CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214373Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 20, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 214373
Product Name and Strength:	Brenzavvy (bexagliflozin) tablet, 20 mg
Applicant/Sponsor Name:	Theracos Sub, LLC (Theracos)
OSE RCM #:	2021-2082-1
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels for Brenzavvy on January 20, 2023. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised Brenzavvy container labels (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 Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Conrad, A. Label and Labeling Review for Brenzavvy (NDA 214373). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Apr 1. RCM No.: 2021-2082.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 20, 2023

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/s/

ARIANE O CONRAD
01/20/2023 11:54:39 AM

IDALIA E RYCHLIK
01/20/2023 12:29:47 PM

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

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

Memorandum

Date: November 21, 2022

To: Suchitra M Balakrishnan., M.D., Medical Officer
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Supendeep Dosanjh, Regulatory Project Manager (DDLO)

Melinda Wilson, Associate Director for Labeling, DDLO

From: Tierra Butler, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP
Charuni Shah, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for BRENZAVVY (bexagliflozin) tablets, for oral use

NDA: 214373

Background:
In response to DDLO's consult request dated November 4, 2022. OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide (MG) for the original NDA for BRENZAVVY (bexagliflozin) tablets, for oral use.

PI/MG:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on November 8, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments sent under separate cover on 11/18/2022.

Thank you for your consult. If you have any questions, please contact Tierra Butler at (301) 796-1368 or tierra.butler@fda.hhs.gov.

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TIERRA N BUTLER
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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:	November 18, 2022
To:	Supendeep Dosanjh, PharmD, MLRHR, CSP Regulatory Project Manager Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
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:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD **Regulatory Review Officer** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	BRENZAVVY (bexagliflozin)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214373
Applicant:	Theracos Sub LLC

1 INTRODUCTION

On October 22, 2021, Theracos Sub, LLC submitted for the Agency's review An original New Drug Application (NDA) 214373 for BRENZAVVY (bexagliflozin) tablets. The proposed indication for BRENZAVVY (bexagliflozin) is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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 Diabetes, Lipid Disorders, and Obesity (DDLO) on December 15, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRENZAVVY (bexagliflozin) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft BRENZAVVY (bexagliflozin) MG received on October 22, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2022.
- Draft BRENZAVVY (bexagliflozin) Prescribing Information (PI) received on October 22, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2022.

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.

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.

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)

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/

KELLY D JACKSON
11/18/2022 01:46:33 PM

ANKUR S KALOLA
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LASHAWN M GRIFFITHS
11/18/2022 01:58:19 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

Division of Pediatrics and Maternal Health Review

Date of Consult Request:	June 27, 2022	**Date of Consult**:	September 6, 2022

From:	Christos Mastroyannis, M.D., Medical Officer, Maternal Health Division of Pediatrics and Maternal Health (DPMH)
Through	Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH
To:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
NDA Number:	214373
Drug:	Bexagliflozin (conditionally acceptable as Brenzavvy)
Applicant:	Theracos Sub, LLC
Indication:	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitation of Use: Not (b) (4) type 1 diabetes mellitus (b) (4) may increase the risk of diabetic ketoacidosis in these patients

Materials Reviewed

- Applicant's submission of October 22, 2021
- Division's Consult request of May 10, 2022, in DARRTS and Reference ID: 4981692

BACKGROUND

Regulatory History

The applicant, Theracos Sub, LLC submitted NDA 214373 for bexagliflozin, conditionally known as Brenzavvy, 20mg tablets for oral use on October 22, 2021. Bexagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The applicant has submitted this original application for approval under the 505(b)(1) pathway.
DDLO has requested DPMH to assist with the labeling to comply with the Pregnancy and Lactation

Labeling Rule (PLLR) format.

Drug Characteristics[1]

Half Life	11.7 hours
Molecular Weight	464.94 g/mol
Protein bound	93%

Mechanism of action: Bexagliflozin is a specific inhibitor of sodium-glucose co-transporter 2 (sodium-glucose linked transporter 2, SGLT2), the renal low-affinity, high-capacity concentrative transporter, responsible for reabsorption of the majority of glucose from the glomerular filtrate by the cells in the initial portion of the renal proximal tubule. SGLT2 co-transports glucose and sodium ions in 1:1 stoichiometry.

REVIEW

Pregnancy

Non Clinical Review

In animal studies, adverse renal changes were observed in rats when bexagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Dose exposures approximately 11 (males) or 139 (females) times that produced by the recommended dose in humans caused renal pelvic and tubular dilatations in rats that were not fully reversible. Bexagliflozin did not cause embryo-fetal toxicity or demonstrate evidence of teratogenic potential when administered to pregnant rats and rabbits during organogenesis at dose exposures up to 552 times or 368 times the exposure at the recommended human dose, respectively.[2] Bexagliflozin was not mutagenic or clastogenic with or without metabolic activation in the in vitro Ames bacterial mutagenicity assay.

Clinical Review

As per applicant, scarce information is available regarding the effects of bexagliflozin in human pregnancy. One clinical trial subject assigned to a bexagliflozin arm became pregnant but ceased dosing promptly following a positive pregnancy test, which occurred 45 days after the last menses. She subsequently delivered a healthy 3.61 kg boy by an uncomplicated induced C-section term delivery.

