CENTER FOR DRUG EVALUATION AND RESEARCH

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

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Reviewer Name(s)	Celeste Will, PharmD, MPH
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Review Completion Date	March 25, 2025
Subject	Evaluation of Need for a REMS
Established Name	gepotidacin
Trade Name	Blujepa
Name of Applicant	GlaxoSmithKine LLC (GSK)
Therapeutic Class	triazaacenaphthylene bacterial type II topoisomerase inhibitor
Formulation(s)	immediate release tablet
Dosing Regimen	1,500 mg orally twice daily (approximately 12 hours apart) for 5 days

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Blujepa (gepotidacin) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKine LLC (GSK) submitted a New Drug Application (NDA) 218230 for gepotidacin with the proposed indication for treatment of uncomplicated urinary tract infections (uUTI) in female adults and adolescents from 12 years of age, both weighing at least 40 kilograms (kg). The anticipated FDA approved indication will be for the treatment of female adult and pediatric patients 12 years of age and older weighing at least 40 kilograms (kg) with uUTI caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii complex*, *Staphylococcus saprophyticus*, and *Enterococcus faecalis*. The risks associated with gepotidacin include QTc prolongation, acetylcholinesterase inhibition, hypersensitivity reactions, *Clostridioides difficile (C. difficile)* infection (CDI), and development of drug resistant bacteria. The applicant did not submit a REMS with this application however they did submit a risk management plan which proposes routine pharmacovigilance activities including adverse reactions reporting and signal detection.

DRM has determined that a REMS is not needed to ensure the benefits of gepotidacin outweigh its risks. The efficacy of gepotidacin was demonstrated in Trial 1 and Trial 2. In Trial 1, gepotidacin was non-inferior to nitrofurantoin for the primary efficacy endpoint of clinical and microbiological response.[1] In Trial 2, gepotidacin was superior to nitrofurantoin for the primary efficacy endpoint of clinical and microbiological response.[1] The clinical reviewer concluded these trials provide evidence to support the proposed indication. The risks of QTc prolongation, acetylcholinesterase inhibition, hypersensitivity reactions, CDI, and development of drug resistant bacteria will be addressed in the warnings and precautions section of the label. The likely prescribers will be primary care providers, such as internal medicine practitioners including nurse practitioners and physician assistants, family physicians, and obstetrics and gynecology practitioners who are expected to be familiar with the management of the risks observed with gepotidacin.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Blujepa (gepotidacin) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKine LLC (GSK) submitted a New Drug Application (NDA 218230) for gepotidacin with the proposed indication for treatment of uncomplicated urinary tract infections (uUTI) in female adults and adolescents from 12 years of age, both weighing at least 40 kilograms (kg). The anticipated FDA approved indication will be for the treatment of female adult and pediatric patients 12 years of age and older weighing at least 40 kilograms (kg) with uUTI caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii complex*, *Staphylococcus saprophyticus*, and *Enterococcus faecalis*.[2] This application is under review in the Division of Anti-infectives (DAI). The applicant did not submit a REMS with this application but proposed a risk management plan that consists of routine pharmacovigilance activities, adverse reaction reporting, and signal detection.[3]

2. Background

2.1. Product Information

Gepotidacin, a new molecular entity[a], is a triazaacenaphthylene bacterial type II topoisomerase inhibitor proposed for treatment of uncomplicated urinary tract infections (uUTI) in female adult and pediatric patients 12 years of age and older weighing at least 40 kg.[2] Gepotidacin inhibits bacterial DNA replication by a distinct binding site, a unique mechanism of action, and provides well-balanced inhibition (for most uUTI uropathogens) of 2 different Type II topoisomerase enzymes and which confers activity against most isolates of UTI uropathogens, such as E*. coli, K. pneumoniae, P. mirabilis, C. freundii complex, S. saprophyticus and E. faecalis*, including those resistant to marketed antibiotics.[4] Due to gepotidacin's distinct binding site and unique inhibition of DNA gyrase and topoisomerase IV, gepotidacin shows no in vitro target-specific cross-resistance with other classes of antibiotics and has excellent in vitro activity against gram-negative and gram-positive clinical isolates, associated with uUTIs, that carry resistance determinants to established agents.[4]

Gepotidacin is proposed as a 1,500 mg immediate release oral tablet.[4] The proposed dosing regimen is gepotidacin 1,500 mg oral tablet twice daily (approximately 12 hours apart) for 5 days.[4] Gepotidacin is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for gepotidacin NDA 218230 relevant to this review:

- 10/28/2013: Fast track designation granted for IND 111885
- 07/26/2024: NDA 218230 submission received for treatment of uncomplicated urinary tract infections (uUTI) in female adults and adolescents from 12 years of age, both weighing at least 40 kg.
- 12/10/2024: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for gepotidacin.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Uncomplicated urinary tract infections, as defined by the FDA Guidance for Industry in 2019, are a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local signs and symptoms such as lower abdominal discomfort and dysuria and 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.[5] Risk factors for

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

uUTI include recent sexual intercourse, use of spermicides, and a history of prior urinary tract infections.[6] Pathogens causing uUTI include *Escherichia coli*, other species of Enterobacteriaceae such as *Proteus mirabilis* and *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus*.[7] Bacterial resistance is an important issue with urinary tract infections, especially with the emergence of infections caused by extended-spectrum beta-lactamase (ESBL) producing bacteria.[8] UTIs are one of the most common bacterial outpatient infections, with a lifetime incidence of 50% to 60% in adult females.[9] It is estimated that 10% to 12% of adult women in the United States have at least one UTI per year, with 20% to 30% of those having a recurrent infection.[b,10] The goal of uUTI treatment is to resolve acute symptoms and reduce the risk of infection progression to the upper urinary tract (e.g., pyelonephritis).[c]

3.2. Description of Current Treatment Options

The *International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases* list a number of first line antimicrobial agents for uUTI.[7] Antimicrobial selection depends on a patient's allergy and compliance history, local practice patterns, local community resistance prevalence, availability, cost, and patient and provider threshold for failure.[7] The following agents are recommended as optimal, first-line treatment for acute uncomplicated cystitis: nitrofurantoin monohydrate/macrocrystals, trimethoprim-sulfamethoxazole, fosfomycin trometamol, and pivmecillinam.[7] The aforementioned guidelines also recommend fluoroquinolones however, while fluoroquinolones are effective for uncomplicated urinary tract infections, there is a propensity for antibiotic resistance, therefore fluoroquinolones should be reserved for important uses other than acute cystitis and thus are considered alternative antimicrobials for acute cystitis.[7] In addition, the guidelines recommend β-lactam agents such as amoxicillin clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil when other recommended agents cannot be used due to inferior efficacy.[7]

Macrobid (nitrofurantoin monohydrate/macrocrystals), a nitrofuran antimicrobial agent, was approved by the FDA in 1991; it is indicated only for the treatment of acute uUTI (acute cystitis) caused by susceptible strains of *Escherichia coli* or *S. saprophyticus*.[10] The serious risks associated with nitrofurantoin monohydrate/macrocrystals include pulmonary reactions, hepatotoxicity, neuropathy, hemolytic anemia, and *Clostridium difficile*-associated diarrhea (CDAD).[10] Monurol (fosfomycin tromethamine), a phosphonic acid derivative, was approved by the FDA in 1996; it is indicated only for the treatment of uUTI (acute cystitis) in women due to susceptible strains of E. coli and Enterococcus faecalis.[11] The serious risk associated with fosfomycin tromethamine include CDAD.[11] Bactrim (sulfamethoxazole and trimethoprim), a combination of a sulfonamide antimicrobial agent and a dihydrofolate reductase inhibitor antibacterial agent, was approved by the FDA in 1973; it is approved for indications including the treatment of urinary tract infections due to susceptible strains of the

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

following organisms: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Morganella morganii*, *P. mirabilis*, and *Proteus vulgaris*.[12] The serious risks associated with sulfamethoxazole and trimethoprim include embryo-fetal toxicity, hypersensitivity and other serious or fatal reactions, thrombocytopenia, Streptococcal infections and rheumatic fever, CDAD, risk associated with concurrent use of leucovorin for *Pneumocystis jirovecii* pneumonia, development of drug resistant bacteria, folate deficiency, hemolysis, hypoglycemia, impaired phenylalanine metabolism, porphyria and hypothyroidism, potential risk in the treatment of *Pneumocystis jirovecii* pneumonia in patients with Acquired Immunodeficiency Syndrome (AIDS), and electrolyte abnormalities.[12]

Recently, Pivya (pivmecillinam), a penicillin class antibacterial agent, was approved by the FDA in 2024 for the treatment of female patients 18 years of age and older with uUTI caused by susceptible isolates of E. coli, P. mirabilis, and S. saprophyticus.[13] The serious risks associated with pivmecillinam include hypersensitivity reactions, severe cutaneous adverse reactions, carnitine depletion, acute porphyria, CDAD, development of drug-resistant bacteria, and interference with newborn screening test.[13] In addition, Orlynvah (sulopenem etzadroxil and probenecid) a penem antibacterial, and probenecid, a renal tubular transport inhibitor was approved by the FDA in 2024 for the treatment of uUTI caused by the designated microorganisms *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.[14] The serious risks associated with sulopenem etzadroxil and probenecid include hypersensitivity reactions, CDAD, and exacerbation of gout.[14]

