Rare Disease Treatments — Evidence, Value, Insights

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OVERVIEW OF RARE DISEASES AND ORPHAN DRUGS

Rare, or "orphan", diseases are those diseases which affect a small percentage of the population, and as a result, have traditionally received less attention in the development of treatments. In the last 30 years, there has been a larger focus on addressing the treatment needs of these diseases. In 1983, orphan drug status was introduced in the U.S. through the Orphan Drug Act,[1] to help incentivize drug manufacturers to develop treatments for very serious rare diseases where, without these incentives, it was considered unlikely that manufacturers would generate a return on the investment and, therefore, not investigate and develop treatments for these rare conditions. The European Medicines Agency (EMA) later established the Orphan Medicinal Product Designation[2] in the European Union, with Japan and other countries following. Orphan drug policies are different in each country and key criteria and benefits are summarized for the U.S., EU and Japan in *Table 1.*

The number of current orphan drug designations has doubled in the past seven years, indicating success in the orphan drug policies. While incentives vary between member states within the EU, one key benefit for all countries in *Table 1* is market exclusivity for a specified number of years. While orphan drug status can mean a lower burden of proof, high willingness to pay, and easier funding compared with non-orphan drugs in some countries (specifically in the EU), this status does not necessarily allow for faster market access, and there are only a few markets where there are different pricing and reimbursement processes for orphan drugs compared with non-orphan drugs. For example, in Germany drugs are now required to undergo a cost-benefit analysis, however, orphan drugs can bypass that requirement if they have a turnover of <50 million Euros/year

(although the Gemeinsamer Bundesausschuss or Joint Federal Committee [GBA] is considering removing this incentive). In the UK, as of late March 2013, orphan drugs are evaluated by the National Institute for Health and Clinical Excellence (NICE), which has cost effectiveness requirements for drug approval, causing concern with patient advocacy groups that this may lead to future orphan drugs being more easily rejected.

ORPHAN DRUG COSTS

In looking at the cost of orphan drugs, there is clear correlation between disease prevalence and cost/patient *(see Table 2)*, which stands to reason if one considers that a disease such as Fabry disease has treatment costs at approximately £100,000/year/patient with a prevalence of 1-5/10,000, while N-acetylglutamate synthetase deficiency treatment costs up to $2 million dollars with a prevalence of only 0.01/10,000. Fewer patients equates to a higher cost/treatment/patient to recoup development costs. With nearly 4,000 orphan drug designations in the EU and U.S., over 500 with market authorization and thousands of potential rare diseases needing new treatments, there will be a considerable impact to payer budgets in the near future. Fifteen years ago, orphan drug sales were approximately 5% of the worldwide prescription drug markets, and today that has risen to 14% with an increase to 16% anticipated in five years. Payers are therefore pushing strongly against the high-cost orphan drugs, unless there is significant demonstrable benefit to patients.

EVIDENCE-BASED VALUE PROPOSITIONS FOR ORPHAN DRUGS

Orphan drug status does have its advantages but does not guarantee positive reimbursement or a favorable view on the therapeutic value of an orphan product, so the development of an evidence-based value story is paramount to addressing the many market access challenges associated with orphan drugs, particularly in pricing and reimbursement negotiations and other stakeholder communications.

KEY CRITERIA AND BENEFITS FOR ORPHAN DRUG POLICIES IN KEY COUNTRIES

Criteria	Regulation Since	1983	2000	1993
	Prevalence	< 200,000	< 5 / 10,000	< 50,000
	Designated / MA	2907 / 447*	965 / 67*	293 / 179**
Benefits/Incentives	Protocol Assistance	Yes	Yes	Yes
	Grants & Lower Fee	Yes	Yes	Yes
	Tax Credits	Yes	By MS	Yes
	Market Exclusivity	7 Years	10 Years	10 Years

**As listed on FDA/EMA websites (26 September 2013) **As listed on MHLW website (12 November 2013)*

table 1

TERMINOLOGY: ULTRA-ORPHAN

Orphan drugs for oncology indications are seen as a distinct class for market access since oncology is a major subgroup within orphan diseases, with only four main oncology areas not receiving orphan drug designation. As a result, we are focusing primarily on non-oncology orphan diseases in this article. It is also worth highlighting here that payers across all markets are seeing a huge growth in the number of expensive orphan drugs, and as a result, orphan drugs across different indications are being viewed as more of a distinct collection or group having a significant budget impact. That has prompted some markets to further define very rare diseases within the orphan group as ultra-orphan *(see Figure 1)*. This has led to a payer perception that the ultra-orphan is now the 'new' orphan since there are so many orphan drugs in the marketplace.

