

Introduction

Should orphan drugs be subjected to a Health Technology Assessment (HTA) such as cost-effectiveness to determine if they should be used?

Myozyme (alglucosidase alfa; Genzyme) is the first orphan drug approved for Pompe disease, which typically results in death from cardiac and/or respiratory failure in infants before the age of one year. Despite “significantly improved survival,” the Scottish Medicines Consortium (SMA - the HTA body in Scotland) decided that the “economic case for using Myozyme has not been made.” Effectively the Health Boards will not fund it for the few babies born each year who would otherwise benefit. For an infant, averaging 10kg body weight, the annual cost of Myozyme would be £38,333.

While Scotland rejected Myozyme outright, in another part of the UK the Welsh HTA group (the All Wales Medicines Strategy Group) approved the drug for infants and juveniles, but denied it to adults. According to Allan Muir of the International Pompe Association some families in Scotland and Wales have relocated to England to access the drug. “The situation is so brutal when compared to that in England where specialist centres have been set up and the Department of Health has expressed its desire that all patients should be allowed to experience the therapy, regardless of age or disease progression,” he said. “For so few patients to be denied something they see being freely administered to their neighbours is quite cruel,” he added.

Affecting fewer than 10,000 people worldwide, Pompe disease is a debilitating and progressive disorder due to an inherited deficiency of acid alpha-glucosidase, the lysosomal enzyme responsible for degrading glycogen. All patients typically experience worsening muscle weakness and breathing difficulty at a rate depending on the age of onset and the extent of organ involvement.

Genzyme began developing Myozyme in 1998 and received marketing approval in both the US and the EU in April 2006. This was the company’s fourth enzyme replacement therapy for a rare genetic disease. The others are Cerezyme (imiglucerase) for type I Gaucher’s disease, Fabrazyme (agalsidase beta) for Fabry disease, and in collaboration with BioMarin, Aldurazyme (laronidase) for MPS I.

The SMC’s Orphan Drug Policy

Along with Myozyme, the Scottish Medicines Consortium has refused to recommend six of 16 other EU-designated orphan drugs with EMEA marketing approval that it has assessed. Table 1 shows their status.

Most of these decisions were arrived at after the SMC’s policy on orphan drugs was announced last year, stating that: “A meaningful attempt needs to be made (by

manufacturers) to produce robust clinical and economic data.” While it requires all submissions to be comprehensive and all sections in the product assessment form to be complete, the SMC recognizes that less information than usual may be available, but it does require detailed data in some areas, e.g. on the relevance and basis for surrogate markets selection.

Table 1: Status of Orphan Drugs in Scotland

Accepted for restricted use by NHS Scotland	Not recommended for use by NHS Scotland
Busilvex (busulfan)	Aldurazyme (laronidase)
Carbaglu (carglumic acid)	Myozyme (alglucosidase alfa)
Evoltra (clofarabine)	Lysodren (mitotane)
Glivec (imatinib)	Nexavar (sorafenib)
Pedea (ibuprofen IV)	Somavert (pegvisomant)
Revatio (sildenafil)	Xagrid (anagrelide)
Tracleer (bosentan)	Xyrem (sodium oxybate)
Ventavis (iloprost)	
Zavesca (miglustat)	

SMC considers additional factors, e.g. whether the drug can reverse rather than stabilize the condition, or whether the drug may bridge the gap to a ‘definitive’ therapy. The overall budget may be considered. Orphan drug submissions must also outline potential extension of use beyond the licensed target group.

NICE’s Position

Only one EU orphan drug, Glivec (imatinib), has received a HTA from NICE (impacting NHS use in England and Wales). It was positive.

NICE had previously appraised drugs for around 12 rare diseases that have orphan status in the US using the same methods and decision criteria as for standard appraisals. No particular scientific or technical problems arose, though many of the products had incremental cost effectiveness ratios (ICERs) “at the high end of what NICE and its appraisal committee consider to be cost effective within the NHS.” As a result, NICE did not consider it necessary to change its processes for ‘conventional’ orphan drugs, though there would be problems with ultra orphan drugs (a UK term for treatments for conditions affecting <0.18 patients per 10,000 population), “largely because of their high costs.”

Preliminary estimated ICERs per QALY quoted included £203,009 for Fabrazyme, £334,880 for Aldurazyme, £116,800 for Zavesca and £23,324 for Ventavis.

