate to consider the findings for each individual drug rather than to invoke class labeling at this time. In examining the data from the ertugliflozin development program, the findings are concerning for an increased risk. Amputations occurred in a greater proportion of ertugliflozin treated patients. While the applicant has pointed to the absence of dose-dependence in the CVOT data, I do not believe this to be reassuring as the mechanism for the increased risk is not understood. The risk may not be dose dependent, or the dosage strengths studied may not be sufficiently different to identify a dose dependent effect.

Cardiovascular Risk Assessment:

In keeping with recommendations outlined in the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes [5], the applicant conducted a meta-analysis of the phase 2 and phase 3 studies to assess the cardiovascular safety of ertugliflozin. This included interim data from an ongoing blinded CVOT.

The results of the meta-analysis for cardiovascular safety excluded an upper bound of 1.8 from the 95% confidence interval for relative risk vs. comparator. For detailed discussion of the cardiovascular risk assessment see Dr. Elande Baro's statistical review.

9. Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting was held to discuss these NDAs.

10. Pediatrics

For ertugliflozin (NDA 209803), the applicant has requested a partial waiver for pediatric subjects < 10 years of age asserting that the population of patients in this age range is small and thus the necessary studies are impossible or highly impractical. The applicant has also requested a deferral for conduct of studies in pediatric subjects 10 to 17 years of age (inclusive) until the efficacy and safety of ertugliflozin have been confirmed in adults.

For the ertugliflozin + sitagliptin FCDP (NDA 209805), the applicant has requested a full waiver asserting that the FCDP does not represent a meaningful therapeutic benefit over existing therapies and that it is not likely to be used in a substantial number of pediatric patients.

For the ertugliflozin + immediate-release metformin FCDP (NDA 209806), the applicant has not proposed any additional clinical studies. The pediatric study to be conducted to evaluate ertugliflozin (NDA 209803) is planned to be on a background of metformin and would be relevant to this NDA.

These plans were discussed with the Pediatric Review Committee (PeRC) on November 14, 2017. The PeRC agreed with these plans.

11. Other Relevant Regulatory Issues

None.

[5] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf

12. Labeling

Prescribing Information

I recommend the following indications for these NDAs:

- NDA 209803 (ertugliflozin): adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

- NDA 209805 (ertugliflozin and sitagliptin): adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when both ertugliflozin and sitagliptin are appropriate

- NDA 209806 (ertugliflozin and metformin): adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are inadequately controlled on a regimen containing metformin or ertugliflozin, or in patients who are already treated with both ertugliflozin and metformin.

Additionally, I recommend the following changes be made to the prescribing information:

1. Given the apparent lack of efficacy in improving glycemic control in patients with an eGFR < 60 mL/min/1.73 m^2, ertugliflozin containing products should not be recommended for use in this population.

2. A Warning & Precaution for lower limb amputations should be included in the prescribing information for all three ertugliflozin containing products.

3. Tables should focus on data as related to HbA1c, and the number of figures should be limited as they do not necessarily provide additional data to support ertugliflozin's glucose lowering ability. The presentation of endpoints not related to glycemic control should be limited. Findings on weight and blood pressure should be descriptive only. One or two representative figures would be reasonable to communicate the expected time to glucose lowering effect.

4. The estimand proposed by the applicant should be replaced with values based on an analysis including data after rescue. This approach best preserves randomization, and does not ignore actual measured values. This also most accurately describes what occurred in the study as designed and conducted. Additional information can be included as a footnote to provide context given the relatively large impact of rescue in some of the studies (e.g., study p003) discussing the proportion of patients receiving rescue or without measurement at 26 weeks, and describing the change from baseline for those subjects with measurements at 26 weeks and without rescue medication.

5. Specific to the ertugliflozin + sitagliptin FCDP (NDA 209805), I recommend (b) (4)

(b) (4)

Other Labeling

The applicant has proposed the following proprietary names for these three drug products:

- NDA 209803 (ertugliflozin): STEGLATRO
- NDA 209805 (ertugliflozin and sitagliptin): STEGLUJAN
- NDA 209806 (ertugliflozin and immediate-release metformin): SEGLUROMET

These have been reviewed by the Division of Medication Error Prevention and Analysis who has not identified any concerns with the proposed proprietary names.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

I do not recommend a REMS for any of these NDAs.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Under the Food and Drug Administration Amendments Act, I recommend the following safety studies for ertugliflozin:

- A cardiovascular outcomes study to demonstrate that there is no increased cardiovascular risk with the use of ertugliflozin.

- Enhanced pharmacovigilance for ketoacidosis

Under the Pediatric Research Equity Act, I recommend the following study for ertugliflozin:

- An efficacy and safety study in pediatric patients (ages 10 to (b) (4) inclusive) with T2DM.

See the approval letter for additional details.

I do not recommend any PMRs or PMCs for the two FCDPs. The safety PMRs for the ertugliflozin mono-product will suffice for all three products, and the pediatric study will suffice for the ertugliflozin and metformin FCDP. No pediatric study will be required for the ertugliflozin and sitagliptin FCDP, as an appropriate study would likely not be feasible given the size of the pediatric population with T2DM.

14. Recommended Comments to the Applicant

None.

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

/s/

WILLIAM H CHONG
12/12/2017

MARY T THANH HAI
12/13/2017