Gram-Negative Infections Due to Multidrug-Resistant Enterobacteriaceae | Decision Base | US | 2014

The increasing prevalence and severity of infections caused by multidrug-resistant (MDR) gram-negative pathogens, particularly MDR Enterobacteriaceae, and the meager pipeline of novel antibiotic therapies in development to treat gram-negative infections (GNIs) have resulted in limited treatment options for an increasing number of patients. Government efforts are under way to promote the development of novel antibiotics to treat these infections, including the Infectious Diseases Society of America’s proposed Limited Population Antibacterial Drug (LPAD) approval pathway. This regulatory pathway was submitted as part of the Antibiotic Development Plan to Advance Patient Treatment Act of 2013 (ADAPT), which was introduced into the House of Representatives in December 2013. The LPAD approval pathway and ADAPT legislation are designed to promote the prompt approval of drugs intended for diseases for which there is high unmet need. Although the regulatory environment for developing new antibiotic therapies has been challenging, the late-stage clinical pipeline for antibiotics against MDR gram-negative pathogens includes two promising cephalosporin/beta-lactamase inhibitor combinations: Cubist’s CXA-201 (ceftolozane/tazobactam) and AstraZeneca/Forest Laboratories’ CAZ-AVI (ceftazidime/avibactam). Other promising therapies in development include Tetraphase’s IV and oral tetracycline eravacycline; Achaogen’s next-generation aminoglycoside plazomicin; and Merck’s Primaxin plus MK-7655 (imipenem/cilastatin + MK-7655), a combination carbapenem/beta-lactamase inhibitor therapy. Despite these developments, opportunities remain for more therapies that can improve clinical cure rates and reduce all-cause mortality in patients with GNIs due to MDR Enterobacteriaceae. Recent changes to FDA and EMA guidelines for antibiotic drug development now provide pathways moving forward for manufacturers developing new antibiotics to treat serious GNIs for which treatment options are limited.

Questions Answered in This Report:

- Clinical cure and microbiological eradication are key goals in the treatment of GNIs due to *Enterobacteriaceae*. What are the key primary and secondary clinical trial end points with which new therapies are evaluated? How do U.S. and European infectious diseases (ID) specialists weight specific efficacy end points and other drug attributes in their prescribing decisions for GNIs due to *Enterobacteriaceae*?

- Increased microbiological eradication rates in patients with GNIs due to MDR *Enterobacteriaceae* (e.g., *Enterobacteriaceae* spp. that produce carbapenemases and/or
extended-spectrum beta-lactamases [ESBLs]) and drug availability in interchangeable intravenous (IV) and oral formulations are key areas of unmet need for GNIs due to Enterobacteriaceae, according to the insights of surveyed U.S. and European ID specialists. Which therapies in development for GNIs due to Enterobacteriaceae are poised to fulfill these needs? What clinical and/or regulatory challenges must drug developers overcome to capitalize on these areas of unmet need? What degree of improvement over currently available therapies do surveyed U.S. hospital pharmacy directors (PDs) seek from new therapies on key clinical attributes for which surveyed physicians indicate there is high unmet need?

- Clinical cure rates and 28-day all-cause mortality rates are key drivers of physicians’ prescribing decisions and are the focus of drug development for new therapies for GNIs due to Enterobacteriaceae. What trade-offs across these and other clinical attributes are U.S. ID specialists willing to make when considering the use of emerging therapies for the treatment of GNIs due to Enterobacteriaceae? Based on the trade-offs in price and performance across key drug attributes that U.S. ID specialists are willing to make, how do physician preference and prescribing likelihood vary across different target product profiles for GNIs due to Enterobacteriaceae?

- By 2022, eravacycline will emerge as the gold-standard therapy in our Drug Comparator Model because of its superior clinical profile over the key current therapies we evaluated. On what clinical attributes is eravacycline most differentiated from its competitors? Which current therapies are at greatest risk of being replaced by eravacycline?

**Scope:**

Attributes included in conjoint analysis based assessment of target product profiles for GNIs due to Enterobacteriaceae:

- Microbiological cure rate in patients with GNIs due to Enterobacteriaceae
- 28-day all-cause mortality rate in patients with HAP due to drug-resistant Enterobacteriaceae
- Activity against ESBL-producing Enterobacteriaceae
- Activity against carbapenem-resistant Enterobacteriaceae (CRE)
- Rate of adverse events
- Availability of interchangeable IV and oral formulations
- Drug price for 10- to 14-day course of therapy.

Attributes included in assessment of U.S. payers’ receptivity to new therapies for GNIs due to Enterobacteriaceae:

- Microbiological cure rates in patients with GNIs due to Enterobacteriaceae
- Activity against ESBL-producing Enterobacteriaceae
- Activity against CRE
- Dosing frequency and availability in interchangeable IV and oral formulations

Physicians surveyed: 60 U.S. and 31 European ID specialists.
Payers surveyed: 21 U.S. hospital PDs.

Comprehensive List of Therapies Included in Our Research and Modeling:

Current Therapies
- Piperacillin/tazobactam (Pfizer’s Zosyn/Tazocin, generics)
- Meropenem (AstraZeneca’s Merrem/Meronem, Dainippon Sumitomo’s Meropen, generics)
- Imipenem/cilastatin (Merck’s Primaxin, generics)
- Levofloxacin (Johnson & Johnson’s Levaquin, Sanofi’s Tavanic, Daiichi Sankyo’s Cravit, generics)
- Tigecycline (Pfizer’s Tygacil/Taigashiru)

Emerging Therapies
- Ceftolozane/tazobactam (Cubist’s CXA-201)
- Ceftazidime/avibactam (AstraZeneca/Forest Laboratories’ CAZ-AVI)
- Eravacycline (Tetraphase)
- Plazomicin (Achaogen’s ACHN-490)
- Imipenem/cilastatin plus MK-7655 (Merck’s Primaxin plus MK-7655)

Report Details
- Pub Date: April 2014