Reviewer Comment

Bexagliflozin is a specific inhibitor of sodium-glucose co-transporter 2, responsible for reabsorption of the majority of glucose from the glomerular filtrate by the cells in the initial portion of the renal proximal tubule. Dose-dependent increases in urinary glucose excretion (UGE) accompanied by increases in urine volume were observed in healthy subjects and in patients with type 2 diabetes following single- and multiple-dose administration of bexagliflozin. Therefore, increased diuresis is expected with the use of the drug (mode of action). The sentence in the labeling provided by the applicant, (b) (4) *has been deleted because in consultation with Clinical, it was agreed that this statement was not necessary. It is not present in the labelings of any of the other ..flozins.*

[1] (b) (4)

[2] As per non clinical evaluation and provided in the labeling

Applicant's Review
The applicant has not provided any additional information. Pregnant women were excluded from the clinical trials.

DPMH searched PubMed, Reprotox and GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation for use of bexagliflozin during pregnancy. No publications have been identified.

Summary
Bexagliflozin is a specific inhibitor of SGLT2. In animal studies, adverse renal changes were observed in rats when bexagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Based on animal findings, all SGLT2 inhibitors are not recommended during the second and third trimesters of pregnancy.

Lactation
Non Clinical Review
Bexagliflozin was excreted in the milk of lactating rats. On post-parturition day 14, bexagliflozin was found in the plasma of male and female offspring of rats administered 40 mg/kg/day at 2.3 and 2.2 times, respectively, the human Cmax for the 20 mg recommended human dose. Juvenile rats directly exposed to bexagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.[1]

Clinical Review
Neither the applicant nor this reviewer have identified any publications about bexagliflozin and lactation. Lactating women were excluded from clinical trials.

Summary
There is no information regarding the presence of bexagliflozin in human milk, the effects on the breastfed infant or the effects on milk production. When a drug is present in animal milk, it is likely that the drug will be present in human milk. 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. Therefore, bexagliflozin is not recommended when breastfeeding.

Females and Males of Reproductive Potential
No information was identified by either the applicant or this reviewer on the effects of bexagliflozin in females and males of reproductive potential. Therefore, because there are no recommendations about contraception or pregnancy testing prior or during treatment with bexagliflozin and because no effects on fertility have been identified, DPMH recommends subsection 8.3 Females and Males of Reproductive Potential to be omitted from the labeling.

CONCLUSION
Bexagliflozin is not mutagenic or clastogenic. Bexagliflozin is a specific inhibitor of SGLT2, the renal low-affinity, high-capacity concentrative transporter, responsible for reabsorption of the majority of glucose from the glomerular filtrate by the cells in the initial portion of the renal proximal tubule. SGLT2 co-transports glucose and sodium ions in 1:1 stoichiometry. Based on animal juvenile toxicity data showing adverse renal effects, bexagliflozin is not recommended during the second and third trimesters of pregnancy and is not recommended when breastfeeding. The available human data on use of bexagliflozin during pregnancy are insufficient to determine a

drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CHRISTOS MASTROYANNIS
09/06/2022 03:40:21 PM

TAMARA N JOHNSON
09/06/2022 04:18:53 PM

Clinical Inspection Summary

Date	July 15, 2022
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Division Director Jenn Sellers, M.D., Ph.D., Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Kristen Pluchino, M.D., M.P.H., Clinical Reviewer Michael Nguyen, M.D., Clinical Team Leader Supendeep Dosanjh, Pharm.D., Regulatory Project Manager Division of Diabetes, Lipid Disorders and Obesity (DDLO)
NDA #	214373
Applicant	Theracos Sub, LLC
Drug	Bexagliflozin
NME (Yes/No)	Yes
Review Priority	Standard
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Consultation Request Date	December 13, 2021
Summary Goal Date	August 22, 2022
Action Goal Date	September 22, 2022
PDUFA Date	October 22, 2022; Extended to January 22, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from six Phase 3 trials (Studies THR-1442-C-419, THR-1442-C-423, THR-1442-C-448, THR-1442-C-450, THR-1442-C-476 and THR-1442-C-480) were submitted to the Agency in support of this New Drug Application (NDA) for bexagliflozin, for the proposed indication of as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Eight domestic clinical investigators (CIs): Drs. Dario Altamirano, John Gabriel, Scott Rigby, Syal Parvin, Jane Rohlf, Teresa Sligh, Mohammad Tahir, and Jeffrey Wayne were inspected for these six studies.

Overall, the CI inspections found no significant regulatory violations. Based on the results of inspections and regulatory assessments, Studies THR-1442-C-419, THR-1442-C-423, THR-1442-C-448, THR-1442-C-450, THR-1442-C-476 and THR-1442-C-480 appear to have been conducted adequately, and the data generated by the CI sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Theracos Sub, LLC submitted an NDA for bexagliflozin oral tablets, a sodium-glucose linked transporter 2 (SGLT2) inhibitor, as an adjunct to diet and exercise to improve glycemic control in

adults with T2DM on 10/22/2021. Data from six Phase 3 studies THR-1442-C-419, THR-1442-C-423, THR-1442-C-448, THR-1442-C-450, THR-1442-C-476 and THR-1442-C-480 were submitted to support the approval of the drug.

