CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218230Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns
Version: 2024-09-13

Date:	03/13/2025
Product Name(s):	Gepotidacin (BLUJEPA)
Application Type/Number(s):	NDA 218230
Sponsor/Applicant:	GlaxoSmithKline
NEXUS Task Tracking Tool ID #:	2024-10261
Reviewer(s):	Ikponmwosa Osaghae, MD, PhD, Epidemiologist, Division of Epidemiologist II Yan Li, PhD, Team Lead (Acting) Division of Epidemiology II Natasha Pratt, PhD, Master Epidemiologist Division of Epidemiology II
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Sentinel Program Lead:	Patricia Bright, PhD, MSPH

1. BACKGROUND INFORMATION

1.1. Medical Product

BLUJEPA (gepotidacin), a first-in-class triazaacenaphthylene bacterial type II topoisomerase inhibitor is indicated for the treatment of uncomplicated urinary tract infections (uUTI) among female adults, and pediatric patients 12 years of age and older weighing at least 40 kilograms (kg). The proposed dose is 1500mg taken twice daily for five days. Gepotidacin is a new molecular entity (NME) and is under a priority review with a PDUFA goal date of March 26, 2025.

1.2. Describe the Safety Concern

Data from animal studies suggest safety signals of adverse pregnancy outcomes. In embryo-fetal development studies, decreased fetal weights were observed in rats at gepotidacin doses of 450 mg/kg/day or greater (approximately equal to the maximum recommended human dose [MRHD]). In mice, decreased fetal weights and increased late fetal resorptions were observed at gepotidacin doses of 500 mg/kg/day or greater (approximately 0.8-times the MRHD). No malformations were observed in rats or mice at exposures up to 750 mg/kg/day (approximately 4-times the MRHD) or 1,000 mg/kg/day (approximately 3-times the MRHD), respectively. More so, in pre- and post-natal developmental study in mice, there was no evidence of fetal or developmental toxicity throughout pregnancy and lactation at doses of 1,000 mg/kg/day (approximately 3-times the MRHD).

Although pregnant women were excluded from the clinical trials during the clinical development program, the Applicant reported one pregnancy in a subject in Trial 212390 who completed a full five-day course of gepotidacin. The first day of her last menstrual period was about 2.5 weeks before her first dose of gepotidacin. She reported pregnancy between test-of-cure (day 12) and follow-up visit (day 32). However, the outcome of the pregnancy was unknown as the subject was lost to follow-up.

Given the first-in-class new molecular entity status, safety signals in animal studies at doses close to the MRHD, and the potential widespread use in treatment of uUTI, a common condition in pregnancy, additional data in the post marketing setting is needed to evaluate the safety of gepotidacin in pregnancy. Based on the available data, the strength of the primary safety concern for small-for-gestational-age births (decreased fetal weights) is at a moderate level, while the strength of the safety concern for spontaneous abortions (increased late fetal resorptions) is at a low level.[a] Although animal studies did not reveal signals for other adverse pregnancy outcomes such as major congenital malformations, still births, and preterm births, there is need to further examine these adverse pregnancy outcomes, especially since the clinical relevance of these animal data to humans is unclear.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Ensure that the selected purpose(s) is consistent with the other PMR documents in DARRTS. More than one purpose may be chosen.

☐ Assess a known serious risk

[a] Strength of safety concern takes into account both the signal strength (magnitude of the association, quality of the source of safety information, and validity and reliability of the data to support the safety signal) and the level of clinical concern (seriousness of the safety concern, magnitude of risk, and prevalence of exposure).

☒ Assess signals of serious risk
☐ Identify unexpected serious risk when available data indicate potential for serious risk

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant individuals exists and exposure is expected.
☐ No approved indication in pregnant individuals, but practitioners may use product off-label in pregnant individuals.
☒ No approved indication in pregnant individuals, but there is the potential for inadvertent exposure before a pregnancy is recognized.
☒ No approved indication in pregnant individuals but use in individuals of childbearing age is a general concern.

2.2. Regulatory Goal[b]

☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest*.
☒ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome*.
☐ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a targeted or multiple safety concern(s)/health outcome(s)*.
  ☐ Targeted evaluation of specific safety concern
  ☐ Simultaneous identification of multiple unspecified adverse outcomes

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☐ Other, please specify: *Click here to enter text.*

2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.

Epidemiologic Domain	Explanation on ARIA insufficiency

[b] Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.

☐ Study Population	
☐ Exposures (and Comparators)	
☒ Outcomes	Small-for-gestational-age (SGA) births. The performance of code-based algorithms to capture SGA births in previous validation studies is inconsistent with positive predictive values (PPVs) ranging from 34% to 92% across ICD-9 and ICD-10 coding eras.[c,d,e,f] Of note, the only available study in the ICD-10 coding era found a PPV of 34%.[2] Therefore, it is unclear how well an ICD-10 code based algorithm would perform in the Sentinel system. Given that the purpose of PMR is signal refinement, it is necessary to require outcome validation or chart review to accurately define SGA and minimize outcome misclassification. ARIA is insufficient due to the lack of access to medical charts.
☐ Covariates	
☐ Analytic Tools	
Overall ARIA sufficiency determination	
☒ Insufficient ☐ Sufficient	

2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.

PMR-1: Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a registry-based cohort study design that compares the maternal, fetal, and infant outcomes of women exposed to gepotidacin during pregnancy with comparator population(s) unexposed to gepotidacin. Align the study protocol with protocol(s) outside the U.S. to reach a target sample size.

The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR-2: Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess small-for-gestational-

[c] Chomistek AK, Phiri K, Doherty MC, et al. Development and Validation of ICD-10-CM-based Algorithms for Date of Last Menstrual Period, Pregnancy Outcomes, and Infant Outcomes. Drug Safety. 2023;46(2):209-222.
[d] He M, Huybrechts KF, Dejene SZ, et al. Validation of algorithms to identify adverse perinatal outcomes in the Medicaid Analytic Extract database. Pharmacoepidemiology Drug Safety. 2020;29(4):419-426.
[e] Phiri K, Hernandez-Diaz S, Tsen LC, et al. Accuracy of ICD-9-CM coding to identify small for gestational age newborns. Pharmacoepidemiology Drug Safety. 2015 Apr;24(4):381-8.
[f] Wang X, Wang Y, Zhu Y, et al. Validation of Diagnosis Codes for Low Birth Weight and Small-for-Gestational Age in the Medicaid Analytic Extract Database. American Journal of Epidemiology. 2025;14:kwae472.

age births, spontaneous abortions, major congenital malformations, stillbirths, and preterm births in individuals exposed to gepotidacin during pregnancy compared to appropriate comparator population(s).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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CDER Division of Neurology 1

Consultation for Division of Anti-Infectives

NDA:	218230
Drug:	Blujepa (gepotidacin) tablet
Sponsor:	GlaxoSmithKline LLC (GSK)
Proposed Indication:	Uncomplicated UTI in females ≥12 years of age
Consultation Requestor:	Rebecca Levorson, MD CDER/OND/OID/DAI
Date Review Completed:	2/10/2025
Reviewer:	Julie Goldrich, MD Division of Neurology I

Gepotidacin is a triazaacenaphthylene antibacterial indicated for the treatment of uncomplicated urinary tract infections (uUTI) in female adults and adolescents from 12 years of age. This consult reviews the possibility of acetylcholinesterase inhibition contributing to the adverse events identified in the New Drug Application (NDA) for gepotidacin submitted July 26, 2024, to identify potential risks, mitigation strategies and appropriate labeling.

I. Background

On October 3, 2024, the Division of Neurology I (DNI) received a consult from the Division of Anti-infectives (DAI) to aid in determining whether dysarthria, an adverse event identified in several cases in the clinical studies submitted with the new drug application (NDA) 218230, was secondary to the use of gepotidacin. Non-clinical and Phase 1 studies identified acetylcholinesterase inhibition (AChE-I) adverse events associated with gepotidacin administeration and additional nonclinical studies confirmed mild reversible AChE-I. While most adverse events (AEs) attributed to AChE-I have manifested as gastrointestinal AEs, other potentially AChE-I associated AEs have been reported. Although many of these AChE-I associated AEs have been nonspecific (e.g., headaches, dizziness, fatigue, tachycardia), six cases of dysarthria have been reported, including one serious adverse event (SAE) of dysarthria for which a neurological evaluation was conducted. In response to an information request, the applicant has provided patient narratives for the six subjects who developed dysarthria after exposure to gepotidacin. Those cases, as well as other signs and symptoms of acetycholinesterase inhibition, are reviewed in this consult to determine causation and need for specific labeling to highlight these clinical concerns in the Prescribing Information (PI).

II. Introduction

Acute cholinergic symptoms secondary to acetylcholinesterase inhibition can present with a myriad of clinical findings. These signs and symptoms are caused by the stimulation of both muscarinic and nicotinic receptors. Stimulation of muscarinic receptors can lead to hypotension, skin erythema, miosis, visual disturbances, salivation, lacrimation, bronchorrhea, bronchospasm, diaphoresis, abdominal pain, vomiting, diarrhea, urination (incontinence), bradycardia, heart block or prolonged QTc. Stimulation of nicotinic receptors can cause tremor, fasciculations, proximal muscle weakness, paralysis, decreased

tendon reflexes, tachycardia, and hypertension.[1] Other symptoms including muscle spasms, headaches and seizures have been described.

There are several AChE-I's currently on the market to treat diseases such as Alzheimer's dementia, Parkinson's dementia, myasthenia gravis and for reversal of non-depolarizing neuromuscular blocking agents post operatively. This class of drugs includes, but is not limited to, donepezil, rivastigmine, galantamine, pyridostigmine, and neostigmine. Among the more prominent side effects seen in these drugs is gastrointestinal disturbances. However, other side effects which may be attributed to cholinergic activity have been described, including cardiovascular conditions, muscle weakness, tremors, seizures, headaches, pulmonary conditions etc. In the post marketing experience section of the USPI for neostigmine they list dysarthria under nervous system disorders. Case reports have indicated that it may be a manifestation of cholinergic activity secondary to drugs or toxins.

One drug of interest is irinotecan, a topoisomerase inhibitor indicated for the treatment of colon and rectal cancer. Several case reports have been identified describing transient dysarthria post administration. One case involved a 46-year-old patient with metastatic rectal carcinoma who developed repeated transient dysarthria, in the absence of other neurological symptoms, following each administration of irinotecan. Patient underwent MRI imaging, which was normal, and comprehensive medical assessment. During an evaluation by an otolaryngologist and speech therapist, it was determined that his dysarthria was secondary to "reduced capacity in fine-tuning of motor functions of the tip of the tongue", an area innervated by the hypoglossal nerve. This nerve is particularly susceptible to acetylcholine stimulation given the high density of muscarinic cholinergic receptors as compared to other brainstem nuclei. The parent compound of irinotecan binds to the active site of acetylcholinesterase and causes functional inhibition. The author hypothesized that given irinotecan's known cholinergic effects this was likely the underlying cause of his dysarthria.[2]

In another article by Matsuoka et al. they detail a case of a 64-year-old male who developed dysarthria after folfirinox treatment (combined fluorouracil, leucovorin, irinotecan and oxaliplatin), as well as reviewed four cases of dysarthria among the nine patients who had received folfirinox at their hospital. In the case of the 64-year-old male patient, the dysarthria was accompanied by rhinitis, diaphoresis, acute onset diarrhea and abdominal pain 90 minutes after starting the irinotecan infusion, lasting 2 hours. In all cases, dysarthria occurred during infusion, persisted for several hours, and then rapidly resolved. Neurological exams and imaging identified no abnormalities. Atropine was given prophylactically for subsequent doses and effectively prevented or alleviated dysarthria. All cases had complete resolution and no dose reduction or treatment interruption occurred.[3] Given the known biological plausibility, positive rechallenges, and response to atropine treatment, it is likely that cholinergic activity was responsible for the dysarthria in these cases.

