Acute Repetitive Seizures | Decision Base | US/EU | 2015

Acute repetitive seizures (ARS)—also known as serial, recurrent, or cluster seizures—is a phenomenon in treatment-refractory epilepsy that is characterized by a close temporal association of seizures that exceeds a patient’s typical baseline seizure frequency. ARS poses a risk of hospitalization and/or evolution into status epilepticus, a life-threatening seizure emergency, which underscores the need for early, effective management. Benzodiazepines are typically used as needed for rescue treatment in this orphan indication, being prescribed adjunctively to patients’ chronic antiepileptic drug (AED) regimen and administered on an as-needed basis. However, treatment in the outpatient setting (by a caregiver) is underserved by current options, particularly in the United States, where the lone FDA-approved outpatient therapy—rectal diazepam (Valeant Pharmaceuticals’ Diastat, Wakodo’s Diapp, generics)—bears obvious and significant delivery shortcomings. As such, a recognized unmet need exists for additional safe, effective, easier-to-administer outpatient rescue therapy alternatives for the treatment of ARS.

Questions Answered in This Report:

- Achieving acute treatment success—i.e., rapid seizure cessation with no seizure recurrence—is the key goal of treatment of ARS. What are the key primary and secondary clinical trial end points with which new therapies are evaluated? How do U.S. and European neurologists weight specific efficacy end points and other drug attributes in their prescribing decisions for ARS?

- Rectal diazepam was the 2013 major-market sales leader for ARS. What weaknesses exist in its profile that would allow emerging therapies to gain traction in the market? Have emerging therapies demonstrated strengths on the attributes that surveyed neurologists indicate are the most important in their prescribing decisions? Which emerging therapies will offer the clinical improvements over currently available therapies that surveyed MCO PDs seek from new therapies?

- Percentage of acute treatment successes and route of administration are key drivers of physicians' prescribing decisions and/or are the focus of drug development for new ARS therapies. What trade-offs across these and other clinical attributes are U.S. neurologists willing to make when considering the use of emerging therapies for the treatment of ARS? Based on the trade-offs in price and performance across key drug attributes that U.S. neurologists are willing to make, how do physician preference and prescribing likelihood vary across different target product profiles for ARS?
By 2018, intranasal midazolam (Upsher-Smith Laboratories’ USL-261) 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 intranasal midazolam most differentiated from its competitors? Which current therapies are at greatest risk of being replaced by intranasal midazolam?

**Scope:**

Attributes included in conjoint analysis-based assessment of target product profiles for ARS:

- Route of administration
- Percentage of patients who are acute treatment successes (i.e., no additional seizures or rescue intervention) during post-dose observation (PDO)
- Hazard ratio vs. placebo for time to next seizure or rescue intervention during PDO
- Percentage of patients with emergency room visits during PDO
- Incidence of cognitive impairment during PDO (overall)
- Incidence of somnolence during PDO (placebo-adjusted)
- Price per dose

Attributes included in assessment of U.S. payers’ receptivity to new outpatient rescue therapies for ARS:

- Route of administration
- Percentage of ARS patients who are seizure-free during PDO
- Percentage of ARS patients requiring emergency room visits during PDO
- Incidence of somnolence

Physicians surveyed: 60 U.S. and 30 European neurologists.

Payers surveyed: 22 U.S. MCO PDs.

Comprehensive List of Therapies Included in Our Research and Modeling:

**Current Therapies**

- Rectal diazepam (Valeant Pharmaceuticals’ Diastat, Wakodo’s Diapp, generics)
- Buccal midazolam (Shire’s Buccolam [Europe], compounded generics [United States])
- Oral clobazam (Sanofi’s Frisium/Noiafren/Urbanyl, Sumitomo Dainippon Pharma/Alfresa’s Mystan, generics; Lundbeck’s Onfi [United States])
- Oral lorazepam (Valeant Pharmaceuticals’ Ativan, Pfizer’s Tavor/Temesta/Wypax, generics)

**Emerging Therapies**

- Intranasal diazepam (Acorda Therapeutics’ Plumiaz)
- Intranasal midazolam (Upsher-Smith Laboratories’ USL-261)
- Intramuscular diazepam (Pfizer’s Vanquix)
- Inhaled alprazolam (Alexza Pharmaceuticals’ AZ-002)
- Inhaled propofol hemisuccinate (Epalex)

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