Study THR-1442-C-419

Study THR-1442-C-419 was a Phase 3, randomized, double-blind, placebo-controlled study to evaluate bexagliflozin in subjects with T2DM who are not adequately controlled by metformin alone.

The primary study objective was to determine the placebo-corrected change in HbA1c from baseline to Week 24 in adults with T2DM who are not inadequately controlled by metformin alone. The primary efficacy endpoint was the change of HbA1c from baseline to Week 24.

All subjects took metformin at an optimal or near-optimal stable dose for ≥ 8 weeks prior to screening. Eligible subjects then entered a one week single-blind, placebo run-in period with diabetes education, diet, and exercise counseling. Subjects with HbA1c values ≥ 7.5% and ≤ 10.5% were randomized at a 1:1 ratio to receive oral bexagliflozin 20 mg or placebo once daily for 24 weeks, in addition to the open-label metformin at a stable dose and frequency. Up to 50 subjects who had HbA1c > 10.5% and ≤ 12.0% at screening were assigned to the high glycemic group to receive open-labeled bexagliflozin 20 mg tablets, in addition to metformin. Subjects were instructed to measure fasting self-monitored blood glucose (SMBG) daily and to contact the clinic if a fasting SMBG was ≥ 270 mg/dL from Week 0-6, ≥ 240 mg/dL after Week 6-12, or ≥ 200 mg/dL after week 12. Hyperglycemia was managed first with diet and exercise counseling and followed by rescue medication if hyperglycemia persisted. Clinic assessments were at Weeks 6, 12, 18, 24 and 26.

The study screened 521 subjects and randomized 351 subjects (included 34 subjects in the high glycemic group) at 45 study sites in the US (28) and Japan (17). The first subject was enrolled on 11/28/2017 and the last subject completed the study on 01/23/2019. A total of 311 subjects completed the study, including 28 subjects in the high glycemic group.

Study THR-1442-C-423

Study THR-1442-C-423 was a Phase 3, randomized, double-blind active-controlled study to evaluate the effects of bexagliflozin versus sitagliptin in subjects with T2DM who have inadequate glycemic control by metformin.

The primary objective was to demonstrate that bexagliflozin was non-inferior to sitagliptin by evaluating the treatment effect on HbA1c reduction at Week 24. The primary efficacy endpoint was that HbA1c reduction at Week 24.

Subjects who had taken metformin at a stable dose of ≥ 1500 mg/day for ≥ 8 weeks, completed a 1-week run-in period with diet and exercise counseling and met all eligibility criteria were randomized at a 1:1 ratio to receive once daily double-blind treatment of bexagliflozin 20 mg or placebo; or sitaglipin 100 mg or placebo for 24 weeks. Open-label metformin was taken at the same regimen. Clinic assessments were at Weeks 6, 12, 18, 24 and 26.

The study screened 563 subjects and randomized 386 subjects at 52 study sites in 6 countries: US (10), Czech Republic (5), Hungary (6), Poland (13), Spain (10), and Japan (8). The first subject was enrolled on 10/12/2017 and the last subject completed the study on 10/31/2018. A total of 369 subjects completed the study.

Study THR-1442-C-448

Study THR-1442-C-448 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the effect of bexagliflozin on HA1c in patients with T2DM and moderate renal impairment.

The primary objective was to determine the effectiveness of bexagliflozin for the reduction of HbA1c in patients with T2DM and moderate renal impairment. The primary efficacy endpoint was the change of HbA1c from baseline to Week 24.

All eligible subjects entered a one-week single-blind, placebo run-in period for diabetes education and optimization of compliance with diet and exercise. Eligible subjects with screening eGFR ≥ 30 and < 60 mL/min /1.73 m^2 and had stable GFR were randomized at a 1:1 ratio to receive bexagliflozin 20 mg or placebo orally once daily for 24 weeks. Background oral hypoglycemic agents (OHA) were taken with the same regimen. Clinic assessments were at Weeks 6, 12, 24 and 26.

The study enrolled 490 subjects and randomized 312 subjects at 54 study sites in 4 countries: US (22), France (5), Spain (9), and Japan (18). The first subject was enrolled on 09/23/2016 and the last subject completed the study on 01/11/2018. A total of 287 subjects completed the study.

Study THR-1442-C-450

Study THR-1442-C-450 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel group study to compare the efficacy and safety of bexagliflozin to placebo in subjects with T2DM and inadequate glycemic control.

The primary efficacy endpoint was the change in HbA1c from baseline to Week 24.

Eligible subjects who were not treatment naïve would discontinue taking their current OHA and entered a 6-week wash-out period. All eligible subjects started a 2-week single-blind placebo run-in period. Subjects who missed < 1 dose of the run-in product, had fasting blood glucose (FBG) ≥ 250 mg/dL on no more than two consecutive days, had an HbA1c 7-10.5% and a FBG < 250 mg/dL were randomized at a 2:1 ratio to receive oral bexagliflozin tablets 20 mg or placebo once daily for 24 weeks. Clinic assessments were at Weeks 6, 12, 18, 24 and 26.

The study screened 463 subjects, randomized 210 subjects at 23 study sites in the US (18) and Canada (5). The first subject was enrolled on 03/29/2016 and the last subject completed the study on 04/28/2017. A total of 188 subjects completed the study.