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[1] Attalla M, Alshamsi F, Perri D, Klimaszyk D. Cholinergic Syndrome (Cholinergic Toxicity). McMaster Textbook of Internal Medicine. Kraków: Medycyna Praktyczna. https://empendium.com/mcmtextbook/chapter/B31.II.20.12. Accessed October 08, 2024.

[2] Dressel AJ, van der Mijn JC, Aalders IJ, Rinkel RN, van der Vliet HJ. Irinotecan-induced dysarthria. Case Rep Oncol. 2012 Jan;5(1):47-51. doi: 10.1159/000336156. Epub 2012 Jan 18. PMID: 22379477; PMCID: PMC3290033.

[3] Matsuoka A, Maeda O, Inada-Inoue M, Ohno E, Hirooka Y, Yokoyama Y, Fujii T, Nagino M, Goto H, Ando Y. FOLFIRINOX-induced reversible dysarthria: A case report and review of previous cases. Oncol Lett. 2015 Oct;10(4):2662-2664. doi: 10.3892/ol.2015.3591. Epub 2015 Aug 11. PMID: 26622908; PMCID: PMC4579986.

In a case report by Ramiirez et al[4], they discuss a case of a 35-year-old female with metastatic colon cancer who experienced dysarthria during her first irinotecan infusion. The dysarthria was accompanied by subjective tongue swelling and bilateral blepharospasm which began 30 minutes into the start of the infusion and began to improve within 1 hour. Treatment was briefly stopped, and patient was treated with famotidine, diphenhydramine, and dexamethasone. After there was substantial improvement in symptoms, the infusion was resumed. The patient experienced only brief episodes of slurred speech during the remainder of the infusion with complete resolution of symptoms after 24 hours. Despite attempts to increase time of infusion, pt developed dysarthria with several subsequent doses. This case is of particular interest given the blepharospasm. Blepharospasm was also identified with one of the patients who developed dysarthria in the gepotidacin study.

While dysarthria remains a rare complication of treatment with irinotecan, these cases propose a plausible mechanism by which other medications with identified acetylcholinesterase inhibition may also manifest with dysarthria. This concern would be further strengthened by the simultaneous presence of other cholinergic symptoms.

III. Overview of Acetylcholinesterase Adverse Events

Gastrointestinal (GI) disturbances are the most common adverse event seen across the class of acetylcholinesterase inhibitors. The most frequently reported gastrointestinal manifestations are nausea, vomiting, and diarrhea. In the pooled Phase 3 studies for gepotidacin, GI potential AChE-I adverse events (AEs), including abdominal pain, nausea/vomiting and diarrhea occurred in 351/1570 (22%) of participants taking gepotidacin as compared to 124/1558 (8%) of participants taking nitrofurantoin. Symptoms typically occurred within 12 hours of study dose but were tabulated up to 60 hours after a dose. Most symptoms were either mild (Grade 1) or moderate (Grade 2) in severity.

Non-GI potential AChE-I adverse events occurred infrequently in Phase 1 and Phase 2 studies with documented symptoms of lacrimation, diaphoresis (hyperhidrosis and “cold sweat”), dyspnea and dysarthria. These events were also only mild (Grade 1) or moderate (Grade 2) in severity. None of the cases reported a serious adverse event (SAE).

In the pooled Phase 3 studies, non-GI potential AChE-I adverse events occurred in~2% of participants. In the gepotidacin treatment group 24/1570 (1.5%) participants developed non-GI adverse events as compared to 33/1558 (2.1%) in participants treated with nitrofurantoin. In the 24 patients in the gepotidacin treated group 77 adverse events were reported as compared to 66 adverse events in the 33 subjects in the nitrofurantoin treated group. Non-GI potential AChE-I search terms were kept broad, at the expense of specificity, which may explain the higher-than-expected number of cases seen in the active control group. The breakdown of non-GI potential AChE-I adverse events in the two pivotal Phase 3 studies are included in the following table.

[4] Ramirez KG, Koch MD, Edenfield WJ. Irinotecan-induced dysarthria: A case report and review of the literature. J Oncol Pharm Pract. 2017 Apr;23(3):226-230. doi: 10.1177/1078155216634181. Epub 2016 Jul 8. PMID: 26911479.

Adverse Event	Gepotidacin Treatment Group	Nitrofurantoin Treatment Group
Asthenia	2	2
Fatigue	9	6
Muscle spasms	3	2
Dizziness	23	16
Dysarthria	2	0
Headache	27	34
Pre-syncope	1	0
Tremor	1	1
Seizure	0	1
Insomnia	1	0
Dyspnea	3	2
Rhinorrhea	2	0
Hyperhidrosis	3	2
Total Events	77	66

All non-GI potential AChE-I adverse events in the Phase 3 studies were determined to be mild (Grade 1) or moderate (Grade 2) in severity with the exception of one case identified as a serious adverse event. This case involved a patient in the gepotidacin treatment group who experienced recurrent episodes of dysarthria which was a SAE (Grade 3) after patient required hospital evaluation and recommended overnight observation. This case will be discussed further in the subsequent section. The median duration of the events was 1 day for the gepotidacin treatment group and 2 days for the nitrofurantoin treatment group.

A significant percentage of the subjects experiencing AChE-I adverse events experienced 2 or more AChE-I event (119/375, 32%) with one subject experiencing up to 7 adverse events. See table below.

	Gepotidacin N=1570	Nitrofurantoin N=1558
Total # of Subjects with AChE-I AE	375	160
1 AChE-I AE	256 (16.3%)	124 (8%)
2 AChE-I AE	80 (5.1%)	23 (1.5%)
3 AChE-I AE	25 (1.6%)	10 (0.6%)
4 AChE-I AE	11 (0.7%)	3 (0.2%)
5 AChE-I AE	2 (0.1%)	0
7 AChE-I AE	1 (0.1%)	0

Of subjects with 2 or more AChE-I adverse events, 62% had GI symptoms only, but 31% had mixed GI and neurological adverse events. While a patient with both GI and neurological symptoms make a causative relationship seem more likely, GI symptoms alone may still represent a link between the cholinergic effects of the drug and the adverse event.

IV. Dysarthria Case Review

Given the five identified cases of dysarthria seen in the combined Phase I and Phase III studies, DAI sent an information request to the sponsor to gain further details on these specific cases for a causal assessment.

In their response to the information request, the applicant provided case narratives for each of the six cases of dysarthria identified in the uUTI and uGC clinical trials. These cases are summarized in the following table and discussed below.

Phase I, Study BTZ115198 was a two-part, randomized, placebo-controlled, single-blind study to investigate the safety, tolerability, and PK of gepotidacin in healthy adult subjects. In Part A, escalating single doses of gepotidacin IV were investigated. Two participants experienced dysarthria in the cohort who received a single dose of gepotidacin 1800 mg IV over 1 hour.

Study 204989 (EAGLE-2) and 212390 (EAGLE-3) were Phase 3, randomized, multicenter, parallel-group, double-blind, double-dummy, comparator-controlled, noninferiority studies in adolescent and adult female participants comparing the efficacy and safety of oral gepotidacin to oral nitrofurantoin in the treatment of uUTI. Participants were randomly assigned in a 1:1 ratio to receive either oral gepotidacin 1500 mg BID for 5 days (total of 10 doses) or oral nitrofurantoin 100 mg BID for 5 days (total of 10 doses).

Study BTZ116577 is a Phase 3, open-label (sponsor-blinded), parallel-group, multicenter, comparator-controlled, noninferiority study in adolescent and adult participants comparing the efficacy and safety of oral gepotidacin (3000 mg administered orally at the study site during the Baseline Visit (Day 1) followed by self-administration of a second oral 3000-mg dose as an outpatient 10 to 12 hours after the first dose) to a single IM ceftriaxone (500 mg) plus a single oral azithromycin (1g) in the treatment of uncomplicated urogenital gonorrhea caused by Neisseria gonorrhea (NG).

Study	Phase I BTZ115198	Phase 1 BTZ115198	Phase 3 204989 (EAGLE-2)	Phase 3 204989 (EAGLE-2)	Phase 3 212390 (EAGLE-3)	Phase 3 uGC BTZ116577
Participant ID	Site 102332 Subject (b) (6)	Site 102332 Subject (b) (6)				(b) (6)
Age/Sex	29 M	20 M	58 F	27 F	38 F	23 M
Grade of AE	1	1	3	1	1	2
Route	IV	IV	PO	PO	PO	PO
Time to Onset	30 min after infusion started	1 hr after infusion started	~45 min after Dose 1,3,5	Day 1- timing not recorded	3 hrs after Dose 1	1.5 hrs after Dose 1, 1 hr after Dose 2
Duration	61 min	6 min	30-60 min	Resolved Day 6-timing not recorded	18 hrs	1st: 3 hrs 2nd: 1.5 hrs
Prior Concurrent Medication	None	None	None	None	None	Amoxicillin 3 months prior

Study	Phase I BTZ115198	Phase 1 BTZ115198	Phase 3 204989 (EAGLE-2)	Phase 3 204989 (EAGLE-2)	Phase 3 212390 (EAGLE-3)	Phase 3 uGC BTZ116577
Overlapping Symptoms	Abdominal pain, dizziness, disorientation, salivation, diarrhea	Dizziness (lasted 1 minute)	Blepharospasm	Diarrhea, "brain fog", coordination abnormal	"relaxed throat"	Dizziness, myoclonus
Reviewer Comment			Pt didn't appreciate dysarthria after doses 2,4 because she went to sleep after dose was taken. Patient was evaluated in the hospital after dose 5 with negative labs and imaging but declined neuro observation in the hospital overnight	Dysarthria was intermittent over 6 days	Pt discontinued from study	
Relationship Assigned by Reviewer	Probable	Unlikely	Probable	Possible	Possible	Possible

Study participant (b) (6) in the Phase I study was designated as unlikely related to study drug. While there was a temporal association, the extremely short duration of symptoms (6 minutes), and the absence of other potential AChE-I AE's occurring simultaneously, makes a causal relationship less likely. With the exclusion of study participant (b) (6) in the Phase I studies, the remaining cases all exhibited a possible or probable causal relationship between gepotidacin and the adverse event of dysarthria. There exists biologic plausibility as identified in pre-clinical in-vitro testing. Temporal association occurs in all cases. In oral dosing, the median Tmax values were 1.5 to 1.92 hours which could explain the timing of symptom onset observed in those patients who were orally dosed. Concurrent symptoms (such as abdominal pain, diarrhea, salivation, blepharospasm and myoclonus) were seen in 3 cases, suggesting possible cholinergic effects. Together, these findings indicate a possible causal relationship.

