Objective

Ultra-orphan diseases are extremely rare conditions many of which are severe, chronic, and progressive with high mortality rates. There is a growing number of therapies for ultra-orphan diseases on the market. Reimbursement decisions for these therapies have been characterized by reduced evidence requirements with unmet need weighing heavily in health technology assessment (HTA) and reimbursement decision-making; as well as a generally wide pricing latitude. To gain insight into evolving market access requirements, we conducted a review of pan-European ultra-orphan therapy HTA requirements and reimbursement decisions.

Methods

Applying the National Institute for Health and Care Excellence (NICE) definition for ultra-orphan diseases (prevalence of ≤ 1/50,000), only full European HTA reports on ultra-orphan disease therapies published through May 2014 were selected and reviewed to identify any reimbursement trends across countries and compare evidence considerations including: Clinical burden of disease; Clinical evidence; Comparator groups utilized in clinical trials; Safety; Quality of life; Evidence on cost-effectiveness; Budget impact; Cost; Reference to a clinical guideline; and whether a patient access scheme was submitted by the manufacturer.

Results

Sixty-nine full HTAs on 20 ultra-orphan disease therapies were identified across 32 markets including Scotland (SMC), Wales (AWMSG), France (HAS), Germany (G-BA), Italy (UVEF), Spain (AQuAS and SECSIS), Portugal (INFARMED), Netherlands (ZNL) and Poland (AHTAPol). These 20 therapies span 17 ultra-orphan disease indications, mostly hereditary disorders, including: Adrenal cortical carcinoma (2 HTAs on Lysonrep); Anthracycline extravasation (3 Saveno); Aplastic hemolytic uremic syndrome 1 (2 Soliris); Congenital bile acid synthesis defect type 1 and 2 (1 Orphacol); Fabry disease (3 Fabrazyme and 4 Replagal); Familial transthyretin amyloidosis (3 Vynadateq); Gaucher disease type 1 and 3 (2 Vpnr, 1 Zavesca and 1 Cerezyme); Hunter syndrome (4 Elaprase); Lambert-Eaton myasthenic syndrome (2 Fintape); Mucopolysaccharidosis type 1 and 6 (4 Aldurase, 2 Elaprase and 1 Naglapyme); Niemann-Pick disease type C (1 Zavesca); Paroxysmal nocturnal haemoglobinuria (6 Soliris); Pulmonary arterial hypertension (10 Replagal, 7 Vpnr, 5 Tracleer, 2 Opsunim and 1 Theofil); and Transthyretin type 1 (1 Orfadin).

No clear trend was identified over the years regarding reimbursement decisions granted. Although the number of HTAs resulting in a reimbursement recommendation, including those with a restriction, was always greater than those that were not recommended for reimbursement. In order, then Scotland, Wales, Spain and the Netherlands had the most HTAs on ultra-orphan disease therapies. The number of HTAs from French agency HAS greatly outweighed any other agency with 22 HTAs receiving a positive decision (3 with restriction). It is important to note that these HTAs represent both original submissions and re-evaluations of already reimbursed therapies. By doing this HAS is able to monitor the long-term efficacy of therapies and update the level of reimbursement according to a drug’s actual benefit. The 2 UK agencies SMC (Scotland) and AWMSG (Wales) tended to grant more restricted or negative recommendations than positive recommendations. This stark difference to France may partly be due to differences in evidence requirements. Until recently, HAS did not require economic evidence when evaluating therapies for reimbursement. Whereas for SMC and AWMSG, economic and budget impact evidence is mandatory. Both INFARMED (Portugal) and AQuAS (Spain) perform HTAs but do not render reimbursement recommendations.

Conclusions

As health care budgets become more strained, ultra-orphan disease therapies priced at a premium have come under increased scrutiny from HTA agencies and payers to demonstrate value for money. In order to achieve optimal market access, manufacturers must consider costs, utilization and long-term real-world evidence which can be captured through a registry. Utilizing registry data helps to influence public policy, ensuring patient access to necessary treatments and sustainable reimbursement.

References


Fig. 1: HTA reimbursement decisions granted over the years

Fig. 2 HTA reimbursement decisions granted across Europe

As ultra-orphan disease therapies are often some of the most expensive drugs on the market, reimbursement decisions were predominately hinged on clinical benefit, cost and budget impact rather than cost-effectiveness. Clinical evidence against placebo was most frequent and was largely accepted across agencies. Data on quality of life is becoming increasingly important with a moderate to high number of HTAs identified with quality of life data. Thirteen of the 56 HTAs received criticism for not submitting quality of life evidence for their product. Only 2 of the 3 patient access schemes proposed to the SMC were accepted. In 8 of 9 HTAs that resulted in a negative reimbursement decision, evaluating committees criticised that a robust economic analysis was not presented. Assumptions applied in these analyses were often considered uncertain. In 7 of these HTAs, clinical evidence was also scrutinised not only for the lack of clinical benefit demonstrated (through the primary outcome) but also in respect to the lack of comparators and quality of life measures used within clinical trials presented. In most circumstances where the drug evaluated was first in market, data comparing to local standard of care, even if non-pharmaceutical, was often required. In 19 of the 50 HTAs that were either recommended or recommended with restricted access, evaluation committees requested the submitting manufacturer for additional real-world evidence on efficacy and safety through ongoing monitoring of patients. For 9 of these reports, it was confirmed that a registry was already in place. In 2 HTAs, the evaluating committee requested the manufacturer to set up a registry. For remaining 7 HTAs, the method adopted to meet monitoring requirements was not specified.

Country (Number of HTAs)  Agency  Clinical Burden  Clinical Evidence  Comparator  Safety  Quality of Life  HE Analysis Cost Effectiveness  Budget Impact  Cost  Strength of Evidence  Clinical Guideline Reference  Patient Access Scheme

France (2)  HAS  4AC / 1SP / 6NC  1AC / 3P  

Germany (4)  G-BA  1AC  

Italy (3)  UVEF  

Netherlands (7)  ZNL  

Poland (2)  AHTAPol  2P  

Portugal (3)  INFARMED  

Scotland (10)  SMC  

Spain (7)  AQuAS / SECSIS  

Wales (5)  AWMSG  7P / 3NC  

<table>
<thead>
<tr>
<th>Percentage of HTAs</th>
<th>80% - 100% of HTAs</th>
<th>60% - 80% of HTAs</th>
<th>40% - 60% of HTAs</th>
<th>20% - 40% of HTAs</th>
<th>0% - 20% of HTAs</th>
<th>Criticism</th>
<th>Active Comparator</th>
<th>Placebo</th>
<th>No Comparator</th>
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