Nitrofurantoin monohydrate/macrocrystals, sulfamethoxazole and trimethoprim, fosfomycin tromethamine, pivmecillinam, and sulopenem etzadroxil and probenecid do not have a boxed warning in their respective labels and none of these drugs have a REMS. Please refer to DAI integrated review for gepotidacin for a detailed clinical review on treatment armamentarium relevant to the proposed indication.[1]

4. Benefit Assessment

The trials supporting this application for gepotidacin consisted of two phase 3, randomized, multicenter, double-blind, active-controlled noninferiority clinical trials in adolescent and adult females with uUTI, Trial 1 (NCT04020341) and Trial 2 (NCT04187144).[1, 2] In both trials, patients were randomized to gepotidacin 1500 mg administered orally twice daily for 5 days or the active control nitrofurantoin 100 mg twice daily for 5 days.[1] The primary efficacy endpoint in both trials was a composite endpoint assessing clinical and microbiological response using a prespecified noninferiority margin of 10%.[1] Clinical cure was defined as resolution of all signs and symptoms of acute cystitis present at baseline and no new signs and symptoms without the patient receiving other systemic antimicrobials.[2] Microbiological response was defined as having all qualifying uropathogens found at baseline at ≥105 CFU/mL reduced to <103 CFU/mL without the patient receiving other systemic antimicrobials.[2] Both trials demonstrated noninferiority with the therapeutic endpoints (therapeutic, clinical, and microbiological success) to nitrofurantoin 100 mg twice daily for the treatment of uUTI in female patients at test of cure (TOC).[1]

In Trial 1, 1680 subjects were screened and 1531 subjects were randomized.[1] Conclusion of efficacy was based on interim analysis as pre-specified in the protocol.[1] The interim analysis was conducted when 607 subjects in the micro-ITT NTF-S set achieved the TOC visit.[1] The composite response was defined as participants who experienced both a reduction of all qualifying bacterial pathogens on baseline culture (microbiological success) and complete resolution of all signs and symptoms of uUTI present at baseline (clinical success), without receipt of other systemic antimicrobials.[1] Clinical success was assessed for each participant by the study investigators.[1] Treatment with gepotidacin [162/320 (50.6%)] demonstrated non-inferiority to the active control of nitrofurantoin [135/287 (47.0%)] with a treatment difference of 4.3% (-3.6, 12.1) in eligible nitrofurantoin-susceptible organisms and 95% confidence interval of -3.6%, 12.1%.[1] Superiority was not demonstrated.[1]

In Trial 2, 1731 subjects were screened and 1605 subjects were randomized.[1] Conclusion of efficacy was based on interim analysis as pre-specified in the protocol.[1] The interim analysis was conducted when 541 subjects in the micro-ITT NTF-S set achieved the TOC visit. Treatment with gepotidacin [162/277 (58.5%)] demonstrated non-inferiority to the active control of nitrofurantoin [115/264 (43.6%)] with a treatment difference of 14.6% (6.4, 22.8) in eligible nitrofurantoin-susceptible organisms and 95% confidence interval of 6.4%, 22.8%.[1] Superiority of gepotidacin to nitrofurantoin was also demonstrated.[1]

The clinical reviewer concluded that based on review of all available efficacy data, gepotidacin provides substantial evidence of effectiveness.[d,1]

5. Risk Assessment & Safe-Use Conditions

The safety of gepotidacin was primarily focused upon the data from the two phase 3 studies, Trial 1 and Trial 2; summarized results from a third phase 3 study were submitted during the review and were reviewed by the clinical team.[1] The third phase 3 study investigated the efficacy and safety of gepotidacin in Japanese females with uUTI however complete datasets were not submitted and were not incorporated into the primary safety analysis.[1] The safety database consists of 1570 subjects who received at least one dose of gepotidacin.[1] The overall incidence of Treatment-Emergent Adverse Events (TEAEs) was 35.1% in the gepotidacin arm and 23.4% in the nitrofurantoin arm.[1] Most TEAEs were mild or moderate in severity.[e,1] The rate of serious adverse events (SAEs) was balanced between gepotidacin (0.4%) and nitrofurantoin arms (0.5%).[1] No grade 4 or 5 TEAEs were observed, and no deaths were observed.[1] TEAEs leading to permanent discontinuation of study drug occurred more frequently in the gepotidacin arm (79/1570, 5%) compared to the nitrofurantoin arm (30/1558, 1.9%).[1] Adverse reactions