The adverse event of dysarthria seen in patient 102332-(b) (6) from the Phase 1 Study BTZ115198 was designated as having a probable causal relationship. Symptoms had a temporal relationship with administration of drug. In addition, concurrent symptoms including diarrhea, abdominal pain, dizziness,

and salivation occurred. These simultaneous symptoms can be attributed to acetylcholinesterase inhibition strengthening the causal relationship, thus designating this event as probably related.

In the case of patient (b) (6) in the Phase 3 EAGLE-2 study, it was also designated as having a probable causal relationship between gepotidacin and the adverse event of dysarthria. Pt had a very similar presentation with each episode of dysarthria. Each event had similar time to onset from study drug dose and comparable duration of symptoms with multiple positive rechallenges. Furthermore, additional evaluation and testing after dose 5, including both laboratory and imaging, failed to identify an alternate cause of her dysarthria. The concomitant blepharospasm was of particular interest given the case report of irinotecan which had a similar clinical presentation.

Despite the possible association seen in these cases, there remains a <1% chance of occurrence of dysarthria in the patients treated with gepotidacin. None of the cases required intervention and all symptoms resolved spontaneously.

V. Sponsor Risk Management and Labeling

In non-clinical studies, potential acetylcholinesterase inhibition was identified in dogs and monkeys. They exhibited signs that included miosis, ptosis, lacrimation, salivation, emesis and/or diarrhea. Subsequent in vitro testing showed gepotidacin to be a reversible inhibitor of acetylcholinesterase. In human studies, there were adverse events potentially consistent with AChE-I including gastrointestinal (GI) events (diarrhea, nausea, vomiting, abdominal pain) and non-GI events (dyspnea, dysarthria, diaphoresis, and pre-syncope). The majority of these events resolved in 5 or less days.

Events associated with AChE-I were deemed not important for inclusion in the list of safety concerns in the risk management plan (RMP). The outlined reasoning provided by the sponsor was that “adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated” should not be included. "In the case of AChE-I, there was a low incidence of non-gastrointestinal (GI) AChE-I events in pooled global Phase 3 uUTI studies (<1%). The majority of potential AChE-I events were GI related. Routine pharmacovigilance and risk management is considered appropriate. The product information provides guidance on appropriate prescribing including exclusions of certain concomitant medications and medical conditions.” Despite adding additional preferred terms (PT’s), in the clinical analysis performed by the FDA, there were still infrequent events of non-GI AChE-I events in the gepotidacin treatment arm (1.5%). This increased sensitivity is also at the expense of specificity. Thus, this approach appears acceptable.

The applicant proposed the following labeling for the risk of acetylcholinesterase inhibition.

> 5.2 Acetylcholinesterase Inhibition
>
> BLUJEPA is a (b) (4) reversible acetylcholinesterase inhibitor. (b) (4) Adverse Reactions (6)]. Increased cholinergic effects can be associated with severe adverse (b) (4) including atrioventricular block, seizures/convulsions, bronchospasm, and

vasovagal syncope. Patients with medical conditions that may be exacerbated by acetylcholinesterase inhibition should be monitored.

BLUJEPA, as an acetylcholinesterase inhibitor, may exaggerate the neuromuscular effects of succinylcholine-type muscle relaxation during anesthesia. BLUJEPA may (b) (4) the effects of other acetylcholinesterase inhibitors (b) (4) Patients should be monitored for exaggerated neuromuscular blockade or excessive cholinergic effects.

(b) (4) BLUJEPA may antagonize the effects of systemic anticholinergic medications (b) (4) nondepolarizing neuromuscular blocking agents, patients should be monitored if BLUJEPA is concomitantly administered with these medications [see Drug Interactions (7)].

VI. Discussion

In vitro testing of gepotidacin showed it to be a reversible inhibitor of acetylcholinesterase. This property may explain several of the adverse events identified in both non-clinical and clinical studies. Adverse events potentially secondary to acetylcholinesterase inhibition seen in human studies can be broken down into GI-adverse events and non-GI adverse events. Gastrointestinal symptoms, while common in patients treated with gepotidacin, cannot solely be explained by acetylcholinesterase inhibition. Anti-bacterial agents are known to cause GI intolerance and can alter bacterial flora in the gut causing GI symptoms, such as diarrhea. This is evident in the fact that several cases of clostridium difficile were identified in the gepotidacin treatment groups. It can be difficult to ascertain whether GI events are a result of antibiotic related changes in GI tolerability or increased levels of acetylcholine. However, while diarrhea and nausea were the most common AEs in both treatment groups, they were reported more frequently in the gepotidacin treatment group than the nitrofurantoin group. Diarrhea (including diarrhea, faeces soft, and frequent bowel movements) was reported in 275/1570 (17.5%) on gepotidacin versus 50/1558 (3.2%) in the nitrofurantoin group. Nausea/vomiting/retching was reported in 153/1570 (9.7%) in the gepotidacin group versus 62/1558 (4%) in the nitrofurantoin group. It is plausible that acetylcholine may have a contributory role in these adverse events given the imbalance between groups. In addition, the median time to onset for GI potential AChE-I events was 10 hours. This rapid time of onset would be unexpected in cases of dysbiosis seen with antimicrobials and lends further support to an acetylcholine mediated process in these cases with early onset gastrointestinal symptoms.

The non-GI adverse events that are potentially secondary to cholinergic effects are infrequently observed in the clinical trials (<2% occurrence). Dysarthria showed the largest discrepancy between groups with six cases identified in the Phase 1 and Phase 3 uUTI and uGC studies. However, despite the one serious adverse event of dysarthria, there was no intervention needed in any of the cases and no long-term sequela. In a 90 Day Safety Update, covering a reporting period of May 16, 2024, to September 8, 2024, for Study 214144 (EAGLE-J), a Phase 3, multicenter, randomized, active reference, double blind, double-dummy study in adolescent and adult Japanese females for the treatment of uUTI, 2 additional cases of dysarthria were identified from a total of 281 subjects. These two cases, representing 0.7% of subjects in the gepotidacin treatment group, were once again rated Grade 1 and Grade 2 on the severity scale. One case involved a 24-year-old female patient that experienced dysarthria in association with blepharospasm and diarrhea one hour following her first oral dose of gepotidacin. This case is of particular interest given the concomitant symptoms (blepharospasm and

diarrhea) which can be attributed to cholinergic effect. Blepharospasm was also seen in the case designated as a serious adverse event in the EAGLE-2 study. Dysarthria remains a very rare adverse event of cholinergic activation, but the symptom may prompt emergent evaluation to exclude an acute stroke.

In determining the appropriate language to include in the labeling I refer to the Guidance on Warnings and Precautions. This section is "intended to identify and describe a discrete set of adverse reactions that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management."[5] In these clinical trials there are several mild or moderate symptoms that may be attributed to acetylcholinesterase inhibition that are self-limiting. However, acetylcholinesterase inhibition can have far more potentially serious clinical outcomes. Risks include cardiac manifestations (AV block, bradycardia, etc.) as well as seizures, bronchospasm, and syncope. While no events were captured during the clinical trials, we see evidence of cholinergic effects causing other symptoms, notably dysarthria. These other risks may be more evident when marketed to a larger population. Because of this potential I think it's important to highlight this clinical concern in the Warnings and Precautions Section.

I propose the additional language to be added to the proposed applicants suggested labeling in section 5.2 (new additions highlighted in blue):

> 5.2 Acetylcholinesterase Inhibition
>
> BLUJEPA is a (b) (4) reversible acetylcholinesterase inhibitor. Dysarthria has been observed in clinical trials. Other adverse events that have been reported with BLUEJEPA and may be secondary to acetylcholinesterase inhibition include nausea/vomiting, diarrhea, abdominal pain, hypersalivation, presyncope, diaphoresis, and dyspnea. (b) (4) Adverse Reactions (6)]. Increased cholinergic effects can be associated with severe adverse reactions (b) (4) including atrioventricular block, bradycardia, seizures/convulsions, bronchospasm, and vasovagal syncope. Monitor patients with medical conditions that may be exacerbated by acetylcholinesterase inhibition ~~should be monitored~~.
>
> BLUJEPA, as an acetylcholinesterase inhibitor, may exaggerate the neuromuscular effects of succinylcholine-type muscle relaxation during anesthesia. BLUJEPA may (b) (4) ~~t~~ exaggerate the effects of other acetylcholinesterase inhibitors (b) (4) ~~Patients should be monitored~~ Monitor patients for exaggerated neuromuscular blockade or excessive cholinergic effects.
>
> (b) (4) Because BLUJEPA may antagonize the effects of systemic anticholinergic medications (b) (4) or nondepolarizing neuromuscular blocking agents, monitor patients ~~should be monitored~~ if BLUJEPA is concomitantly administered with these medications [see Drug Interactions (7)]
>
> 7.3 Cholinergic/Anticholinergic Drugs
>
> As gepotidacin is an acetylcholinesterase inhibitor, there is potential for an exaggerated effect of concomitantly administered succinylcholine-type neuromuscular blocking agents resulting in a

✓

[5] Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format

delay in recovery of neuromuscular function. Gepotidacin may augment the effect of other acetylcholinesterase inhibitors ~~(e.g., donepezil).~~ Monitor for exaggerated neuromuscular blockade or excessive cholinergic effects [see Warnings and Precautions (5.2)].

There is potential for an antagonistic effect with systemic anticholinergic medications ~~(e.g., benztropine)~~ or non-depolarizing neuromuscular blocking agents. Consider the potential for this interaction if BLUJEPA is administered concomitantly with anticholinergic medications [see Warnings and Precautions (5.2)].

After reviewing DAI's amendments to these sections, I agree that the proposed changes are consistent with Section 5 and are appropriate for labeling.

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/s/

JULIE W GOLDRICH
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Clinical Inspection Summary (CIS)

Date	02/11/2025
From	John Lee, M.D., Primary Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI) Office of Compliance, CDER
To	Brittany Goldberg, M.D., Medical Officer Rebecca Levorson, M.D., Medical Officer Mukil Natarajan, M.D., Team Leader Peter Kim, M.D., M.S., Division Director J. Christopher Davi, Regulatory Project Manager Division of Anti-Infectives (DAI) Office of Infectious Diseases (OID), Office of New Drugs, CDER
Application	NDA 218230
Applicant	GlaxoSmithKline, LTD
Drug	Gepotidacin (Blujepa®)
NME or Original NDA	Yes
Proposed Indication	Treatment of uncomplicated urinary tract infection in women and girls (age $\geq$ 12 years), body weight $\geq$ 40 kg
Consult Date	09/26/2024
CIS Goal Date	2/14/2025
Review Clock	Priority Review
Action Goal Date	03/26/2025
PDUFA Due Date	03/26/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Garev, Kester, Ajani, and Lambert, as well as the sponsor, GlaxoSmithKline, LLC, were inspected in support of this application, covering Protocols 204989 and 212390. No significant GCP deficiencies or regulatory violations were observed for any of the four CIs or the sponsor. The data generated by the four inspected CIs and submitted by the sponsor appear to be acceptable in support of the proposed indication, i.e., treatment of uncomplicated urinary tract infection (uUTI) in women and adolescent girls, age 12 years or older with a body weight of at least 40 kg.