Study THR-1442-C-476

Study THR-1442-C-476 was a Phase 3, double-blind, placebo-controlled study to evaluate the effects of bexagliflozin on HA1c in patients with T2DM and increased risk of cardiovascular adverse events.

The primary efficacy endpoint was the placebo-adjusted change in HbA1c from baseline to Week 24.

The screening period was up to 21 days, during which subjects were assigned to the 3 cardiovascular risk groups per their medical history and received diet and exercise counseling. A subject qualified for more than one group was assigned to the group with the anticipated highest risk. Then eligible subjects entered the single-blind placebo run-in period and took placebo once daily for 13 ± 2 days. Adjustments of treatment for hypertension or dyslipidemia were not permitted. Subjects were not eligible for randomization if they had FBG ≥ 300 mg/dL on two or more consecutive days, had omitted > one dose of the run-in product, or were deemed inappropriate for the study by the investigator during the run-in period.

Randomization was stratified by HbA1c (> or ≤ 9.5%), eGFR (< or ≥ 60 mL/min/1.73 m^2), body mass index (BMI; < or ≥ 25 kg/m^2) and history of heart failure. Subjects were randomized at a 2:1 ratio to receive bexagliflozin 20 mg or placebo for 52 weeks. Office visits were at Weeks 6, 12, 24, 36 and 48. After week 48, clinic visits were every 24 weeks with a phone interview at 12 weeks after each clinic visit, until the 52 weeks treatments have completed. A follow-up visit was at 4 weeks after the conclusion of treatment.

During the first 24 weeks of the treatment period, hyperglycemia was managed with diet and exercise counseling and changes in the diabetic medical regimen if clinically indicated. Intensification of the antidiabetic regimen adhered to pre-formulated guidelines upon the report by a study subject of two fasting SMBG exceeding the following on consecutive days: ≥ 270 mg/dL from Week 1-6; ≥ 240 mg/dL between Week 6-12; and ≥ 200 mg/dL between Week 12-24. Rescue medications included any approved antidiabetic medication except an SGLT2 inhibitor. After Week 24, the investigator could adjust the anti-diabetic therapies if hypoglycemia occurred. Background OHAs were taken with the same regimen.

The study screened a total of 3270 subjects and randomized 1701 subjects at 167 study sites in 10 countries: US (71), Canada (13), Czech Republic (16), Denmark (3), Republic of Korea (8), Mexico (9), Netherlands (9), Poland (20), Russian (11), and Taiwan (7). The first subject was enrolled on 11/05/2015 and the last subject completed the study on 11/06/2019. A total of 1469 subjects completed the study.

Study THR-1442-C-480

Study THR-1442-C-480 was a Phase 3, randomized, double-blind, active-controlled study to evaluate the effects of bexagliflozin versus glimepiride in subjects with T2DM who have inadequate glycemic control by metformin.

The primary efficacy endpoint was the change in HbA1c from baseline to Week 60.

Subjects who completed the 2-week single-blind run-in period, during which they self-administer the bexagliflozin placebo and the glimepiride placebo once daily and remained eligible were randomized at a 1:1 ratio to the bexagliflozin arm (bexagliflozin 20 mg and glimepiride placebo each day) or the glimepiride arm (bexagliflozin placebo and glimepiride capsule, 2, 4 or 6 mg, each day). Subjects continued to take the same metformin regimen for the duration of the study. Randomization to each treatment arm was stratified by HbA1c at baseline visit (≤ or > 8.5%), treatment background (metformin or metformin plus another OHA), and eGFR at the screening visit (eGFR ≥ or < 90 mL/min/1.73 m^2). The treatment period was 96 weeks with a follow-up visit at Week 98 or two weeks after the last dose. Visits were at Weeks 2, 4, 6, 12, 24, 36, 48, 60, 72, 96 and 98.

The study screened a total of 812 subjects and randomized 427 subjects at 46 study sites in 4 countries: US (12), Germany (8), Poland (16), and Spain (10). The first subject was enrolled on 08/15/2016 and the last subject completed the study on 06/19/2019. A total of 357 subjects completed the 98-weeks study.

Rationale for Site Selection
Eight domestic CIs: Drs. Dario Altamirano, John Gabriel, Scott Rigby, Syal Parvin, Jane Rohlf, Teresa Sligh, Mohammad Tahir, and Jeffrey Wayne were requested for clinical inspections for the 6 Phase 3 studies in support of the application. These sites were selected based on enrolling a high number of subjects to the study that may have an impact in the review division's clinical decision-making process.

III. RESULTS (by Site)

NOTE: Site inspections focused on review of informed consent forms (ICFs), institutional review board (IRB) approvals and correspondences, Form FDA 1572s/investigator agreements, financial disclosures, training records, CI's and sub-CIs' qualifications with licenses, delegation of duties, protocols and protocol amendments, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records (including visit data, laboratory tests, HbA1c levels and ECGs), concomitant medication records, adverse events (AEs) and serious AEs (SAEs) reports, diabetic ketoacidosis (DKA) source, investigational product (IP) accountability, paper source documents with electronic Case Report Forms (eCRFs) entries and electronic data capture (EDC) audit, protocol deviations and related regulatory documents (e.g., staff training logs, Clinicaltrials.gov registration and records retention). Source records were compared to the sponsor's data line listings in the NDA submission.