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

reported with gepotidacin included diarrhea, nausea, abdominal pain/discomfort, flatulence, headache, feces soft, dizziness, and vomiting.[15]

The risks associated with gepotidacin include QTc prolongation, acetylcholinesterase inhibition, hypersensitivity reactions, *Clostridioides difficile (C. difficile)* infection (CDI), and development of drug resistant bacteria.[1]

5.1. QTc Prolongation

Gepotidacin can cause QTc prolongation at the proposed uUTI dose.[1] Analysis of cardiac TEAEs suggest that the risk of QTc prolongation in individuals who receive gepotidacin is generally very low, particularly in the absence of cardiac risk factors.[1] Therefore, most individuals do not need ECG monitoring while receiving gepotidacin.[1] The proposed label recommends to avoid gepotidacin in patients with a history of QTc interval prolongation or those with relevant preexisting cardiac disease, patients taking antiarrhythmic agents or other medications that may potentially prolong the QTc interval, concomitant administration of gepotidacin with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole), in patients with severe hepatic impairment (Child-Pugh Class C), or in patients with severe renal impairment (eGFR < 30 mL/min), and if administration of gepotidacin cannot be avoided, patients should be monitored for serum electrolyte abnormalities and corrected in addition to collecting an ECG prior to administration and during treatment, as clinically indicated.[2]

5.2. Acetylcholinesterase Inhibition

Cholinergic TEAEs occurred in subjects who received gepotidacin in the two phase 3 studies (375, 24%).[1] These cholinergic TEAEs included dysarthria, presyncope, muscle spasms, diarrhea, nausea, vomiting, abdominal pain, hypersalivation, and hyperhidrosis.[2] Most cholinergic TEAEs were gastrointestinal in nature (diarrhea [14.8%], nausea/vomiting [8.7%], and abdominal pain [2.7%]).[1] Most study subjects experienced a single acetylcholinesterase inhibition event that was mild or moderate in severity.[1] Additionally, the majority of cholinergic TEAEs occurred within the first 24 hours after study drug initiation.[1] No cholinergic TEAEs were considered ongoing at the time of study completion.[1] The proposed label recommends to monitor patients with medical conditions that may be exacerbated by acetylcholinesterase inhibition, for exaggerated neuromuscular blockade or excessive cholinergic effects, and patients concomitantly administered systemic anticholinergic medications or non-depolarizing neuromuscular blocking agents.[2]

5.3. Hypersensitivity Reactions

Twenty-one subjects exposed to gepotidacin in the clinical studies reported TEAEs of hypersensitivity, drug hypersensitivity, pruritis, rash, or mouth swelling.[1] The clinical review team attributes 11 hypersensitivity reactions that occurred during the clinical studies to gepotidacin, all of which were classified as mild events.[1] The proposed label recommends to carefully inquire about previous hypersensitivity reactions to gepotidacin before therapy with gepotidacin is instituted and if an allergic reaction to gepotidacin occurs, discontinue the drug and institute appropriate supportive measures.[2]

5.4. *Clostridioides difficile*-Infection

C. difficile infection (CDI) has been reported with nearly all systemic antibacterial drugs, including gepotidacin. Infections due to hyper toxin-producing strains of *C. difficile* may be serious with an increased morbidity and mortality.[2] The proposed label states CDI must be considered in all patients who present with diarrhea following antibacterial drug use.[2] Careful medical history is necessary since CDI has been reported to occur over 2 months after the administration of antibacterial agents.[2] In addition, if CDI is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued and appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.[2]

5.5. Development of Drug Resistant Bacteria

As with other antibacterial agents, using gepotidacin in the absence of a proven or strongly suspected susceptible uUTI may increase the risk of the development of drug-resistant bacteria. See Section 8 for further discussion. If approved, this risk will be communicated in the warnings and precautions section of the label.

6. Expected Postmarket Use

Uncomplicated urinary tract infection (uUTI) is typically diagnosed in ambulatory care settings such as urgent care, emergency departments, telemedicine visits, or physician offices. Patients diagnosed with uUTI may otherwise be healthy. The likely prescribers will be primary care providers, such as internal medicine practitioners including nurse practitioners and physician assistants, family physicians, and obstetrics and gynecology practitioners. If approved, gepotidacin will likely be dispensed from retail pharmacy settings and primarily be self-administered by the patient at home for short term treatment. It is possible that gepotidacin might be dispensed from an inpatient hospital pharmacy and administered by a healthcare provider in a hospital setting. Based on the anticipated medication use process, monitoring for QTc prolongation, acetylcholinesterase inhibition, hypersensitivity reactions, CDI, and development of drug resistant bacteria should be a collaborative effort between the prescriber and the patient or patient's caregiver.