II. BACKGROUND

The applicant GlaxoSmithKline, LLC (GSK) seeks the approval of gepotidacin (Blujepa™), a bactericidal antibiotic developed "*for the treatment of uncomplicated urinary tract infections (uUTI) in female adults and adolescents from 12 years of age weighing at least 40 kg*." Gepotidacin is a novel triaza-acenaphthylene bacterial type II topoisomerase inhibitor which selectively inhibits bacterial DNA replication, showing in vitro activity against most drug-resistant pathogens, including those resistant to fluoroquinolones.

The two nearly identical pivotal Studies 204989 and 212390 (same title and design) supporting this original NME NDA were identified for BIMO review-based inspections, including four CIs (two per study) and the sponsor GSK. No NDA review concerns were identified to direct these otherwise routine inspections.

Protocols 204989 and 212390

A Phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)

The primary objective of this randomized, double-blind, active-controlled study (~2500 subjects) was to demonstrate the non-inferiority of gepotidacin relative to nitrofurantoin in treating women with uUTI (acute cystitis) expected to respond to nitrofurantoin therapy (qualifying bacteria) as assessed at the Test-of-Cure (TOC) visit.

- Study visits: (1) baseline (Day 1); (2) on-therapy (Days 2-4); (3) TOC (Days 10-13); and (4) follow-up (Day 28)
- Randomization in equal ratio to 5 days of twice daily oral therapy: (1) gepotidacin 1500 mg, or (2) nitrofurantoin 100 mg

Major Endpoints and Analyses

- Primary Efficacy: Therapeutic Response (TR) at TOC, as evidenced by reduction in bacterial count (from $\geq 10^5$ to $< 10^3$ / mL, microbiology culture reports) and resolution of all signs and symptoms of acute cystitis present at baseline (turbid foul-smelling urine and frequent urgency with burning on micturition, by clinic visit interview and documented in clinic/progress notes)
- Key Secondary Efficacy: TR at follow-up visit at Day 28

III. INSPECTION RESULTS

1. Lazar Garev, M.D.

18 Sv Kiril And Metodiy Street
Pleven 5800, Bulgaria

Inspection Dates: January 06 – 09, 2025

Study 204989, Site 240951: 156 subjects were screened, 140 were enrolled, and 140 completed the study. This BIMO review-based inspection included the review of protocol adherence, Institutional Review Board (IRB) oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 40 subjects. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, protocol deviations (PDs), and use of non-study (concomitant) medications.

No significant GCP deficiencies or regulatory deviations were observed. Verbally discussed (non-cited) minor isolated findings (unlikely to be significant) included:

- Use of one expired (by 19 days) blood sample collection kit
- Uncorrected numbers for 2 blood sample collection kits (use of correct kits confirmed)
- Lab reports not always available as source records for urine tests

The study records otherwise showed adequate compliance with the applicable regulations and standards for GCP (including): informed consent, AE monitoring (including management and reporting), and PD monitoring (including corrective actions and reporting). The major safety and efficacy data (per Section II) were verifiable.

2. Steven Kester, M.D.

550 SW 3rd Street, 305
Pompano Beach, FL 33060

Inspection Dates: December 09 – 13, 2024

Study 204989, Site 241378: 75 subjects were screened, 66 were enrolled, and 63 completed the study. This BIMO review-based inspection included the review of protocol adherence, IRB oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 19 subjects. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study medications.

No significant GCP deficiencies or regulatory deviations were observed. Verbally discussed (non-cited) minor findings included late, incomplete, or inaccurate electronic record-keeping (unlikely to be significant). Source paper records were available for verification of accurate data reporting. The study records otherwise showed adequate compliance with the applicable regulations and

standards for GCP (including): informed consent, AE monitoring (including management and reporting), and PD monitoring (including corrective actions and reporting). The major safety and efficacy data (per Section II) were verifiable.

3. Dilawar Ajani, M.D.

10101 Bissonnet Street, Suite 105-A
Houston, TX 77036

Inspection Dates: December 10 – 16, 2024

Study 212390, Site 244063: 65 subjects were screened, 62 were enrolled, and 58 completed the study. This BIMO review-based inspection included the review of protocol adherence, IRB oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 15 subjects. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study medications.

No significant GCP deficiencies or regulatory deviations were observed. The study records showed adequate compliance with the applicable regulations and standards for GCP (including): informed consent, AE monitoring (including management and reporting), and PD monitoring (including corrective actions and reporting). The major safety and efficacy data (per Section II) were verifiable.

4. Joseph O. Lambert, M.D.

4351 Booth Calloway Road, Suite 101
North Richland Hills, TX 76180

Inspection Dates: December 09 – 16, 2024

Study 212390, Site 245376: 46 subjects were screened, 44 were enrolled, and 41 completed the study. This BIMO review-based inspection included the review of protocol adherence, IRB oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 15 subjects. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study medications.

No significant GCP deficiencies or regulatory deviations were observed. Verbally discussed (non-cited) minor isolated findings (unlikely to be significant) included:

- Study records not consistently well-organized to assure adequate record-keeping
- Documentation of adequate staff training

The study records otherwise showed adequate compliance with the applicable regulations and standards for GCP (including): informed consent, AE monitoring (including management and reporting), and PD monitoring (including corrective actions and reporting). The major safety and efficacy data (per Section II) were verifiable.

5. GlaxoSmithKline, LLC

1250 South Collegeville Road
Collegeville, PA 19426-0989

Inspection Dates: November 18 – 22, 2024

Studies 204989 and 212390: The BIMO review-based sponsor inspection of these two studies consisted of: (1) general records review, to evaluate compliance with the GCP principles, laws, and regulations as applicable to the sponsor; and (2) review of CI financial disclosure, staff training, and site monitoring, including detailed review of data reporting from the CI sites. No significant GCP deficiencies or regulatory violations were observed. Drug accountability and the sponsor's oversight monitoring of the CI sites appeared adequate to assure subject safety and data reliability.

{See appended electronic signature page}

John Lee, M.D., Primary Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D., Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

OID / DAI / Regulatory Project Manager / Christopher Davi
OID / DAI / Clinical Reviewer / Brittany Goldberg
OID / DAI / Clinical Reviewer / Rebecca Levorson
OID / DAI / Team Leader / Mukil Natarajan
OID / DAI / Director / Peter Kim

OSI / Director / David Burrow
OSI / Deputy Director / Laurie Muldowney
OSI / DCCE / Director / Kassa Ayalew
OSI / DCCE / GCPAB / Chief / Jenn Sellers
OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein
OSI / DCCE / GCPAB / Primary Reviewer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / DCCE / GCPAB / Program Analyst / Loreto-Corazon Lim

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/s/

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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:	February 6, 2025
To:	J. Christopher Davi, MS Senior Regulatory Project Manager **Division of Anti-Infectives (DAI)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Qumerunnisa Syed, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide
Drug Name (established name):	BLUJEPA (gepotidacin)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 218230
Applicant:	GlaxoSmithKline LLC (GSK)

1 INTRODUCTION

On July 26, 2024, GlaxoSmithKline LLC (GSK) submitted for the Agency's review a New Drug Application (NDA) for BLUJEPA (gepotidacin) tablets, for oral use. Gepotidacin (GSK2140944) is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic, developed for the treatment of uncomplicated urinary tract infections (uUTI) in female adults and adolescents from 12 years of age weighing at least 40 kg.

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 Anti-Infectives (DAI) on August 28, 2024 for DMPP and OPDP to review the Applicant's proposed Medication Guide for BLUJEPA (gepotidacin) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft BLUJEPA (gepotidacin) MG received on July 26, 2024, revised by the review division and received by DMPP and OPDP on January 28, 2025.

- Draft BLUJEPA (gepotidacin) Prescribing Information received on July 26, 2024, revised by the review division and received by DMPP and OPDP on January 28, 2025.

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 review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
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QUMERUNNISA B SYED
02/06/2025 09:26:00 AM

LASHAWN M GRIFFITHS
02/06/2025 09:59:46 AM

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

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

Memorandum

Date: February 6, 2025

To: Christopher Davi, Senior Regulatory Project Manager
Division of Regulatory Operations for Infectious Diseases (DRO-ID)

Brittany Goldberg, Clinical Team Leader
Division of Anti-Infectives (DAI)

Abimbola Adebowale, Associate Director for Labeling, OID/DAI

From: Qumerunnisa Syed, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for BLUJEPA (gepotidacin) tablets, for oral use

NDA: 218230

Background:
In response to DAI's consult request dated August 28, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for BLUJEPA (gepotidacin) tablets, for oral use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 28, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on February 4, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Qumerunnisa Syed at 301-796-8897 or Qumerunnisa.syed@fda.hhs.gov.

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MEMORANDUM
REVIEW OF REVISED LABEL

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:	February 4, 2025
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 218230
Product Name, Dosage Form, and Strength:	Blujepa (gepotidacin) Tablets, 750 mg
Applicant Name:	GlaxoSmithKline, LLC (GSK)
FDA Received Date:	February 4, 2025
TTT ID #:	2024-10262-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

GlaxoSmithKline, LLC submitted revised container label received on February 4, 2025 for Blujepa. The Division of Anti-Infectives (DAI) requested that we review the revised container label for Blujepa (Appendix A) to determine if it is 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

GlaxoSmithKline, LLC implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Myers, D. Label and Labeling Review for Blujepa (NDA 218230). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 DEC 09. TTT ID: 2024-10262.

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/s/

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VALERIE S VAUGHAN
02/04/2025 01:48:58 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: January 2, 2025 **Date consulted:** 9/9/2024

From: Kevin Clark, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

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

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

To: Division Anti-Infectives (DAI)

Drug: BLUJEPA (gepotidacin)

NDA: 218230

Applicant: GlaxoSmithKline

Subject: Pregnancy and Lactation Labeling

Indication: For the treatment of female adults and pediatric patients 12 years of age and older, weighing at least 40 kilograms (kg) with uncomplicated urinary tract infections (uUTI) caused by the following susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae*, *Citrobacter freundii* complex, (b) (4) *Staphylococcus saprophyticus,* and *Enterococcus faecalis*.

Materials Reviewed:

- Applicant's NDA submission dated July 26, 2024
- DAI Consult request dated September 9, 2024, DARRTS Reference ID: 5443223

- March 20, 2024, DPMH Review of NDA 216483, Pivmecillinam oral tablet, DARRTS Reference ID: 53446025[1]

Consult Question: "We would like your input on Section 8 of the product labeling including on pregnancy and lactation."

INTRODUCTION AND BACKGROUND

On July 26, 2024, the Applicant (GlaxoSmithKline) submitted a New Drug Application for BLUJEPA (gepotidacin) oral tablets under Section 505(b)(1) of the Food, Drug, and Cosmetic Act. The Applicant is seeking approval of gepotidacin tablets for the treatment of female adults and adolescents from 12 years of age, weighing at least 40 kilograms (kg) with uncomplicated urinary tract infections (uUTI; acute cystitis) caused by the following susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae*, *Citrobacter freundii* complex, (b) (4) , *Staphylococcus saprophyticus,* and *Enterococcus faecalis*. The Division of Anti-Infectives (DAI) consulted the Division of Pediatrics and Maternal Health (DPMH) on September 9, 2024, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

Gepotidacin is a first-in-class triazaacenaphthylene bacterial type II topoisomerase inhibitor antibacterial and is a new molecular entity (NME). The product is not currently approved or marketed in any country. DAI has granted this NDA Priority Review Designation.

