GLOBAL HTA ASSESSMENTS OF ULTRA-ORPHAN PRODUCTS: A CASE STUDY OF ECUILIZUMAB (SOLIRIS) AND IDURONATE-2-SULFATE (ELAPRASE)

Paul A1, Morawski JH1, Spinner DS1, Doyle J2, Faulkner EC3, Ransom JF2
1Quintiles Consulting, Durham, NC, USA; 2Quintiles Consulting Hawthorne, NY, USA; 3Department of Epidemiology and the Department of Healthcare Policy & Management at the Mailman School of Public Health, Columbia University, New York, NY, USA; 4Institute for Pharmacoeconomics and Indications-Based Therapy, Einarow School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA.

Background and Objectives

Ultra-orphan diseases affect a very small patient population, defined by the National Institute for Health and Care Excellence (NICE) as those diseases with a prevalence of ≤ 1:50,000. Medicines for these indications are difficult to develop in part due to challenges associated with recruiting for clinical trials from a small patient population. Within this context, global payer bodies have historically assessed these therapies with modified evidence requirements and opportunity for very high prices. Yet as manufacturers develop more and more products to treat ultra-orphan diseases, payers are increasingly strengthening evidence expectations and scrutinizing products with high prices in unprecedented ways.

We performed a health technology assessment (HTA) review of two ultra-orphan products – eculizumab (Soliris) and idurionate-2-sulfate (IDS) Elaprase – to gain insight into the evolving HTA evidence requirements for ultra-orphan medicines, to comparatively evaluate key decision drivers across geographies, and to determine implications for manufacturers.

Methods

We scanned global HTAs published before the end of November 2014 to identify the two most widely assessed ultra-orphan therapies which have variable reimbursement decision outcomes (eculizumab/Soliris and idurionate-2-sulfate/IDS/Elaprase). To evaluate pivotal decision drivers, we analyzed HTAs across several criteria, including clinical efficacy, unmet need, strength of evidence, cost-effectiveness, burden of illness, drug utilization management, among others. Furthermore, we scanned the literature and public sources to analyze changing evidence requirements, including expectations for new types of evidence and evolving assessment methodologies. Lastly, we conducted an in-depth analysis of three HTA decisions; these decisions were chosen as representatives of wider trends and for significance of impact/insights.

Results

Evolving Approaches Require Active Monitoring

Soliris and Elaprase are considered orphan and even “ultra orphan” products and thereby assessed by Payers through its Special Access Program. In the UK (HST), payers might closely monitor drug utilization as a condition for a positive reimbursement decision. Across markets, two themes emerged – cost-effectiveness analyses, especially for high-priced products, are now expected and will require close monitoring/analysis by manufacturers to tailor successful evidence packages.

Positive Decisions Possible in Cost-effectiveness Markets

In HTAs analyzed, cost-effectiveness was the most critical driver in several markets. Assessments initially rejecting Eculizumab and IDS (e.g., Australia, Canada, UK) did so based on cost-effectiveness. Notably, the NICE Highly Specialized Technology Committee requested unreevaluated/justification of Eculizumab’s pricing (including research and development costs) before reimbursing that product. Some agencies (e.g., Scottish Medicines Consortium [SMC]) preemptively rejected orphans due to a manufacturer’s non-submission of required data. In Australia, Eculizumab gained recommendation alongside a risk-sharing scheme while IDS gained recommendation under Life Saving Drugs Program criteria.

Across markets, two themes emerged – cost-effectiveness thresholds might be relaxed in diseases with extremely high unmet need (when accompanied by rebates or risk-sharing agreements) and payers might closely monitor drug utilization as a condition for a positive reimbursement decision.


In the UK, the HST’s assessment of its first-ever product (Eculizumab) included an unprecedented request: HST’s independent advisory committee asked the manufacturer to “clarification on manufacturing, research and development costs.” A lexicon provided these costs but requested confidentiality of information submitted. In further draft guidance, HST and NICE recommended Eculizumab’s pricing stating “a radical improvement in quality of life” in patients with aHUS, although this recommendation was accompanied by specific conditions. These conditions included coordinating Soliris prescriptions through an “expert center,” which would monitor diagnoses of the disease and the dosages that Soliris patients receive. The center would also collect data “to evaluate when stopping treatment or adjusting the dose of the drug might occur;” HST consulted with stakeholders including clinicians, patients, families, and carers, suggesting that care-giver burden was actively considered. This decision illustrates that payers are becoming proactive in managing dosing and drug utilization, while requiring new types of evidence to justify very-high prices for ultra-orphan products.

Australia: Positive Decision in Cost-effectiveness Market, Accompanied by Managed Entry Scheme and Request for Additional Evidence

In Australia’s assessment of Eculizumab, PBAC conditionally after implementing certain risk-sharing measures and a structured program to collect evidence to assess critical treatment outcomes. Specifically, the sponsor would need to implement the following: a Managed Entry Scheme, including rebates for patients who did not achieve an agreed clinical outcome over an agreed period of time. The sponsor agreed to fund a structured program to collect evidence aimed at resolving areas of uncertainty, specifically duration of therapy. This decision illustrates the potential for positive decisions, despite cost-effectiveness analyses, especially when decisions are accompanied by risk-sharing agreements, rebates, and programs to collect further evidence.

France: Request for Manufacturer-sponsored Registry Data, Including Data on Dosing and Drug Utilization

In France, the Transparency Committee recommended Eculizumab for inclusion on the list of medicines approved for hospital use. The TC recommended additional studies to gather supplementary data on the management of patients with aHUS. Specifically the TC suggested using existing registries of patients with thrombotic microangiopathy to supplement additional data. In particular, data on the criteria for stopping and potential restarting of SOLIRIS were expected. TC also requested data on the use of SOLIRIS outside the indication of marketing authorization. Lastly, the Committee asked for definitive results from follow-up studies beyond 26 weeks of treatment from submitted studies. This decision is illustrative of global agencies’ requests for additional evidence, particularly data to help them manage drug utilization and narrowly define the treatment population.

Key Findings

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<th>Key Findings</th>
<th>Implications for Manufacturers</th>
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<td>1. Payers developing new and evolving approaches to assessing high-priced, orphan products</td>
<td>1. Monitor evolution across global HTA agencies for changing approaches, and tailor product value package to meet evolving payer expectations.</td>
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<td>2. Payers adopting increasingly stringent evidence criteria</td>
<td>2. In the UK, HTA evaluation is actively evolving and manufacturers should be active participants in NHS process of developing evolving methodology for assessment.</td>
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Conclusions

Eculizumab and IDS are among a select list of therapies commanding very high prices globally. This study demonstrates active evolution in decision criteria and drivers across HTA agencies for such high-priced ultra-orphan products, a situation that requires active monitoring of global HTA decisions.

Presentation Code: PH1682 | ISP: 17th Annual European Congress, November 5-12, 2016, Amsterdam, The Netherlands