Anticipated potential care gaps exist in the medication use process for gepotidacin, however, these potential care gaps are similar for new products in general. For example, as a new product, technologies and controls such as alerts built into electronic health records (EHRs) might not be in place at the time the product is first marketed. While the risks of QTc prolongation and acetylcholinesterase inhibition may be less well known adverse events among antibiotics typically used to treat this condition, QTc prolongation is a known adverse event among fluoroquinolone antibiotics and signs and symptoms of acetylcholinesterase inhibition such as gastrointestinal symptoms are common patient experiences from taking antibiotics.[16] Therefore, we expect prescribers of gepotidacin to be able to manage the adverse events associated with gepotidacin.

In addition, health literacy, health coverage and access, and the ability of patients to reliably recognize symptoms of QTc prolongation, acetylcholinesterase inhibition, hypersensitivity reactions, CDI, and development of drug resistant bacteria vary among different patients. The use of a Medication Guide may facilitate communicating these risks to patients and instruct them in when to seek additional medical attention.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for gepotidacin beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of gepotidacin on the basis of the efficacy and safety information currently available.

Uncomplicated urinary tract infections are a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local signs and symptoms such as lower abdominal discomfort and dysuria and occur in females with normal anatomy of the urinary tract and are not accompanied by systemic signs or symptoms. The goal of uUTI treatment is to resolve acute symptoms and reduce the risk of infection progression to the upper urinary tract. Bacterial resistance is an important issue with urinary tract infections, especially with the emergence of infections caused by resistant bacteria. It is estimated that 10% to 12% of adult women in the United States have at least one UTI per year, with 20% to 30% of those having a recurrent infection. The efficacy of gepotidacin was demonstrated in Trial 1 and Trial 2. In Trial 1, gepotidacin was non-inferior to nitrofurantoin for the primary efficacy endpoint of clinical and microbiological response.[1] In Trial 2, gepotidacin was superior to nitrofurantoin for the primary efficacy endpoint of clinical and microbiological response.[1]

The risks associated with gepotidacin include QTc prolongation, acetylcholinesterase inhibition, hypersensitivity reactions, CDI, and development of drug resistant bacteria will be communicated in the warnings and precautions section of the label.[1] None of the risks associated with gepotidacin rise to the level of a boxed warning. Overall, gepotidacin has a favorable safety profile, and risks will be adequately addressed in the warnings and precautions section of the labeling, communicated to patients using a Medication Guide, and monitored in the postmarket setting by routine pharmacovigilance.

Based on the efficacy and risks associated with gepotidacin for the treatment of uUTI, this reviewer's recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks; all risks can be adequately communicated with prescribing information.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, the DAI and DRM agree that a REMS is not necessary for gepotidacin to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety

information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

1. Integrated Review for gepotidacin. 2025.
2. Draft prescribing information for gepotidacin as currently edited by FDA. 2025.
3. GlaxoSmithKine. Global Risk Management Plan. 2024.
4. GlaxoSmithKine. Clinical Overview. 2024.
5. Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry. 2019.
6. Kalpana Gupta M, MPH. Acute simple cystitis in adult females. 2024.
7. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103-120.
8. Steiger SN, Comito RR, Nicolau DP. Clinical and economic implications of urinary tract infections. Expert Rev Pharmacoecon Outcomes Res. 2017;17(4):377-383.
9. Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol. 2019;11:1756287219832172.
10. Kaye KS, Gupta V, Mulgirigama A, et al. Antimicrobial Resistance Trends in Urine Escherichia coli Isolates From Adult and Adolescent Females in the United States From 2011 to 2019: Rising ESBL Strains and Impact on Patient Management. Clin Infect Dis. 2021;73(11):1992-1999.
11. Fosfomycin Tromethamine [Prescribing Information] Available: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aacd04a4-f2d5-45a2-b9e7-0e92244a5880. Accessed February 20, 2025.
12. Bactrim [Prescribing Information] Available: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=017377. Accessed February 20, 2025.
13. Pivya [Prescribing Information] Available: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed February 20, 2025.
14. Orlynvah [Prescribing Information] Available: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed February 20, 2025.
15. FDA Midcycle Meeting. Division of Anti-infectives (DAI).
16. Tilton JJ, Sanoski C, Bauman JL. The Arrhythmias. In DiPiro JT, Yee GC, Posey LM, et al., (Eds). Pharmacotherapy: A Pathophysiologic Approach, 11e. New York, NY: McGraw-Hill Education 2020.

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