Drug Characteristics and Proposed Labeling[2]

- *Drug class:* triazaacenaphthylene bacterial type II topoisomerase inhibitor
- *Mechanism of action (MOA):* inhibits bacterial DNA replication by inhibition of bacterial DNA gyrase and topoisomerase IV
- *Dosage and administration:* 1500 mg twice daily for 5 days
- *Molecular weight:* 580.66 g/mol
- *Half-life:* terminal half-life 9 hours
- *% Protein Bound:* 33%
- *Bioavailability:* approximately 45%
- *Warnings and Precautions:* QT prolongation, acetylcholinesterase inhibition, hypersensitivity reactions (including anaphylaxis), *Clostridioides difficile* infection, development of drug-resistant bacteria
- *Adverse reactions (≥2%):* diarrhea, nausea, abdominal pain, flatulence, headache, and soft feces.

The MOA of gepotidacin is similar to that of the fluoroquinolone antibiotics. Similar to the fluoroquinolones, dose-dependent QTc prolongation has been observed in subjects treated with gepotidacin. QTc prolongation will be included in subsection 5.1 (Warnings and Precautions) of labeling for BLUJEPA. However, the review team did not identify a safety signal for tendinopathy or tendon rupture as noted in labeling for fluoroquinolones.

[1] The consult review for NDA 216483 was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2] Applicant's Proposed labeling for BLUJEPA with edits from DAI team, accessed 12/23/2024

REVIEW
PREGNANCY
Uncomplicated UTI and Pregnancy[3]

- Per the Guidance for Industry, *Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment* (August 2019), uncomplicated UTIs (uUTIs) occur in females with normal anatomy of the urinary tract and are not accompanied by systemic signs or symptoms, such as fever greater than 38 degrees Celsius or costovertebral angle pain. Urinary tract infections in males are characterized as complicated UTIs (cUTIs) because these infections occur in association with urologic abnormalities such as instrumentation or bladder outlet obstruction (e.g., benign prostatic hyperplasia).
- UTIs account for approximately 10 percent of office visits by women, and 15 percent of women will have a UTI at some time during their life. Urinary tract infections are common during pregnancy and may give rise to pyelonephritis which is the most common serious medical condition seen in pregnancy.[4] In pregnant women, the incidence of UTI can be as high as 8 percent.[5] In one study, 3.5% of antepartum admissions were due to UTI.[6]
- During pregnancy, urinary tract changes predispose women to infection. Ureteral dilation is seen due to compression of the ureters from the gravid uterus.[4] Hormonal effects of progesterone may cause smooth muscle relaxation leading to dilation and urinary stasis, and vesicoureteral reflux increases. The organisms which cause UTI in pregnancy are the same uropathogens seen in non-pregnant individuals.[4] A 18-year retrospective analysis found E. coli to be the causative agent in 82.5% of cases of pyelonephritis in pregnant patients.[7]
- Asymptomatic bacteriuria can lead to the development of cystitis or pyelonephritis. All pregnant women should be screened for bacteriuria and subsequently treated with antibiotics, such as nitrofurantoin, sulfamethoxazole, or cephalexin.[8] Ampicillin is no longer used in the treatment of asymptomatic bacteriuria because of high rates of resistance. Pregnant women with urinary group B streptococcal infection should be treated and subsequently should receive intrapartum prophylactic therapy. Pyelonephritis can be a life-threatening illness, with increased risk of perinatal and neonatal morbidity. Recurrent infections are common during pregnancy and require prophylactic treatment. Suppressive antibiotic therapy, usually with nitrofurantoin once daily, is commonly

[3] DPMH Review of NDA 216483, Pivmecillinam oral tablet, March 20, 2024, DARRTS Reference ID: 53446025
[4] Habak PJ, Griggs, Jr RP. Urinary Tract Infection In Pregnancy. [Updated 2022 Jul 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-.
[5] Delzell JE Jr, Lefevre ML. Urinary tract infections during pregnancy. Am Fam Physician. 2000 Feb 1;61(3):713-21. Erratum in: Am Fam Physician 2000 Jun 15;61(12):3567.
[6] Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL. Hospitalizations during pregnancy among managed care enrollees. Obstet Gynecol. 2002 Jul;100(1):94-100.
[7] Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. Am J Obstet Gynecol. 2014 Mar;210(3): 219.e1-6.
[8] Gupta K, et al. Urinary tract infections and asymptomatic bacteriuria in pregnancy. UpToDate.com, accessed 3/4/24.

recommended especially in cases where patients have had a prior UTI.[4] This is typically continued throughout pregnancy and the early postpartum period.

- Schieve et al.[9] conducted a study involving 25,746 pregnant women and found that the presence of UTI was associated with premature labor (labor onset before 37 weeks of gestation), hypertensive disorders of pregnancy (such as pregnancy-induced hypertension and preeclampsia), anemia (hematocrit level less than 30 percent) and amnionitis. Additionally, randomized trials have demonstrated that antibiotic treatment decreases the incidence of preterm birth and low-birth-weight infants.[10]

Nonclinical Experience

In embryo-fetal development (EFD) studies, gepotidacin was administered orally to pregnant rats and mice during the period of organogenesis. In rats, decreased fetal weights were reported at doses approximately equal to the maximum recommended human dose (MRHD) (based on AUC extrapolated from nonpregnant rats) and, in mice, decreased fetal weights and increased late fetal resorptions were reported at doses approximately 0.8-times the MRHD (based on AUC extrapolated from nonpregnant mice). Although the Applicant attributed the adverse findings to maternal toxicity (specifically decreased food intake), the Nonclinical team noted that the decreased food intake was not associated with weight loss in the dams and thus did not consider this finding representative of maternal toxicity. No malformations were reported in rats or mice at exposures up to about 4-times the MRHD (based on AUC extrapolated from nonpregnant rats) or about 3-times the MRHD (based on AUC extrapolated from nonpregnant mice), respectively. In the pre- and post-natal development (PPND) study, when pregnant mice were given oral doses of gepotidacin at approximately 3-times the MRHD (based on AUC exposure extrapolated from nonpregnant mice) throughout pregnancy and lactation, there was no evidence of fetal or developmental toxicity. The Nonclinical Toxicology reviewer considers the lack of fetal malformations and the absence of fetal or development toxicity in the PPND study to be reassuring.[11] Refer to the Pharmacology/Toxicology review by Leah Rosenfeld, PhD.

Review of Pharmacovigilance Database

Gepotidacin has not been marketed in any jurisdiction. During the development program, women with a positive pregnancy test at screening were excluded from clinical trials. The Applicant reported one pregnancy in a subject who was treated with gepotidacin in Trial 212390. The subject was a 27-year-old female who completed a 5-day course of gepotidacin. Pregnancy was reported between the test of cure visit (Day 12) and follow up visit (Day 32). Her last menstrual period was approximately 2.5 weeks prior to her first dose of study treatment. The investigator estimated that the subject was treated with gepotidacin beginning at week 2 of the pregnancy. The outcome of the pregnancy was unknown. The subject was lost to follow up and the site was unable to contact her despite multiple telephone calls and a certified letter.

Review of Literature

[9] Schieve LA, Handler A, Hershow R, Persky V, Davis F. Urinary tract infection during pregnancy: its association with maternal morbidity and perinatal outcome. Am J Public Health. 1994; 84:405-10.
[10] Romero R, Oyarzun E, Mazor M, Sirtori M, Hobbins JC, Bracken M. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. Obstet Gynecol. 1989; 73:576-82.
[11] Personal communication with Nonclinical Toxicology Reviewer Leah Rosenfeld, PhD 12/20/2024

Applicant's Review of Literature
Per the Applicant, no human studies have investigated the potential effect of gepotidacin during pregnancy.[12]

DPMH Review of Literature
DPMH conducted a search of published literature in PubMed and Embase using the search terms "gepotidacin" and "pregnancy", "safety events and pregnancy", "adverse effects AND pregnancy", "pregnancy outcomes", "adverse pregnancy outcomes", "congenital anomalies", "congenital defects", "pregnant women", "pregnancy AND birth defects", "pregnancy AND congenital malformations", "pregnancy AND stillbirth", "pregnancy AND miscarriage", "spontaneous abortion", "prematurity", "low birth weight", "fetal loss", "pregnancy loss", and "teratogenicity". No relevant publications were identified.

No information regarding gepotidacin is available in Micromedex, ReproTox, TERIS, or Shepards.[13]

Reviewer's Comment:
There are no available human data on the use of gepotidacin in pregnant women to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Developmental toxicity (increased late fetal resorptions and decreased fetal weights) was noted in embryofetal development studies in mice and rats at 0.8-1 times the MRHD based on AUC. However, no malformations were reported in rats or mice at exposures up to about 4-times the MRHD based on AUC extrapolated from nonpregnant rats or about 3-times the MRHD based on AUC extrapolated from nonpregnant mice, respectively. Additionally, in the pre- and post-natal development study in which mice received doses approximately 3 times the MRHD, there was no evidence of fetal mortality or effects on parturition, lactation, birth weights, or post-natal growth or development of offspring. Although the nonclinical information regarding pregnancy is sufficient to inform product labeling at the time of approval, more data are needed to further inform a potential risk associated with use of gepotidacin during pregnancy. These data should be obtained in the postmarket setting.

LACTATION
Nonclinical Experience
Gepotidacin concentrations have not been directly measured in animal milk. However, in the pre- and post-natal development study described above, gepotidacin was detected in plasma of lactating pups on post-natal day 10 at 3, 8, and 22 hours after the maternal dose without observed adverse effect. For all 3 doses tested, gepotidacin concentrations were higher at either the 8 or 22 hour timepoint, which is consistent with exposure via milk rather than residual detectable drug from intrauterine exposure. Refer to the Pharmacology/Toxicology review by Leah Rosenfeld, PhD.

[12] Applicant's NDA submission, Summary of Clinical Safety, p.144
[13] Databases accessed via Micromedex (https://www.micromedexsolutions.com/micromedex2/librarian), accessed 11/27/2024

Review of Pharmacovigilance Database

Gepotidacin has not been marketed in any jurisdiction. During the development program, lactating women were excluded from clinical trials. No exposures to gepotidacin during lactation occurred during the development program.

Review of Literature

Applicant's Review of Literature:

Per the Applicant, no human studies have investigated the potential effect of gepotidacin during lactation.[14]

DPMH Review of Literature:

DPMH conducted a search of published literature in PubMed and Embase using the search terms "gepotidacin" and "lactation" and "breastfeeding". DPMH's review of literature identified no publications that described the use of gepotidacin in breastfeeding women or their infants. In addition, no information regarding gepotidacin was found in LactMed[15], Briggs and Freeman: Drugs in Pregnancy and Lactation[16], or Micromedex.[17]

Reviewer's Comment:

There are no available data regarding the presence of gepotidacin in human milk, nor the effect of gepotidacin on the breastfed infant or milk production. Although nonclinical studies have not directly evaluated the concentration in animal milk, gepotidacin was detected in plasma of lactating pups in the pre- and post-natal development study. The nonclinical information submitted by the Applicant confirms the presence of gepotidacin in animal milk. When a drug is present in animal milk, it is likely to be present in human milk.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Per the Nonclinical toxicology reviewer, gepotidacin was positive in an *in vitro* micronucleus test in human peripheral blood lymphocytes and in an L5178Y mouse lymphoma assay, consistent with the known *in vitro* clastogenic effects of topoisomerase inhibitors in *in vitro* mammalian cell assays. Gepotidacin was negative in an *in vivo* micronucleus test or Comet assay in rat. Based on an overall weight of evidence, the Nonclinical Toxicology team concluded that gepotidacin unlikely to be genotoxic.

