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Gepotidacin: The first-in-class triazaacenaphthylene antibiotic approved for the treatment of uncomplicated urinary tract infections

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SUMMARY: Uncomplicated urinary tract infection (uUTI) is a common bacterial infection in women. While the condition typically has a favorable prognosis, the widespread use of antibiotics has led to increasingly bacterial resistance, reducing the efficacy of traditional antibiotics. On March 25, 2025, the US Food and Drug Administration approved gepotidacin for the treatment of uUTIs caused by susceptible bacteria in female adult and pediatric patients 12 years of age and older weighing at least 40 kg. Gepotidacin is the first triazaacenaphthylene antibiotic approved for clinical use. It selectively binds to and inhibits both bacterial DNA gyrase and topoisomerase IV, disrupting bacterial DNA replication through a unique mechanism and thereby killing the pathogen. Results of clinical trials indicated the non-inferiority of gepotidacin compared to the current standard therapy, nitrofurantoin. The most frequently reported adverse reaction to gepotidacin was mild to moderate diarrhea. The approval of gepotidacin represents a progress in antibiotic innovation, offering novel perspectives on drug development while spurring global efforts to tackle the escalating challenge of antimicrobial resistance.

Keywords: gepotidacin, triazaacenaphthylene, uncomplicated urinary tract infection, DNA gyrase, topoisomerase IV

Uncomplicated urinary tract infection (uUTI) refers to a urinary tract infection in patients without functional or anatomical abnormalities of the urinary tract, renal impairment, or other underlying conditions that may predispose to infection or lead to severe complications (*1*). uUTI is a common infectious disease and is particularly prevalent among women, with approximately 50% of women experiencing at least one uUTI in their lifetime (*1*). While uUTI generally has a favorable prognosis, the increasing resistance of bacteria to first-line antibiotics like nitrofurantoin has raised the risk of treatment failure (*2*). The development of innovative therapies is critical to addressing challenges in uUTI management, and especially in cases involving drug-resistant infections.

On March 25, 2025, the US Food and Drug Administration approved gepotidacin for the treatment of female adult and pediatric patients 12 years of age and older weighing at least 40 kg with uUTI caused by the following susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii complex, Staphylococcus saprophyticus, and Enterococcus faecalis* (*3*). Gepotidacin is the first triazaacenaphthylene antibiotic approved that has bactericidal action by simultaneously inhibiting DNA gyrase and topoisomerase IV — two enzymes critical to bacterial DNA replication (*4*). Due to balanced dual-target inhibition by gepotidacin, bacteria require concurrent mutations in both enzymes to significantly reduce their susceptibility, thereby lowering the likelihood of resistance development.

The FDA approval was primarily based on positive data from two pivotal Phase III trials, EAGLE-2 and EAGLE-3 (*5*). Both were randomized, double-blind, non-inferiority studies evaluating gepotidacin (1,500 mg twice daily for 5 days) versus nitrofurantoin (100 mg twice daily for 5 days) for efficacy and safety in treating uUTI (*5*). The primary endpoint was the therapeutic response rate (clinical and microbiological) at the test-of-cure visit (days 10-13). In EAGLE-2, gepotidacin demonstrated non-inferiority with a treatment success rate of 50.6% versus 47.0% for nitrofurantoin (*5*). In EAGLE-3, gepotidacin achieved statistical superiority with a 58.5% success rate compared to 43.6% for the control (*5*). The most frequently reported adverse event (AE) due to gepotidacin was diarrhea (14% in EAGLE-2

and 18% in EAGLE-3) that was predominantly mild to moderate in severity, and no life-threatening or fatal events were observed (*5*).

Gepotidacin is the first novel oral antibiotic approved to treat uUTI in over two decades, offering a new treatment option, particularly in cases of suboptimal efficacy or emerging resistance to existing therapies. A point worth noting is that in a Phase III trial (EAGLE-1) to treat uncomplicated urogenital gonorrhea, gepotidacin demonstrated non-inferiority to the widely used combination therapy of intravenous ceftriaxone and oral azithromycin, suggesting its potential in treating this condition as well (*6*). More clinical studies need to be conducted to demonstrate the safety and efficacy of gepotidacin in the real world, but the approval of gepotidacin represents a progress in antibiotic innovation, offering novel perspectives on drug development while spurring global efforts to tackle the escalating challenge of antimicrobial resistance.

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