Oral Tebipenem Pivoxil is Non-Inferior to IV Ertapenem in Complicated Urinary Tract Infection (cUTI) and Acute Pyelonephritis (AP): ADAPT-PO Study

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Background
• The treatment of cUTI/AP with existing oral agents is complicated by the rapid increase in infections caused by pathogens that are co-resistant to multiple agents.1,2
• ESBL-producing Enterobacterales infections in hospitalized patients were the only major multidrug-resistant (MDR) pathogen in the U.S. with increasing evidence between 2012-2017, driven by a 64% increase in community infections.3
• Carbapenems have emerged as the preferred therapy for many MDR gram-negative bacterial infections, but are currently only available in the US as intravenous or intramuscular formulations.4
• Enterobacterales are co-resistant to multiple agents.1,2
• Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is an orally bioavailable carbapenem prodrug that is rapidly converted to its active metabolite tebipenem and in the plasma to the active moiety TBP-PI-HBr.5
• Tebipenem pivoxil-HBr is currently being developed in the United States as the first oral carbapenem for treatment of serious bacterial infections, including cUTI and AP.

Methods
• ADAPT-PO was a global, double-blind, double-dummy Phase 3 noninferiority study conducted at 95 sites in Central and Eastern Europe, South Africa, and the United States.

Primary objective was to evaluate the efficacy and safety of oral TBP-PI-HBr vs. intravenous (IV) ertapenem in hospitalized adult patients with cUTI or AP.
• The primary endpoint was overall response (composite clinical cure and microbiologic eradication) at the test-of-cure (TOC) visit (Day 19 ± 2) in the micro-ITT population (-12.5% NI Margin).

Results
• Infections caused by resistant Enterobacterales accounted for 88.4% in the safety population and 92.1% in the ITT population. (Table 1)
• Clinical improvement occurred in over 97% of patients in both treatment groups at EOT and were high and similar between treatment groups at EOT (>94% in both groups).
• In a phase 3 non-inferiority trial conducted in hospitalized patients with cUTI/AP, the primary objective was met: OR of ≥94% in both groups.
• In January 2021, the FDA granted Priority Review designation and confirmed the acceptance for substantive review of the NDA.6
• Drug-related SAE occurred in 0.3% patients in the TBP-PI-HBr group vs. 1.7% in the ertapenem group (Table 4).

Conclusions
• Oral tebipenem pivoxil hydrobromide is an investigational carbapenem antibiotic currently in development for the treatment of cUTI, including acute pyelonephritis.
• In a phase 3 non-inferiority trial conducted in hospitalized patients with cUTI/AP, the primary objective was met-tebipenem pivoxil hydrobromide (800mg PO q12h) was non-inferior to ertapenem (1g IV q24h).
• Overall response rates at TOC were similar between treatment groups (approximately 55% in the TBP-PI-HBr group vs. 62% in the ertapenem group) and were high and similar between treatment groups at EOT (>94% in both groups).
• Clinical improvement was observed in ≥94% of patients in both treatment groups at EOT and were high and similar between treatment groups at TOC and LFU.
• Safety tolerability of tebipenem pivoxil hydrobromide were comparable to the IV carbapenem comparator with most TEAEs categorized as mild or moderate in severity and non-treatment limiting.

References

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Table 1. Demographic and baseline characteristics (Safety Population).

Table 2. Uropathogens isolated from urine and/or blood at baseline (micro-ITT).

Table 3. Baseline pathogens isolated from urine and/or blood at baseline (micro-ITT).

Table 4. Incidence of adverse events (safety population, ITT).

Figure 1. Baseline pathogens isolated from urine and/or blood at baseline.

Figure 2. ADAPT-PO Study Design.

Figure 3. ADAPT-PO Analysis Populations.

Figure 4. Per-patient clinical response by visit (micro-ITT).

Figure 5. Primary and secondary efficacy endpoints at Test-of-Cure visit (micro-ITT population).

Figure 6. Per-patient microbiological response by visit (micro-ITT).