In animal fertility studies with gepotidacin, exposures up to about 3-times the exposure (AUC extrapolated from mice orally administered the same dose in other studies) at the MRHD, had no adverse effects on fertility (male and female) in rats.

Review of Pharmacovigilance Database

[14] Applicant's NDA submission, Summary of Clinical Safety, p.144

[15] LactMed. National Library of Medicine. National Center for Biotechnology Information. https://www.ncbi.nlm.nih.gov/books/NBK501922/#IX-E

[16] Briggs and Freeman: Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Ovid: Ovid: Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.

[17] https://www.micromedexsolutions.com/micromedex2/librarian, Accessed 9/26/2024

Gepotidacin has not been in marketed in any jurisdiction. The development program only included female subjects and did not evaluate the effect of gepotidacin on female fertility. The proposed indication is treatment of uncomplicated UTI in females only.

Review of Literature

Applicant's Review of Literature:
The Applicant did not conduct a literature review regarding the effect of gepotidacin on male or female fertility.

DPMH Review of Literature:
DPMH conducted a search of published literature in PubMed and Embase using the search terms "gepotidacin" and "fertility", "infertility", and "reproduction". The literature search identified no relevant publications.

Reviewer's comment:
There is no available literature regarding the effect of gepotidacin on human fertility. However, based on the nonclinical toxicology findings, the Applicant's proposal to omit subsection 8.3 Females and Males of Reproductive potential from labeling appears reasonable.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no available human data on the use of gepotidacin in pregnant women to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Developmental toxicity (increased late fetal resorptions and decreased fetal weights) was noted in embryofetal development (EFD) studies in mice and rats at 0.8-1 times the MRHD based on AUC. However, no malformations were reported in rats or mice at exposures up to 750 mg/kg/day (about 4-times the MRHD based on AUC extrapolated from nonpregnant rats) or 1000 mg/kg/day (about 3-times the MRHD based on AUC extrapolated from nonpregnant mice), respectively. Additionally, in the pre-and post-natal development (PPND) study in which mice received doses approximately 3 times the MRHD, there was no evidence of fetal mortality or effects on parturition, lactation, birth weights, or post-natal growth or development of offspring. Although the Applicant attributed the adverse findings to maternal toxicity (specifically decreased food intake), the Nonclinical team noted that the decreased food intake was not associated with weight loss in the dams and thus did not consider this finding representative of maternal toxicity. The adverse findings in the EFD studies were also not associated with fetal malformations and there were no adverse findings observed in the PPND study. As such, DPMH concludes that nonclinical data do not demonstrate a need for a Warning & Precaution regarding embryofetal toxicity nor a recommendation for pregnancy testing or contraception. However, DPMH concludes that additional data is needed and should be obtained in the postmarket setting. DPMH recommends including the nonclinical information in subsection 8.1 Pregnancy, under Risk Summary and Data headings. Because urinary tract infections are more common in females than males, particularly during pregnancy, gepotidacin use in females of reproductive potential and during pregnancy is likely to be substantial. Because of this, and because gepotidacin is a first-in-class NME, and because animal data suggest a potential risk of decreased fetal weight with gepotidacin use during pregnancy, there is a need for a postmarketing requirement (PMR)

to evaluate this potential safety concern. As such, DPMH will recommend that DAI issue a PMR for a pregnancy exposure registry and a complementary study.

Lactation

There are no available data regarding the presence of gepotidacin in human milk, nor the effect of gepotidacin on the breastfed infant or milk production. Although nonclinical studies have not directly evaluated the concentration of the drug in animal milk, gepotidacin was detected in plasma of lactating pups in the pre- and post-natal development study, demonstrating presence of drug in animal milk with no observed adverse effects. If a drug is present in animal milk, it is likely to be present in human milk. DPMH recommends including this information in subsection 8.2 Lactation, under Risk Summary heading. Because gepotidacin is likely to be used in lactating women, DPMH will recommend that DAI issue a PMR for a clinical lactation study. Such a study would ideally be conducted in women who are taking gepotidacin therapeutically as part of routine clinical care so that adverse event data could be collected on exposed infants.

Females and Males of Reproductive Potential

There is no available literature regarding the effect of gepotidacin on human fertility. However, in a nonclinical study, gepotidacin had no effect on male or female fertility in rats at doses 4.3 times the MHRD. As such, based on the nonclinical toxicology findings, the Applicant's proposal to omit subsection 8.3 Females and Males of Reproductive Potential from labeling appears reasonable.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 1/21/2025. DPMH recommendations are below. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEVIN L CLARK
01/22/2025 08:59:02 AM

TAMARA N JOHNSON
01/22/2025 09:45:42 AM

LYNNE P YAO
01/29/2025 12:12:12 PM

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:	December 9, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 218230
Product Name, Dosage Form, and Strength:	Blujepa (gepotidacin) Tablets, 750 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	GlaxoSmithKline, LLC (GSK)
FDA Received Date:	July 26, 2024 and October 21, 2024
TTT ID #:	2024-10262
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 INTRODUCTION

As part of the approval process for Blujepa (gepotidacin) Tablets, the Division of Anti-Infectives (DAI) requested that we review the proposed Blujepa Prescribing Information (PI), Patient Information, and container label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND/REGULATORY HISTORY

On July 26, 2024, GlaxoSmithKline (GSK) submitted their 505(b)(1) Original New Drug Application (NDA) 218230 for Blujepa (gepotidacin).[a]

On October 21, 2024, (b) (4) GSK submitted their revised proposed draft container label.[b]

2 MATERIALS CONSIDERED

This section lists the materials considered for our review of NDA 218230.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Label and Labeling	B

3 CONCLUSION

The proposed Blujepa Prescribing Information (PI), Patient Information, and container label may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Anti-Infectives (DAI) in Section 4 and for GlaxoSmithKline, LLC in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented in subsection 2.2 *Important Dosing Information*, the	Passive voice creates ambiguity regarding the correct action to take.	To provide clarity regarding the intended action, we recommend starting this

[a] Cover Letter: Original Submission: Original New Drug Application (NDA) for Gepotidacin Tablets (NDA 218230). Philadelphia (PA): GlaxoSmithKline, LLC; 2024 JUL 26. Available from: \\CDSESUB1\EVSPROD\nda218230\0001\m1\us\102-cover-letters\cover.pdf.

[b] Cover Letter: Other Document Description: Revised Draft Carton Label for Gepotidacin Tablets (NDA 218230). Philadelphia (PA): GlaxoSmithKline, LLC; 2024 OCT 21. Available from: \\CDSESUB1\EVSPROD\nda218230\0017\m1\us\102-cover-letters\cover.pdf.

Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	text in the first sentence is presented in passive voice (i.e., "BLUJEPA tablets should be taken…").		sentence with the action word, "Take" and deleting the passive text "should be taken." Revised to: "Take BLUJEPA tablets…"
2.	As currently presented in subsection 2.2 *Important Dosing Information*, the text in the second sentence is presented in passive voice (i.e., "If a dose is missed, it should be taken…").	See rationale associated with line 1 above.	To provide clarity regarding the intended action, we recommend starting the phrase "…it should be taken…" with the action word, "take" and deleting the passive text "should be taken." Revise to: "If a dose is missed, take it as soon as possible."
3.	As currently presented in subsection 2.2 *Important Dosing Information*, the text in the third sentence is presented in passive voice (i.e., "Double doses should not be taken to make up…").	See rationale associated with line 1 above.	To provide clarity regarding the intended action, we recommend adding the action words, "Do not take" and deleting the passive text "should not be taken." Additionally, to provide increase the prominence of the negative word "not" we recommend underlining the word "not" in the sentence. Revise to: "Do <u>not</u> take double doses to make up…"
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the description of the dosage form is provided for one side (i.e., yellow, capsule shaped, and debossed with "GS GU3" on one side). However, does not include the description that the	A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(4)(ii).	Provide a description of identifying characteristics of both sides of the tablet in accordance with 21 CFR 201.57(c)(4)(ii).

Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	tablets are plain on the other side.		

The following editorial revisions are recommended to improve readability and/or clarity:

1. In the *Highlights of Prescribing Information*, under "*Dosage and Administration*" following the text "1,500 mg" add the clarifying text "(two 750 mg tablets)", for example:

(b) (4)

2. In subsection 2.1 *Uncomplicated Urinary Tract Infection* following the text "1,500 mg" add the clarifying text "(two 750 mg tablets)" *and* add a comma following the text "…12 hours apart)", for example:

(b) (4)

3. In Section 16 *How Supplied/Storage and Handling*, the salt form would be best presented in Section 11 *DESCRIPTION*. Additionally, we recommend the removal of (b) (4) (b) (4) as this extraneous information that is not needed. To simplify, we recommend: "BLUJEPA is supplied as an immediate release tablet containing 750 mg of gepotidacin." For example,

(b) (4)

4. In Section 16 *How Supplied/Storage and Handling*, in the storage statement we recommend replacing the hyphens with their intended meaning "to", for example:

(b) (4)

5. In the Patient Information, under the heading "*How should I take BLUJEPA?*" we recommend revising the three occurrences of the text "don't" to instead "do not", for example:

Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) [redacted]		
	6. In the Patient Information, under the heading "How should I store BLUJEPA?" we recommend add the text "room temperature" and the units (°F and °C) for clarity, for example, (b) (4) [redacted]		

5 RECOMMENDATIONS FOR GLAXOSMITHKLINE, LLC

Table 3. Identified Issues and Recommendations for GlaxoSmithKline, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	We note that a Medication Guide is being proposed for this product. As currently presented, the statement "Dispense the enclosed Medication Guide to each patient" is not prominently displayed on the principal display panel (PDP).	Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.	Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).

Table 3. Identified Issues and Recommendations for GlaxoSmithKline, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, the numbers associated with the barcode appear to be a placeholder (i.e., 9 999999 999999), and do not include the national drug code (NDC) (e.g., 0173-0922-45).	21 CFR 201.25 requires a bar code that contains, at a minimum, the appropriate NDC number.	When the NDC number is finalized, replace the placeholder numbers associated with the barcode (i.e., 9 999999 999999), with the human readable NDC (e.g., 0173-0922-45).
3.	Consider revising the statement of dosage (b) (4) (b) (4) to read as "Recommended Dosage: see Prescribing Information."		

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Blujepa received on July 26, 2024 from GlaxoSmithKline, LLC.