1. Dario Altamirano, D.O. (Sites #1001 for THR-1442-C-450 and THR-1442-C-480)
900 West 49th Street, Suite 430
Hialeah, FL 33012

This CI was inspected on 01/24-02/09/2022 as a data audit for Studies THR-1442-C-450 and THR-1442-C-480. This was the fourth FDA inspection for Dr. Altamirano. Previous inspections were classified as no action indicated (NAI) in 2013, voluntary action indicated (VAI) in 2011 and 2018 for failure to inform subjects of new unanticipated risks, failure to re-consent subjects to the most current IRB approved ICF, and failure to review, and maintain safety labs.

For Study THR-1442-C-450, the study site screened 27 subjects, enrolled 18 subjects, randomized 14 subjects with 12 subjects completed the study. The first subject consented on 04/19/2016 and the last subject's last visit was on 03/17/2017. All source records were reviewed for the 27 screened subjects.

For Study THR-1442-C-480, the study site screened 20 subjects, enrolled 16 subjects, randomized 14 subjects with 10 subjects completed the study. The first subject consented on 09/29/2016 and the last subject's last visit was on 01/09/2019. All source records were reviewed for the 20 screened subjects.

In general, the submitted data were verifiable with source records reviewed at the study site. Primary efficacy data source of HbA1c level were verified with no discrepancy. There was no underreporting of SAEs. However, there was underreporting of AEs as described below.

At the end of the inspection, a Form 483 (Inspectional Observations) was issued with the Observation that "An investigation was not conducted in accordance with the signed statement of investigator".

Specifically,
1). Underreporting of AEs:
Study THR-1442-C-450:

- For Subject #(b) (6) (Bexagliflozin group), "abdominal cramps" (mild, resolved) on (b) (6) at Visit 5 and "UTI" (urinary tract infection; mild) on 1(b) (6) at Visit 9 were not reported. In addition, the subject's use of Cipro 500 mg to treat UTI was not reported as a concomitant medication use.
- For Subject #(b) (6) (placebo group), "hyperuricemia" with a uric acid level of 10.6 mg/dL on (b) (6) at Visit 10 was not reported.

Study THR-1442-C-480:

- For Subject #(b) (6) (Bexagliflozin group), 4 episodes of "hypoglycemia" based on SMBS readings of ≤ 70 on (b) (6) (68), (b) (6) (43), (b) (6) (70), and 1(b) (6) (44) were not reported.
- For Subject #(b) (6) (Bexagliflozin group), SMBG readings of ≤ 70 on (b) (6) (41) and on (b) (6) (36) were not reported.

Reviewer's Comments:

- *The review division may consider including the above AEs in the safety evaluation. The CI responded to the FDA 483 on 02/22/2022 and admitted the oversight of reporting the AEs and provided document trainings to the staff with new SOPs.*
- *Of note, for Study THR-1442-C-450, the FDA 483 listed Subject #(b) (6)'s "UTI" on (b) (6) at Visit 9 was not reported. In the 483 response submitted, the CI stated that the subject's urine culture on (b) (6) was negative and the subject was not treated subsequently. The event was not reported as an AE. For Study THR-1442-C-480, Subject #(b) (6) (Bexagliflozin group)'s "UTI" event at Visit 12 was reported at Visit 13 after a positive urine culture came back.*

2). Protocol deviations:
Study THR-1442-C-450:

- For Subject #(b) (6) (Bexagliflozin group), chemistry panel was not completed due to "incorrect specimen type" on (b) (6) at Visit 10.
- For Subject #(b) (6) (placebo group), DKA source record was not assessed for Visit 8 on (b) (6) and was not completed for Visit 10 and 11.

Study THR-1442-C-480:

- For Subject #(b) (6) (Glimepiride group), chemistry panel was not completed due to "required testing unavailable" on (b) (6) at Visit 11.
- For Subject #(b) (6) (Bexagliflozin group), urinalysis test was not completed due to "incorrect specimen type" on (b) (6) at Visit 15.
- Four subjects (Subject #(b) (6) and #(b) (6) in the Glimepiride group; Subjects #(b) (6) and #(b) (6) in the Bexagliflozin group) had a brief physical examination instead of the required full physical examination at Visit 18.
- Subject #(b) (6) did not use the sponsor provided glucometer for SMBG and missed SMBG readings for 5 days at Visit 11 on (b) (6). The subject did not have readings from Visit 12-18.

Reviewer's Comments:

- *The CI responded to the FDA 483 on 02/22/2022 and admitted the oversight of reporting the above protocol deviations and provided document trainings to the staff with new SOPs.*
- *Regarding the protocol deviations of not completing full physical exams on 4 subjects at Visit 18, an email from the sponsor on 11/06/2018 confirmed that the deviations were caused by the incorrect Visit 18 Forms that the sponsor provided. They are not the responsibilities of the CI. However, these should have been reported as protocol deviations.*
- *Of note, for Study THR-1442-C-480, the FDA 483 listed Subject #(b) (6)'s abnormal lipid panel (cholesterol of 306 mg/dL and triglyceride of 644 mg/dL) on (b) (6) at Visit 17 as not repeated. The lipid panel was repeated on (b) (6) with a cholesterol of 319 mg/dL and triglyceride of 453 mg/dL.*
- *Although the above protocol deviations should have been reported, these deviations are unlikely to have significant impact on the efficacy and safety results.*

2. John Gabriel, M.D. (Sites #1081 for THR-1442-C-476)
4351 Booth Calloway Road, Suite 101
North Richland Hills, TX 76180-7319

This CI was inspected on 03/22-25/2022 as a data audit for Study THR-1442-C-476. This was the fifth FDA inspection for Dr. Gabriel. The previous inspection in 02/2018 was classified as NAI.

