Category

Best Pharmaceutical Product

General Information

Company Name *

Innoviva Specialty Therapeutics, Inc.

Product/Solution Name *

Xacduro

Compound/Tech Name*

Sulbactam - Durlobactam

Trade Name *

Xacduro

Corporate Name *

Sulbactam - Durlobactam

Date of Approval *

2023-05-23

Indications *

XACDURO® (sulbactam-durlobactam) is indicated in patients 18 years of age and older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of Acinetobacter baumannii-calcoaceticus complex.

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468

Therapeutic Areas *

Pathogen - Targeted Antibacterial

Infectious Disease

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Background information and need for drug / device
(please be as specific as possible in your description; limit 500 words)

Bacterial antimicrobial resistance (AMR) is one of the most pressing global health threats of our time. In 2019 alone, it was directly responsible for 1.27 million deaths and contributed to nearly 5 million more (WHO, 2022). This silent pandemic undermines the very bedrock of modern medicine-jeopardizing surgeries, cancer treatments, and even childbirth.

The World Health Organization and US Centers for Disease Control and Prevention have both highlighted the alarming rise of AMR, predicting that without immediate and decisive intervention, AMR could cripple the global healthcare system, potentially costing it a staggering $1 trillion by 2050 (CDC, WHO 2024, World Bank).

One of the gravest AMR threats is Acinetobacter baumannii, a virulent gram-negative bacterium highlighted by the World Health Organization as a priority 1 pathogen, and by the US CDC as a critical and urgent threat pathogen, due to its role in lethal hospital-acquired infections such as pneumonia and bloodstream infections. Mortality rates for these infections can skyrocket to 70%, emphasizing the dire need for urgent intervention.

There are two key drivers for this growing threat. One - Acinetobacter baumannii boasts an unparalleled ability to acquire and upregulate an array of resistance mechanisms, rendering it impervious to nearly all antibiotic classes. Two - its astounding resilience allows it to persist in various healthcare settings for prolonged periods. These alarming characteristics were especially eye opening for clinicians treating US service members deployed to Iraq. These infections, were so challenging to treat that doctors referred to this lethal pathogen as "Iraqibacter."

Carbapenem-resistant Acinetobacter baumannii (CRAB) currently ranks as the fifth leading cause of AMR-associated death globally, claiming over 450,000 lives in 2019 alone. And due to COVID-related disruptions, CRAB infections in U.S. hospitals rose by 78% between 2019 and 2020 (CDC 2022). This alarming rise has left clinicians without a reliable standard-of-care treatment-until now.

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- Background_ISTTemplate.pptx

History of the development of the solution/product *
(please be as specific as possible in your description; 500 words)

For decades, the antibacterial sulbactam was used as the mainstay therapy for Acinetobacter infections. However, its effectiveness has waned significantly due to the gauntlet of resistance mechanisms, rendering the therapy increasingly ineffective.

Instead of discarding sulbactam altogether, the development program devised an innovative strategy to protect it from resistance. In essence, "rearming" sulbactam with a resistance inhibitor, to tackle the multidrug-resistant strains of Acinetobacter baumanii that have become prevalent in the hospital setting.

That breakthrough resistance inhibitor is durlobactam. Through cutting-edge, rational drug design, IST developed durlobactam, a unique beta lactamase inhibitor with an expanded spectrum, including class D beta lactamase enzymes - the key target for restoring sulbactam's activity against carbapenem-resistant Acinetobacter baumannii. The combination of sulbactam and durlobactam (XACDURO) has proven to be a potent combination, demonstrating robust activity against large numbers of multidrug resistant Acinetobacter globally (Karlowsky 2022).

The clinical program was designed in alignment with the FDA, utilizing an optimized pharmacokinetic/pharmacodynamic (PK/PD) package and a streamlined clinical trial model uniquely tailored to the challenges posed by rare, resistant pathogens. It included eight clinical studies in total, culminating in a pivotal Phase 3 trial conducted amidst the unprecedented global disruption of the COVID-19 pandemic.

In this pivotal Phase 3 trial, XACDURO demonstrated non-inferiority to colistin in 28-day all-cause mortality with a difference of 13.2% in favor of XACDURO. Clinical cure rates were 21.6% higher, and microbiologic success was 26% higher than colistin. Importantly, the XACDURO-treated patients had significantly less nephrotoxicity compared to colistin-13% versus 38%-providing a far safer alternative for critically ill patients.

Beyond clinical trials, XACDURO's Expanded Access Program (EAP), launched in 2020, has provided a lifeline for patients battling life-threatening infections-including COVID-related pneumonia, severe burns, and complex surgical infections. Real-world success cases, such as the recovery of patients with meningitis, underscores its unparalleled life-saving potential.

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Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition *

XACDURO is a bold departure from traditional antibiotic development, which has long prioritized broad-spectrum agents-a practice that can inadvertently fuel resistance and disrupt patient microbiomes. In contrast, XACDURO is a pathogen-targeted antibiotic - a precision medicine designed to treat one of the world's deadliest and most drug-resistant bacteria. This precision-focused approach marks a groundbreaking shift in the fight against severe infections, offering a targeted solution where it is needed most.

Despite numerous obstacles - technical, regulatory, and commercial - IST accomplished what few believed possible, the development and successful market introduction of a highly specific, effective, and safer antibiotic for CRAB. This achievement was realized through an innovative, collaborative, and forward-thinking alignment with the FDA and a pioneering clinical trial model that may serve as a template for future antimicrobial innovation and approval.

Specifically, that alignment focused on several principles from the FDA 2017 guidance): (1) focus on carbapenem-resistant Acinetobacter in HABP/VABP and bloodstream infections, which represent serious infections and areas of high unmet medical need; (2) provide extensive PK/PD profiling to optimize dosing; and (3) conduct a single, pivotal, Phase 3 noninferiority clinical trial, leveraging safety data from Phase 1 and 2 studies.

This flexibility in clinical trial design allowed IST to recruit from a smaller patient population while ensuring a statistically rigorous registrational trial. In the FDA advisory committee briefing book, the FDA acknowledged that XACDURO is the first example of a streamlined clinical development program for a targeted therapy addressing a high-unmet-need pathogen (FDA 2023). It should also be noted that this trial was conducted in a hospital setting in the height of the COVID-19 pandemic, a time that was prohibitive for many clinical trials across disease areas (Sathian 2020; Hillman 2022).

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- InnovationXacduro.pptx

Please provide appropriate references (PubMed, Abstract, Website) *

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