Table 4. Relevant Product Information for Blujepa	
Initial Approval Date	N/A
Active Ingredient	gepotidacin
Indication	For the treatment of female adults and adolescents from 12 years of age, both weighing at least 40 kilograms (kg) with uncomplicated urinary tract infections (uUTI; acute cystitis) caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii* complex, (b) (4) *Staphylococcus saprophyticus*, and *Enterococcus faecalis*.
Dosage Form	Tablets
Strength	750 mg
Route of Administration	oral
Dose and Frequency	1,500 mg (two 750 mg tablets) taken orally, twice daily (approximately 12 hours apart), for 5 days.
How Supplied	Bottles of 20 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].
Container Closure	Packed into 60 cc opaque, white High Density Polyethylene (HDPE) bottles with 33 mm (b) (4) closures (b) (4)

APPENDIX B. LABEL AND LABELING

B.1 List of Label and Labeling Reviewed

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

- Prescribing Information (PI) (images not shown) received on July 26, 2024:
  - Cleaned proposed (Draft) PI available at the following link: \\CDSESUB1\EVSPROD\nda218230\0001\m1\us\114-labeling\1141-draft\blujepa-uspi-original-nda-draft-clean.docx.
  - Annotated (reline) Draft PI available at the following link: \\CDSESUB1\EVSPROD\nda218230\0001\m1\us\114-labeling\1141-draft\blujepa-uspi-original-nda-pdf-draft-annotated.pdf.
- Patient Package Insert (Patient Information) received on July 26, 2024, is displayed at the bottom of the clean proposed (Draft) PI available at the following link: \\CDSESUB1\EVSPROD\nda218230\0001\m1\us\114-labeling\1141-draft\blujepa-uspi-original-nda-draft-clean.docx.
- Container label received on October 21, 2024

B.2 Container Label Image

Container Label:

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
12/09/2024 04:05:31 PM

VALERIE S VAUGHAN
12/09/2024 04:18:21 PM

Memorandum

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

Date: October 24, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Associate Director, Cardiac Safety IRT, DCN

To: Chris Davi, RPM
DAI

Subject: QT Consult to NDA 218230 (SDN 1)

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

This memo responds to your consult to us dated 8/6/2024 regarding the Applicant's QT risk assessments and labelling. We reviewed the following materials:

- QT study report BTZ115775 (NDA 218230 / SDN 1; link);
- Phase III study 204989 (EAGLE-2) report (NDA 218230 / SDN 1; link);
- Phase III study 212390 (EAGLE-3) report (NDA 218230 / SDN 1; link);
- Phase III study 214144 (EAGLE-J) report (NDA 218230 / SDN 14; link);
- Day 90 safety update (NDA 218230 / SDN 14; link);
- Previous IRT reviews for IND 111885 dated 06/06/2016; 12/03/2014; 08/05/2014) in DARRTS;
- Proposed labeling (NDA 218230 / SDN 1; link); and
- Highlights of clinical pharmacology included in the summary of clinical pharmacology studies, Table 1 (NDA 218230 / SDN 1; link).

1 Responses for the Division

Consult request: Please review the QTc study submitted by sponsor (contained within phase 3 study 212390 EAGLE-3), associated safety data and draft label. Please provide comments on benefit-risk assessment, any potential safety concerns and proposed labeling mitigations.

IRT's response: Gepotidacin prolongs the QTc interval in a dose- and concentration-dependent manner as demonstrated in a thorough QT (TQT) study of gepotidacin 1000 mg (mean ΔΔQTc = 12 msec) and 1800 mg (mean ΔΔQTc = 22 msec) administered by IV infusion over 2 hours (see

IRT review dated 06/06/2016 section 2.5 for a brief summary. Considering the hERG safety margin (52-fold) it is likely that the QTc prolongation could be a result of blocking the hERG potassium channel – see section 2.3 for additional details.

We have reviewed the available safety data from EAGLE-2, EAGLE-3, and EAGLE-J. Our analysis of EAGLE-3 is consistent with the Applicant's findings showing absence of significant QTc prolongation (i.e., >500 msec or >60 msec over baseline) (Table 2). There were no QTc prolongation >500 msec in EAGLE-J; however, two participants discontinued treatment because of an increase in QTc increase > 60 msec. No other AEs related to QTc prolongation were observed in either participant. Scheduled post-dose ECGs were not collected in EAGLE-2. There were few treatment-emergent AEs included in the broad custom query for AEs related to QTc prolongation or Torsade de pointes across EAGLE-2, EAGLE-3, and EAGLE-J. Overall no significant safety findings were identified in EAGLE-2, EAGLE-3 and EAGLE-J. See section 2.4 for additional details.

Based on the concentration-QTc relationship for gepotidacin observed in the TQT study the increase ΔΔQTcF for the therapeutic dose and high clinical exposure scenario (i.e., severe hepatic impairment) is predicted to be ~8 and ~17 msec, respectively (Table 3). However, there is uncertainty in this estimate because: 1) the predictions assume that gepotidacin is the only moiety that contributes to the QTc prolongation; and 2) the high clinical exposure scenario (16.9 µg/mL) exceeds the highest concentration in the TQT study (13.6 µg/mL). Additionally, it is uncertain how the M4 exposures compare between the TQT study and the proposed therapeutic dose and no assessment of the effects of M4 on hERG have been performed.

While there is uncertainty in the magnitude of QTc prolongation for the proposed therapeutic dose, we nevertheless expect QTc prolongation for the proposed dose, which warrants inclusion of a warning and precaution for QTc prolongation in the label, as proposed by the Applicant. However, considering the observations of the TQT study and findings from EAGLE-2, EAGLE-3, and EAGLE-J we do not consider ECG monitoring in all subjects is required and instead recommend collection of ECGs in patients at increased risk prior to dosing and as clinically indicated.

Below are our proposed edits to the label submitted to SN 0001. Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. We omitted sections 8.6, 8.7, and 10, which also mentions QT, because the proposed text looks reasonable, except we proposed to use QTc rather than QT for these sections.

Please note that our recommendations are only suggestions and that we defer final labeling decisions to the Division.

(b) (4)

Reviewer's comment: *We do not recommend including example drugs, because it can give the impression that listed drugs are the most important. We also recommend including recommendations for administration of gepotidacin if treatment cannot be avoided and to use QTc instead of QT.*

(b) (4)

Reviewer's comment: *We do not recommend including example drugs, because it can give the impression that listed drugs are the most important. We also recommend QTc instead of QT.*

(b) (4)

Reviewer's comment*: We recommend QTc instead of QT and defer to the Division concerning the need to include a description of the increase in HR. We also recommend including a comparison of gepotidacin exposure following the IV administration in the TQT study to the recommended oral dosing.*

2 BACKGROUND

2.1 Product Information

Gepotidacin (GSK 2140944) is a triazaacenaphthylene antibacterial that inhibits bacterial DNA gyrase and topoisomerase IV, thereby inhibiting DNA replication. In the current NDA submission, the Applicant is seeking approval for indication for treatment of uncomplicated urinary tract infections (uUTI) in female adults and adolescents from 12 years of age, both weighing at least 40 kg. The recommended dose is 1500 mg BID for 5 days. The drug product is formulated as oral tablets at strength of 750 mg of gepotidacin.

2.2 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety.

The absolute bioavailability of gepotidacin is 45%. Following repeat oral twice daily administration of gepotidacin 1,500 mg to females with uUTI infection, median Tmax values were 1.50 to 1.92 hours. Steady-state plasma exposure was attained by Day 3. Food has no meaningful effect on gepotidacin plasma exposure.

Unchanged gepotidacin was the predominant circulating component in humans after both oral and IV administration. All circulating human metabolites were minor (<10% of DRM), except for M4 (oxidation of the triazaacenaphthylene moiety), which represented 10.8% of DRM after a single oral dose of [14C]-gepotidacin to humans. However, the Applicant did not specify if M4 is pharmacologically active.

Table 1: Summary of dose and exposure assessment[1]

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	1500 mg BID, oral tablets	8.4[2] µg/mL ($C_{max,ss}$)
Sponsor's High clinical exposure scenario	1.9-fold increase in patients with severe hepatic impairment	16.9[3] µg/mL
Highest dose in QT assessment	1800 mg IV	13.6 µg/mL
C_{max} Ratio	13.6 / 16.9 = 0.8	

[1]Although blood samples for metabolite profile were collected in some studies. There are no reports of M4 (GSK3445826) exposure in any of the reports of the PK studies.
[2]See summary of clinical pharmacology studies, Table 10
[3]8.4*1.9=16.9 µg/mL

Reviewer's comments: *The expected mean QTc prolongation at the proposed therapeutic dose regimen and high clinical scenario are provided in Table 3. The predictions assume that gepotidacin is the only moiety that contributes to the QTc prolongation, which we cannot confirm. We also want to note that the highest dose of 1800 mg in TQT study does not cover the Cmax at high clinical scenario, which adds additional uncertainty to the predicted increase in QTc.*

2.3 Nonclinical Cardiac Safety

The Applicant evaluated the effects of gepotidacin on hERG current in the study report (WD2010/00521/00V29256, link). The hERG current was assessed at room temperature using manual patch clamp assay. The hERG IC_{50} was 1.31 mM, which corresponds to a hERG safety margin of 52-fold (MW: 448.52 g/mol; PB: 33%) using the high clinical exposure scenario (see Table 1). The Applicant has not evaluated the effects of M4 on hERG.

The Applicant also evaluated the effects of gepotidacin on late sodium (Nav1.5) current (2020N451703_00, link) using the CS-IRT recommended protocol (Version 06.13.2018) at room temperature, which includes 150 nM ATX-II to induce the late Nav1.5 current. The inhibition during the ramp step for the positive control 100 uM ranolazine was 88% compared to no inhibition of gepotidacin at the highest concentration (100 µM). Considering the IC_{50} for hERG of 1.31 mM, it is unclear why the Applicant did not study higher concentrations than 100 µM.

The in vivo QT study (2011N125338_00, link) assessed the effects of gepotidacin on ECG parameters following IV administration of 0, 50, 100, 250 mg/kg divided into two doses administered 6 hours apart in male cynomolgus monkeys using a Latin square design (N=4). The Cmax at the highest dose is predicted to be ~53 µg/mL based on the tox studies in the same species ([2010n108579, link] and [2011n115793, link]). Protein binding was reported as 16% in a cynomolgus monkeys (RH2010-00038, link). The highest dose therefore provides ~4-fold coverage over high clinical. QT was corrected for heart rate based on individual correction. Dose-dependent QTc prolongation was observed in this study: 10 msec (50 mg/kg), 10 msec (100 mg/kg), 17 msec (250 mg/kg). Dose-dependent increase in HR and shortening in PR was also observed. QRS was only prolonged at the highest dose. The Applicant states that the AUC_{0-24} for M4 following the highest dose in the in vivo QT study is 14.8 µg*h/mL, which is 1.8-fold the 1500 mg BID exposure (Pharmacokinetic summary, section 8; link).

The in vivo QT study (CD2010-00166, link) assessed the effects of gepotidacin in beagle dogs using the same dosing and study design as the monkey study. The Cmax of the highest dose is predicted to be ~43 µg/mL based on the tox study in the dog (CD2009/00911, link). Protein binding was reported as 19.5% in a dogs (RH2010-00038, link). The highest dose therefore provides ~3-fold coverage over high clinical. QT was corrected for heart rate based on individual correction. No prolongation of the QTc interval was observed in this study. Increase in HR was observed.

The Applicant also evaluated the effects of gepotidacin on pseudo-ECG parameters in the isolated, arterially-perfused rabbit left ventricular wedge preparation (2011N116120_00, link) at the pacing rate of 1 s. This study included doses ranging from 30 – 600 uM. QT intervals were prolonged by ~25 ms, ~65 ms, ~99 ms and ~99 ms at concentrations of 30 µM (~1.2x the high clinical exposure), 100 µM (~4x the high clinical exposure), 300 µM (~12x the high clinical exposure) and 600 µM (~24x the high clinical exposure), respectively. The dose-dependent QT prolongation caused by gepotidacin is likely a result of its hERG current inhibition. QRS intervals were prolonged by ~6 ms at 300 µM and ~14 ms at 600 µM, suggesting gepotidacin may also inhibit the inward sodium current at high concentrations.