The study site screened 51 subjects, enrolled 24 subjects, with 20 subjects completed the study. The first subject consented on 03/15/2016 and the last subject completed the study on 10/10/2019. All source records were reviewed for the 51 screened and 24 enrolled subjects.

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported.

Discussed items were:

- Concomitant medications use not documented in the eCRF
  - Insulin titration changes for Subjects #(b) (6) on (b) (6), #(b) (6) on (b) (6), #(b) (6) on (b) (6) and #(b) (6) on (b) (6)
  - Subject #(b) (6)'s use of rescue medication of Actos on (b) (6)
  - Subject #(b) (6)'s use of cipro for a UTI on (b) (6)
- Subject #(b) (6) did not have a "repeat test within 48-72 hours" to confirm hepatic enzyme elevation per the protocol, for an AST > 2.5 upper limit normal (ULN). The subject's retest in 4-8 weeks was < 2.5 ULN.

In general, the submitted data were verifiable with source records at the study site. Primary efficacy data source of HbA1c level were verified. Secondary efficacy data source of fasting plasma glucose and systolic blood pressure were also verified. There were no underreporting of AEs or SAEs. A Form 483 (Inspectional Observations) was not issued.

3. Scott Rigby, M.D. (Site #1020 for THR-1442-C-448)
4466 Darrow Road
Stow, OH 44224

This CI was inspected on 01/24-28/2022 as a data audit for Study THR-1442-C-448. This was the first FDA inspection for Dr. Rigby.

The study site screened 21 subjects, enrolled 17 subjects, with all 17 subjects completed the study. The first subject consented on 09/27/2016 and the last subject completed the study on 08/14/2017. All source records were reviewed for the 21 screened and 17 enrolled subjects.

The submitted data were verifiable with source records at the study site. The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The primary efficacy data source of HbA1c levels were verified with no discrepancies noted. There were no underreporting of AEs or SAEs. A Form 483 (Inspectional Observations) was not issued.

4. Parvin Syal, M.D. (Site #1004 for THR-1442-C-480)
1174 Amazon Way
Simi Valley, CA 93065

This CI was inspected on 02/07-11/2022 as a data audit for Study THR-1442-C-480. This was the first FDA inspection for Dr. Syal. Dr. Syal started the study as a sub-CI on 01/04/2018 and became the CI on 03/25/2019 when the site's original CI, Dr. Juan Frias, became the sub-CI due to "workload balance". The change of PI was approved by the IRB on 03/25/2019 and was reported to the FDA.

The study site screened 56 subjects, enrolled 28 subjects, with 20 subjects completed the study. Six subjects were lost to follow up, one subject withdrew the consent due to schedule conflict and one subject (#(b) (6)) withdrew after an SAE of myocardial infraction. The first subject consented on

09/08/2016 and the last subject completed the study on 04/18/2019. Source records of 25/28 enrolled subjects were reviewed.

The inspection found adequate source documentation for the inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source of HbA1c levels were verified with no discrepancies found. There was no underreporting of SAEs. A Form 483 (Inspectional Observations) was not issued.

It was noted that Subject # (b) (6)'s "fatigue" with a SMBS of 65 on (b) (6) was not reported as an AE of hypoglycemia.

Reviewer's Comment:
Subject # (b) (6) was randomized in the Glimepiride control group and a SMBS of 65 was recorded before dinner due to "skipped meal" per source record.

5. Jane Rohlf, M.D. (Site #1037 for THR-1442-C-419, THR-1442-C-423 and THR-1442-C-450)
708 Chambers Street
Trenton, NJ 08611

This CI was inspected on 03/28-31/2022 as a data audit for Studies THR-1442-C-419, THR-1442-C-423 and THR-1442-C-450. This was the fourth FDA inspection for Dr. Rohlf. The last inspection was in May 2018 and was classified as NAI.

For Study THR-1442-C-419, the study site screened 9 subjects, enrolled 7 subjects, with all 7 subjects completed the study. The first subject consented on 04/06/2018 and the last subject completed the study on 01/14/2019. Source records of all 9 screened subjects were reviewed.

For Study THR-1442-C-423, the study site screened and enrolled 6 subjects, with 5 subjects completed the study. The first subject consented on 11/09/2017 and the last subject completed the study on 07/02/2018. Source records of all 6 enrolled subjects were reviewed.

For Study THR-1442-C-450, the study site screened 10 subjects, enrolled 3 subjects, with all 3 subjects completed the study. The first subject consented on 04/18/2016 and the last subject completed the study on 02/02/2017. Source records of all 10 screened subjects were reviewed.

The inspection found adequate source documentation for the inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source of HbA1c levels were verified with no discrepancies. There were no underreporting of AEs or SAEs. A Form 483 (Inspectional Observations) was not issued.

