Gepotidacin Receives FDA Approval for uUTIs in Adult, Pediatric Female Patients

Key Takeaways

- Gepotidacin is a first-in-class antibiotic approved for uUTIs in females aged 12 and older, effective against resistant strains.
- EAGLE-2 and EAGLE-3 trials showed gepotidacin's non-inferiority and superiority over nitrofurantoin in treating uUTIs.
- The drug's unique mechanism targets bacterial DNA replication, requiring specific mutations to affect susceptibility.
- Gastrointestinal adverse events were the most common, with most being mild to moderate in severity.

Gepotidacin is indicated for female patients who are at least 12 years of age and weigh at least 40 kg with uncomplicated urinary tract infections (uUTIs) caused by certain microorganisms.

The FDA approved gepotidacin (Blujepa; GSK) for the treatment of female adult and pediatric patients aged 12 years and older and weighing at least 40 kg with uncomplicated urinary tract infections (uUTIs) caused by the following susceptible microorganisms: Escherichia coli (E coli), Klebsiella pneumoniae, Citrobacter freundii complex, Staphylococcus saprophyticus (S saprophyticus), and Enterococcus faecalis. The approval is based on positive results from the phase 3 EAGLE-2 (NCT04020341) and EAGLE-3 (NCT04187144) clinical trials.[1,2]

Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that prevents bacterial DNA replication through a distinct mechanism of action and a unique binding site, delivering well-balanced inhibition of 2 type II topoisomerase enzymes. This provides activity against most target uropathogens—such as E coli and S saprophyticus—and Neisseria gonorrhoeae, including isolates resistant to current antibiotics. Because of the well-balanced inhibition for most pathogens, gepotidacin target-specific mutations in both enzymes are needed to significantly affect the susceptibility to the agent.1,2 In October 2024, it received a priority review from the FDA for this indication following safety and efficacy data in the EAGLE clinical trials.[3]

“The approval of [gepotidacin] is a crucial milestone, with uUTIs among the most common infections in women. We are proud to have developed [gepotidacin], the first in a new class of oral antibiotics for uUTIs in nearly 3 decades, and to bring another option to patients given recurrent infections and rising rates of resistance to existing treatments,” Tony Wood, chief scientific officer of GSK, said in a news release.[1]

EAGLE-2 and EAGLE-3 are randomized, multicenter, parallel-group, double-blind, double-dummy phase 3 clinical trials that compared the efficacy and safety of gepotidacin to nitrofurantoin (Furadantin; Casper Pharma) in female patients aged 12 years and older with uUTIs. The trials enrolled 1531 and 1605 patients, respectively, and randomly assigned them to receive either 1500 mg of gepotidacin or 100 mg of nitrofurantoin, both of which were administered orally twice per for 5 days. Across both trials, the planned duration of follow-up for participants was about 28 days.[1,2]

The primary end point was a stringent composite measure of efficacy, which combined clinical and microbiological response at the Test-of-Cure (ToC) visit that occurred days 10 through 13 in patients with qualifying uropathogens susceptible to nitrofurantoin.1,2 Safety analyses included patients who were randomly assigned and who received at least 1 dose of study treatment, noted the investigators.[2]

In EAGLE-2, gepotidacin showed non-inferiority in therapeutic success, occurring in approximately 50.6% (n = 162) of participants compared with 47.0% (n = 135) for nitrofurantoin (95% CI [-3.6, 12.1]). In EAGLE-3, gepotidacin demonstrated statistically significant superiority when compared with nitrofurantoin (1-sided p-value: .0003). Additionally, therapeutic success occurred in about 58.5% (n = 162) of participants compared with 43.6% (n = 115) of those treated with nitrofurantoin (95% CI [6.4, 22.8]).[1,2]

The safety and tolerability profile of gepotidacin observed in the EAGLE trials was consistent with prior research trials. The most reported adverse events (AEs) in patients receiving gepotidacin were gastrointestinal (GI), of which diarrhea (16%) and nausea (9%) were the most common. Additionally, among the participants who reported GI AEs in the gepotidacin group, the most common maximum severity was mild (69%; grade 1) and moderate (28%; grade 2). Participants with grade 3 GI AEs accounted for 3% of all patients with GI events and occurred. Across both trials, only 1 drug-related serious AE occurred in each treatment arm, according to the investigators.[1,2]

"For many, uUTIs can be a burden that severely impacts daily life. With an increasing number of patients experiencing recurrent infections, there remains a clear need for continued research of antimicrobials to help address ongoing patient challenges and the strain on health care systems," Thomas Hooton, MD, professor of clinical medicine, University of Miami School of Medicine, said in the news release.[1]

About the Trials

EAGLE-2

Trial Name: A Study to Evaluate Efficacy and Safety of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (UTI)

ClinicalTrials.gov ID: NCT04020341

Sponsor: GlaxoSmithKline

Completion Date (Estimated): November 30, 2022

EAGLE-3

Trial Name: Comparative Study to Evaluate Efficacy and Safety of Gepotidacin to Nitrofurantoin in Treatment of Uncomplicated Urinary Tract Infection (UTI)

ClinicalTrials.gov ID: NCT04187144

Sponsor: GlaxoSmithKline

Completion Date: December 1, 2022

REFERENCES

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