2.4 Clinical Cardiac Safety

2.4.1 Phase 1 and Phase 2 studies

Refer to Summary of Clinical Safety; link

Of 16 Phase 1 and Phase 2 studies, cardiovascular (CV) AESI occurred in 4 studies (BTZ116576, 207729, 209611, 213678). Across the 4 studies, gepotidacin was administered orally (1500 mg single dose, 3000 mg single dose, or 2×3000 mg [6 or 12 hours apart]) to healthy adolescents, healthy adults, or adults with uncomplicated urogenital gonorrhea.

By PT, the CV events occurring with gepotidacin administration were:

- tachycardia (BTZ116576 [1 participant], 207729 [1 participant], 209611 [1 participant], and 213678 [1 participant])
- arrhythmia (209611 [1 participant])
- supraventricular extrasystoles (209611 [1 participant])
- ventricular extrasystoles (213678 [1 participant])
- atrioventricular block first degree (213678 [1 participant])

All CV AESI were mild/Grade 1 in maximum severity with the exception of tachycardia in Study 207729 which was Grade 2 in maximum intensity. All CV AESI were considered recovered/resolved and non-serious. The majority of CV AESI were not considered related to study treatment with the following considered related to study treatment: tachycardia (BTZ116576), supraventricular extrasystoles (209611), ventricular extrasystoles (213678).

2.4.2 EAGLE-2

Study Eagle-2 (204989) was a Phase III, randomized, multicenter, parallel-group, double-blind, double-dummy study in adolescent and adult female participants comparing the efficacy and safety of gepotidacin to nitrofurantoin in the treatment of uncomplicated urinary tract infection.

Participants were treated with 1500 mg gepotidacin BID or 100 mg nitrofurantoin BID for 5 days. No scheduled post-dose ECGs were included in this study.

No treatment-emergent AEs related to QTc prolong or Torsade de pointes were identified using our custom query in this study.

2.4.3 EAGLE-3

Study Eagle-3 was a Phase III, randomized, multicenter, parallel-group, double-blind, double-dummy study in adolescent and adult female participants comparing the efficacy and safety of gepotidacin to nitrofurantoin in the treatment of uncomplicated urinary tract infection.

Participants were treated with 1500 mg gepotidacin BID or 100 mg nitrofurantoin BID for 5 days. Triplicate 12-lead ECGs were collected at baseline and on-therapy visit (Day 2 - 4) for the first approximately 1200 patients at 2 hours (ideally 1.5 – 4 h) postdose (i.e., Tmax).

No participants had a QTc > 500 msec or an increase over baseline of > 60 msec. There were more participants had an increased QTcF in the gepotidacin 1500 mg BID compared to the nitrofurantoin 100 mg BID group. The results are consistent with the Applicant's analysis.

Two participants experienced a treatment-emergent AE related to QTc / Torsade de pointes based on our custom query. One in the gepotidacin 1500 mg BID group (QTc prolongation: mild) and one in the nitrofurantoin 100 mg BID group (seizure: mild).

Table 2: Maximum post-dose QTcF and QRS in EAGLE 3, Safety Population

Parameter Level	Gepotidacin 1500 mg BID[1] N=804 n/Nw (%)	Nitrofurantoin 100 mg BID N=798 n/Nw (%)
QTcF, high, (msec)		
Level 1 (>480)	1/718 (0.1)	1/729 (0.1)
Level 2 (>500)	0/718 (0.0)	0/729 (0.0)
Level 3 (>500 & CFB > 60)	0/718 (0.0)	0/729 (0.0)
QTcF, high (delta), (msec)		
Level 1 (>30)	12/718 (1.7)	4/729 (0.5)
Level 2 (>60)	0/718 (0.0)	0/729 (0.0)
QRS, high, (msec)		
Level 1 (>120)	11/725 (1.5)	8/739 (1.1)
Level 2 (>120 & >25%)	0/725 (0.0)	0/739 (0.0)

[1]: Includes two participants treated with gepotidacin 1500 mg BID and nitrofurantoin 100 mg BID.

Source: Reviewer's analysis

2.4.4 EAGLE-J

Study Eagle-J was a Phase III, randomized, multicenter, parallel-group, double-blind, double-dummy study Japanese female participants comparing the efficacy and safety of gepotidacin to nitrofurantoin in the treatment of uncomplicated urinary tract infection.

Participants were treated with 1500 mg gepotidacin BID or 100 mg nitrofurantoin BID for 5 days. Triplicate 12-lead ECGs were collected at baseline and on-therapy visit (Day 2 - 4) for the first approximately 1200 patients at 2 hours (ideally 1.5 – 4 h) postdose (i.e., Tmax).

The Applicant reports QTcF > 500 msec in any participant.

Two participants were discontinued due to QTc prolongation (increase from baseline > 60 msec) in gepotidacin-treatment group:

- (b) (6) (73-year-old female): Baseline QTcF of 412 msec. The Applicant states that the baseline is 427 msec in the 90-day summary, but this is not consistent with Listing 12. The QTc was increased to 492 msec (ΔQTc = 80 msec) on day 4 when treatment was discontinued. On day 10 the QTcF was 427 msec. No other AEs related to QTc prolongation were reported for this participant. The Applicant states that the QTc prolongation was not confirmed via manual over-read.

- (b) (6) (79-year-old female): Baseline QTcF of 367 msec. After the first dose, the QTcF was reported as 460 msec (ΔQTc = 93 msec) and treatment was discontinued. The Applicant states that the QTc prolongation was not confirmed via manual over-read.

Additionally, one participant was discontinued from gepotidacin due to ST-elevation.

The Applicant also reports two additional AEs (grade 1) of QTc shortening and ventricular extrasystoles, both in the gepotidacin group.

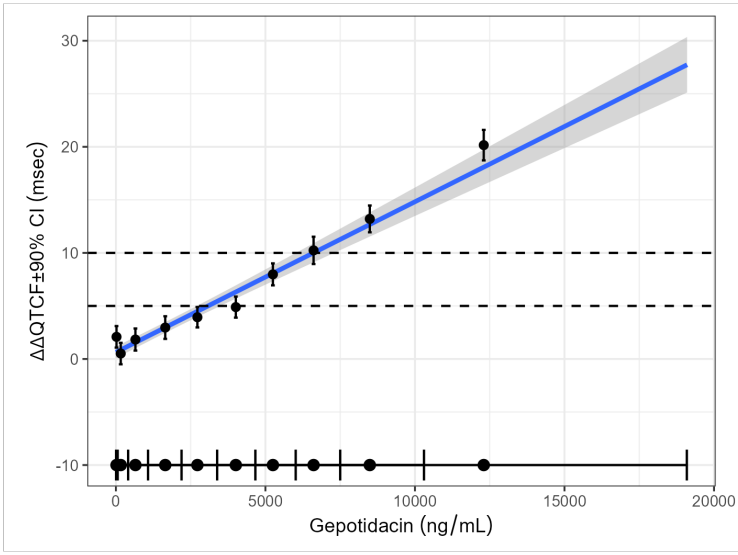
2.5 Summary results of prior QTc assessments

The Applicant previously conducted a TQT study (4-way cross-over study) for gepotidacin using an IV formulation. We previously reviewed the TQT study under IND 111885 and concluded that gepotidacin was associated with an increase in QTc and HR (DARRTS 06/06/2016). The increase in HR was 6.7 and 10.4 beats/min for the 1000 and 1800 mg IV, respectively.

Figure 1 shows the goodness-of-fit plot for QTcF for the TQT study analyzed using the concentration-QTc model proposed in the white paper. The predicted increases in ΔΔQTcF for the clinical and high clinical exposures are shown in Table 3. These predictions assume only gepotidacin concentrations contribute to the observed QTc prolongation. While the lack of hysteresis between gepotidacin ΔΔQTc could suggest that gepotidacin might be the most significant contributor (Figure 2), we are unable to confirm this because M4 was not measured in the TQT study. Moreover, it is uncertain how the M4 exposures following the IV administration in the TQT study compares to repeat oral administration. Consequently, it is uncertain if the predicted ΔΔQTc can be used to predict the increase in QTc after oral administration.

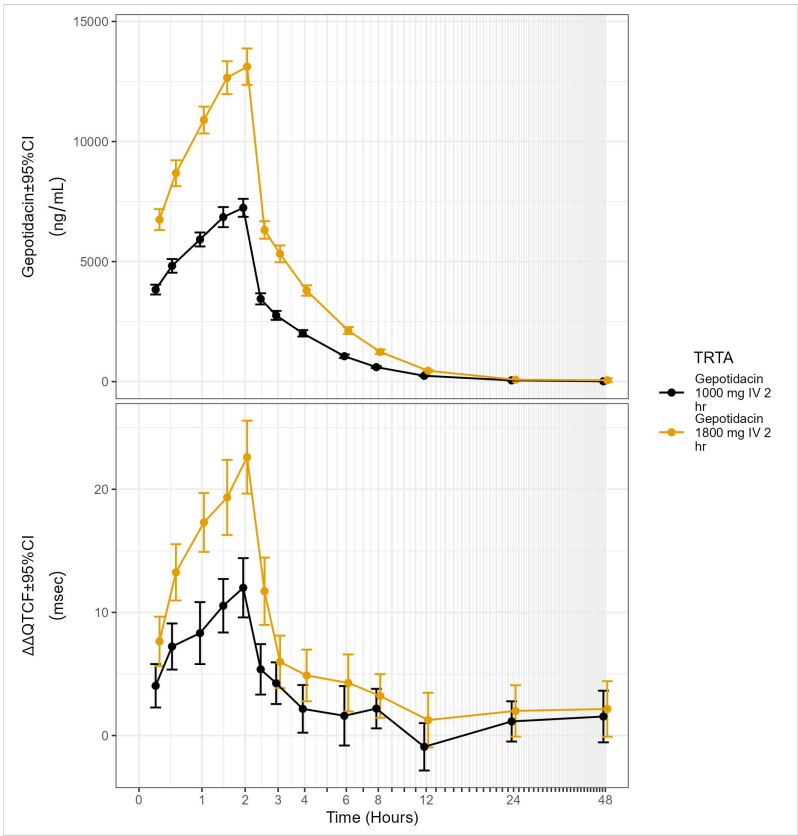
Concentration-dependent QRS prolongation was also observed, however, the magnitude of QRS prolongation is minimal (i.e., ~1 msec at the 1800 mg IV dose).

Figure 1: Goodness-of-Fit Plot for QTcF



Source: Reviewer's analysis

Figure 2: Time-Course of Drug Concentration (Top) and QTcF (Bottom)



Source: Reviewer's analysis

Table 3: Predicted increase in ΔΔQTcF

Actual Treatment	Gepotidacin (µg/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
1500 mg BID, oral tablets	8.44	12.6	(11.5 to 13.7)
1.9-fold increase in patients with severe hepatic impairment	16.88	24.6	(22.3 to 26.9)

Source: Reviewer's analysis

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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