6. Teresa Sligh, M.D. (Site #1375 for THR-1442-C-419)
6400 Laurel Canyon Blvd. Suite 300A
North Hollywood, CA 91606

This CI was inspected on 03/23-28/2022 as a data audit for Study THR-1442-C-419. This was the second FDA inspection for Dr. Sligh. Previous inspection in 07/2016 was VAI for not retaining IPs for a bioequivalence study.

The study site screened 33 subjects, enrolled 21 subjects, with 13 subjects completed the study. The first subject consented on 12/12/2017 and the last subject's last visit was on 12/18/2018. Source records of 22/33 screened subjects were reviewed.

The inspection found adequate source documentation for the inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source of HbA1c levels were verified with no discrepancies found. The secondary efficacy endpoint data of weight and systolic blood pressure were verified for 8 random selected subjects with no discrepancies. There were no underreporting of AEs or SAEs. A Form 483 (Inspectional Observations) was not issued. The IP accountability was verified with no concerns.

Protocol deviations were noted including Subject #(b) (6)'s out of window visit for Visits 7 and 8; and Subject #(b) (6)'s miss of 10 SMBS readings. These were not listed in the major protocol deviation list.

7. Mohammad Tahir, M.D. (Site #1054 for THR-1442-C-476)
11155 Dunn Road, Suite 315E
St. Louis, MO 63136

This CI was inspected on 02/08-14/2022 as a data audit for Study THR-1442-C-476. This was the first FDA inspection for Dr. Tahir.

The study site screened 92 subjects, enrolled 48 subjects, with 37 subjects completed the study. The first subject consented on 12/14/2015 and the last subject completed the study on 10/10/2019. Source records of 25/48 enrolled subjects and 10 screen failed subjects were reviewed.

The inspection found adequate source documentation for the inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source of HbA1c levels were verified with no discrepancies. Secondary efficacy endpoints were also verified. There were no underreporting of AEs or SAEs. A Form 483 (Inspectional Observations) was not issued.

8. Jeffrey Wayne, M.D.
(Site #1357 for THR-1442-C-423, Site #1058 for THR-1442-C-448 and THR-1442-C-476)
160 Gateway Drive, Suite 100
Lincoln, CA 95648

This CI was inspected on 03/14-25/2022 as a data audit for Studies THR-1442-C-423, THR-1442-C-448 and THR-1442-C-476. This was the first FDA inspection for Dr. Wayne.

For Study THR-1442-C-423, the study site screened and enrolled 2 subjects, with both subjects completed the study. The first subject consented on 12/01/2017 and the last subject's last visit was on 06/29/2018. Source records of both the subjects were reviewed.

For Study THR-1442-C-448, the study site screened 4 subjects, enrolled 2 subjects, with 1 subject completed the study (1 subject was lost to follow up). The first subject consented on 04/12/2017 and the last subject completed the study on 11/16/2017. Source records of all 4 screened subjects were reviewed.

For Study THR-1442-C-476, the study site screened 39 subjects, enrolled 19 subjects, with 15 subjects completed the study. Four subjects did not complete the study: two subjects due to AEs or SAEs (Subjects #(b) (6) and (b) (6)), 1 subject withdrew consent (Subject #(b) (6)), and 1 subject due to relocation (Subject #(b) (6)). The first subject consented on 11/16/2015 and the last subject completed the study on 10/03/2019. Source records of all 19 enrolled subjects were reviewed.

The inspection found adequate source documentation for the inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source of HbA1c levels were verified with no discrepancies. There were no underreporting of AEs or SAEs. At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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OSI\DCCE\Program Analysts\Yolanda Patague

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/s/

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JENN W SELLERS
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	April 1, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 214373
Product Name, Dosage Form, and Strength:	Brenzavvy (bexagliflozin) tablet, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Theracos Sub, LLC (Theracos)
FDA Received Date:	October 22, 2021 and November 29, 2021
OSE RCM #:	2021-2082
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Brenzavvy (bexagliflozin), the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed Brenzavvy prescribing information and container labels for areas of vulnerability that may lead to medication errors.

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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our 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 prescribing information (PI) and container labels for Brenzavvy to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We identified some areas of concern for the proposed PI and the proposed container labels, and we provide our recommendations below in Section 4.1 for the Division and Section 4.2 for Theracos.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for Brenzavvy are not acceptable from a medication error perspective and we have provided recommendations below in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF DIABETES, LIPID DISORDERS, AND OBESITY (DDLO)

A. Prescribing Information

1. Dosage and Administration Section 2

    a. We recommend revising the recommended dosage statement in Section 2.1 to read as follows for improved clarity: "The recommended dose of BRENZAVVY is 20 mg once daily in the morning with or without food."