After deliberations, NICE decided that it “should consider paying premium prices for drugs to treat ultra orphan diseases.” It concluded that future ultra orphan drug decision rules should be based on those ultra orphans currently on the UK market (e.g. a ten-fold increase in cost per QALY over conventional appraisals). To prevent

manufacturers “gaming the system” (extending the indications for an ultra orphan drug after its price has been established), NICE requested that the Department of Health should refer additional indications to NICE for review under its conventional appraisal system.

Other Countries

A 2004 pan-EU survey of the first 12 approved orphan drugs was carried out by Eurordis, the European rare disease patients’ lobby. They found one year after approval that only in **Denmark** were all 12 available. Today, Denmark remains a leader, with 25 of the 32 orphan drugs to receive marketing approval up to the end of January 2007 on its reimbursement list.

The situation in neighbouring **Sweden** is less encouraging, with 14 of the 32 currently without a reimbursement price. The difference here may be because the Swedish Pharmaceutical Benefits Board routinely requires evidence of “cost effectiveness”.

In the **Netherlands**, however, the obligation on companies with NCEs to provide pharmacoeconomic data is waived for orphan drugs. Specific funds are also available for these products.

A full refund is obtained from the Ministry of Health, Welfare and Sport for hospital orphan drugs that account for at least 5% of drugs costs of 8 university hospitals. Orphan drugs, like other high cost pharmaceuticals in the Netherlands, may also be eligible for an 80% government subsidy when their costs exceed 0.5% of the national hospital drug budget. In other situations, the hospital pays for orphan drugs out of its own budget,

In ambulatory care, orphan drugs are only reimbursed if they are on the GVS list. Most are, though some including Naglazyme, Evoltra, Trisenox, Ventavis, Litak and Onsenal are currently not.

France is the most active European country promoting treatment of orphan conditions. All orphan drugs for hospital usage are on the high-cost list, exempting them from the *tarification à l’activité* (T2A) prospective payment system, with direct funding from social security.

Away from Europe, the situation with orphan drugs in **Canada** appears the most problematic among major markets. One reason is the Common Drug Review process, which since 2003 has reviewed all NCEs and provides formulary listing recommendations to all publicly-funded drug benefit plans except Quebec. Only two orphan drugs – Actelion’s Tracleer (bosentan) and Pfizer’s Revatio (sildenafil), both for pulmonary arterial hypertension – have received a positive CDR recommendation. “Cost effectiveness” figures strongly in the CDR agenda. Canada is also the only major country without its own orphan drug act.

Next month marks the seventh anniversary of the EU Orphan Drug Regulation (141/2000). Though it arrived 17 years and 7 years respectively after similar legislation in the US and Japan, the European Commission and the EMEA are rightly proud of their achievements.

As of end-January 2007, over 600 orphan drug designation applications have been made to the EMEA’s Committee on Orphan Medicinal Products (COMP), resulting in about 380 designation decisions by the

Commission. Thirty two orphan drugs for treating 28 different orphan conditions from 23 different sponsors have received pan-EU marketing approval through the centralised procedure.

Orphan drug sponsors receive a number of incentives under the Regulation (e.g. protocol assistance, reduced/waived EMEA fees, 10-year marketing exclusivity). An updated inventory of additional member states’ incentives has just been published.

While orphan drug availability since the Regulation has theoretically resulted in over one million EU patients with rare diseases benefiting, it is clear that the situation varies significantly from country to country.

Addressing the 2005 European Conference on Rare Diseases, Eurordis CEO and COMP patient representative Yann Le Cam, argued:

“Some pretend that orphan drugs are expensive, or even too expensive. What does ‘too expensive’ mean exactly? They are not worth it? What would a scientific assessment of the positive risk/benefit mean if yet another stakeholder states I am not worth the product as a patient? The debate is unfair and should be closed.”

Unfortunately, for patients with rare diseases and the sponsors of orphan drugs, the debate is far from closed.

Implications for Strategy Development

A major problem is that some pricing authorities believe that all new drugs should reach minimum standards of cost effectiveness. Some economists say that despite their clinical efficacy, equity in resource application should also be valued and that the funding of orphan drugs is not efficient in that it does not maximise health gains when compared to other conditions.

Companies developing orphan drugs must take into account that they will have to provide some economic justification for the price of the product. More countries are likely to make this a requirement in the future. To ignore this may mean that fewer patients will get access to these often life-saving drugs.

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