4.2 RECOMMENDATIONS FOR THERACOS SUB, LLC

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

A. Container Labels

1. We note that the established name for drug products should include the finished dosage form. Therefore, we recommend revising the presentation of the established name to include the "tablet" dosage form as follows: "(bexagliflozin) tablet". In addition, after moving "tablet" to a separate line, we recommend listing the strength as "20 mg" below the established name and using a larger font for improved visibility.
2. We note that the statement "each tablet contains: bexagliflozin 20 mg" is located on the principal display panel (PDP). However, we note that this statement is duplicative; thus, we recommend moving this information to the side panel.
3. To ensure consistency with the Prescribing Information, we recommend that you revise the statement, (b) (4) to read "Dosage: See prescribing information" per 21 CFR 201.55. In addition, relocate this statement on the label's side panel as it is not required on the PDP.
4. We note (b) (4) While the net quantity statement should appear on the PDP, this information should be less prominent than the statement of strength (e.g., it should not be highlighted, boxed, or bolded). Therefore, we recommend removing (b) (4).
5. Decrease the prominence of the statement "Rx Only" by removing the bold font as this information appears more prominent than the established name and product strength on the principal display panel.
6. We note that your proposed prescribing information indicates that there will be a Medication Guide for your product. However, we note that you did not submit one for review. Therefore, we recommend that you submit your proposed Medication Guide for review. In addition, add the statement "Dispense the enclosed Medication Guide to each patient" on the PDP per 21 CFR 208.24(d).
7. We note that the NDC numbers are currently denoted by a placeholder (82381-XXXX-XX) and we request that you submit this information for review.

8. We note that the GTIN number (denoted by a placeholder) is currently located on the PDP. Move this statement to the label's side panel as it is not required on the PDP.
9. As currently presented, there are two barcodes on the bottle label in very close proximity. Since the linear barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers. Therefore, we recommend you increase the white space around the barcode containing the NDC number, and present it in a size that does not compete with or distract from the presentation of other required or recommended information on the label.
10. Remove the (b) (4) on the side panel as that is not required information
11. We note the statement (b) (4) appears on the PDP; however, it doesn't appear that this statement is consistent with the information in the prescribing information. Please provide your justification for including this information on the are label.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brenzavvy received on November 29, 2021, from Theracos Sub, LLC.

Table 2. Relevant Product Information for Brenzavvy	
Initial Approval Date	N/A
Active Ingredient	bexagliflozin
Indication	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Route of Administration	oral
Dosage Form	tablet
Strength	20 mg
Dose and Frequency	20 mg once daily
How Supplied	30 and 90 count bottles
Storage	Store at 25 °C (77 °F); excursions permitted to 15 – 30 °C (59 – 86 °F) [see USP Controlled Room Temperature]

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Brenzavvy labels and labeling submitted by Theracos Sub, LLC.

- Container labels received on November 29, 2021
- Prescribing Information received on November 29, 2021
    - \\CDSESUB1\evsprod\nda214373\0005\m1\us\draft-labeling-text.docx

B.2 Label and Labeling Images

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

ARIANE O CONRAD
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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 6, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Supendeep Dosanjh
DDLO

Subject: QT Consult to NDA 214373 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/12/2021 regarding the sponsor's QT related question. We reviewed the following materials:

- Thorough QT Clinical Study Report (NDA214373 / 0001; link);
- Previous IRT review(s) for IND 103822 dated 10/30/2013 in DARRTS (Link);
- Summary of clinical pharmacology studies (NDA214373/001; Link);
- BRENZAVYY proposed labelling (NDA214373 / 001; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA214373 / 001; link).

1 Responses for the review division

Question from the review division: We request that the IRT-CS confirm that the sponsor's QT assessment is sufficient to support NDA 214373 as well at the proposed labeling language for cardiac electrophysiology

IRT's response to the review division: *We have previously reviewed the the sponsor's TQT study report and data under IND* 103822 *and confirm that a single dose of 100 mg bexagliflozin does not cause drug related QT prolongation. This study is sufficient to support NDA214373. We have proposed labelling language for cardiac electrophysiology which is based on recommendations in the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.*

2 Internal Comments for the Division

- *NA*

3 BACKGROUND

Bexagliflozin is a sodium-glucose co-transpoter 2 (SGLT2) inhibitor that is proposed for improvement of glycemic control, in adjunct to diet and exercise, in adults with type 2 diabetes mellitus. The recommended therapeutic dosing for this indication is 20 mg once daily, taken in the morning with or without food. The highest exposure scenario is when bexagliflozin is administered with food causing about 1.3-fold increase in Cmax, a higher fold increase compared to effects of hepatic impairment (1.06-fold) or drug interaction with exenatide (1.25-fold increase). The reported bexagliflozin geometric mean Cmax when co-administered with food was 176 ng/mL.

The sponsor conducted a thorough QT study to assess proarryhthimic potential of bexagliflozin. Based on the results from the IUT analysis of the partially double blind, randomized, 3-period cross-over study which assessed ECG effects of 100 mg dose of bexagliflozin, the sponsor concluded that, at exposures up to 100 mg dose, bexagliflozin does not have QT prolongation risk (negative TQT study). The studied dose of 100 mg meets the recommendation for exposure coverage in a TQT study, since it produced mean Cmax of 1276 ng/ml, which is 7.25-fold higher than Cmax at the highest exposure scenario.

The sponsor's TQT study results were previously reviewed by the QT-IRT, and the reviewer's independent analysis of the TQT data yielded similar results to those reported by the sponsor.

The sponsor has compiled a New Drug Application package with the following proposed labelling language with regard to ECG effects of bexagliflozin. Our changes are highlighted (addition, ~~deletion~~). We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

Cardiac Electrophysiology

(b) (4)

At 5 times the maximum recommended dose, DRUG does not prolong the QTc interval to any clinically significant extent.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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