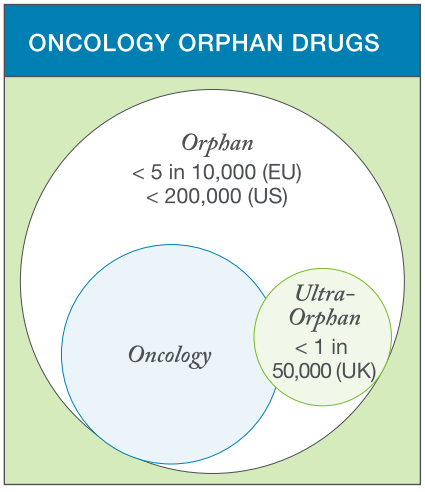

figure 1

COST OF ORPHAN DRUGS				
Drug	*Indication*	*Disease prevalence (per 10,000)***	*Approximate annual cost per patient**	*Date of marketing authorization*
Agalsidase alfa	Fabry disease	1 to 5	£110,000	May 4 2001 EU
Ivacaftor	Cystic fibrosis (G551D mutation)	1 to 5 (4% to 5% have G551D mutation)	$360,000 £182,625	Dec 20 2006 US May 24 2012 EU
Imiglucerase	Gaucher disease type I	0.1 to 0.9	$520,000 £290,000	May 23 1994 US Nov 17 1997 EU
Eculizumab	Paroxysmal nocturnal haemoglobinuria	0.01 to 0.09	$545,000 £250,000	Mar 19 2007 US Oct 17 2003 EU
Idursulfase	Mucopolysaccharidosis II	0.01 to 0.09	$675,000 £410,000	Jul 24 2006 US Jan 8 2007 EU
Alglucosidase alfa	Pompe disease	0.1 to 0.9	$850,000 £260,000	Apr 28 2006 US Mar 29 2006 EU
Carglumic acid	N-acetylglutamate synthetase deficiency	<0.01	$2,140,000 £745,000	Jan 20 1998 US Oct 18 2000 EU

**UK price calculations based on unit costs obtained from British National Formulary 2012, U.S. prices from average wholesale price in the Red Book 2012. All calculations based on prescribing information in a patient of 70kg except idursulfase, which is based on a patient of 48kg.*
***Orphanet. Rare disease prevalence. 2012; http://www.orpha.net/consor4.01/www/cgi-bin/Disease.php. Accessed October 2012.*

table 2

When starting to develop value stories, it is imperative to address questions from the payer perspective.

1. Burden of illness/unmet need
   a. Why does the disease need to be treated? How bad is it? Why aren't the existing treatments good enough?
   b. If there are no existing options (e.g., for some ultra-orphan diseases), is supportive care good enough or is a disease-modifying treatment really needed?

2. Clinical value
   a. What makes the product unique (e.g., dosing, mechanism of action, safety)?
   b. Does the product work?
   c. How well does the product work?
   d. What is the efficacy from the randomized controlled trials?
   e. How does it compare to other options, including competitor treatments?

3. Economic/outcomes value
   a. Is the product worth the money? (addressing cost-effectiveness)
   b. What is the budget impact of the treatment? Is it affordable? (often a more useful argument than cost-effectiveness since the overall budget impact tends to be minimal to modest given the rarity of the disease)
   c. What is the value to patients, caregivers and families? Does the product offer meaningful benefits in terms of quality of life and other patient perspective issues?

CHALLENGES AND STRATEGIES IN DEVELOPING AN EVIDENCE-BASED VALUE STORY

Burden of illness/unmet need

Since orphan diseases are, by definition, rare, there is usually less research and literature to establish the burden of illness. So although healthcare decision makers may have true empathy for patients and caregivers, they often do not have much awareness about the clinical, humanistic, and economic burden of a particular disease. Unfortunately, this can result in extreme or unrealistic restrictions on patient access to life-changing therapies.

Likewise, when a population is so small, sometimes the unmet need goes unnoticed. Patients often undergo invasive, inconvenient, and often ineffective therapies that would not even be considered acceptable for larger populations. Additionally, patients often have to travel long distances to get access to care at specialist centers, which can severely impact quality of life issues, such as jobs, school attendance, etc. Lastly, because these diseases can be very severe, patients may not reach appropriate therapeutic goals with the existing standards of care, but they often accept sub-optimal outcomes

as "the best they can hope for". With scientific innovation bringing forth products that can be life-changing, it becomes important to emphasize that mediocre quality of life is not acceptable for patients simply because they have a rare disease.

When addressing these issues with payers, it can be helpful to provide expanded disease background information, including solid evidence of the burden on patients and caregivers. Emphasizing sub-optimal outcomes that exist with the current standard of care is also helpful, and this can be done using registration trials for the new product that show baseline data on the patients without any disease-modifying treatment. Collecting real-world data to show patient and caregiver burden can be challenging, however, due to the low population with the disease which makes identifying patients and caregivers difficult in some cases.

While baseline data on patients enrolled in a clinical trial sometimes can be a relevant source of evidence about the health status of patients receiving standard care, additional data are usually collected to address the data gaps. Patient and/or caregiver surveys can help demonstrate the true burden of an under-recognized illness and unmet need. The studies are typically conducted by working in close collaboration with patient advocacy groups, centers of excellence or existing registries. However, it is also increasingly common to explore the feasibility of identifying patients in extremely large databases of medical claims or electronic medical records and also linking these with patient surveys and chart reviews. As few of the orphan diseases have specific codes, a sophisticated approach is essential to use these databases, which typically includes investing in development of coding algorithms to identify the relevant cases and confirming these are capturing data collected from the intended patient population. The appropriate approaches vary widely among different treatments and diseases.

Clinical efficacy and comparative effectiveness

Demonstrating clinical efficacy and comparative effectiveness is essential for any type of drug, whether the disease is rare or not, but there are some particular challenges associated with rare diseases. Although there is some leniency on the part of healthcare decision makers when it comes to orphan diseases, there can be situations where healthcare decision makers challenge the trial design for orphan drugs. Trials are typically very small due to the patient population being very small, and the pivotal trials for a drug may use surrogate endpoints, particularly if it is a chronic disease. Since there is not always time to wait for long-term clinical endpoints to occur, biomarkers or other types of short-term endpoints may be used, so the combination of a small trial and potentially only surrogate endpoints can lead to questions and challenges about the trial design.

Another issue is that some payers have a strong preference for comparative effectiveness, head-to-head trials, which may not be available if a drug is the only available disease-modifying treatment. If the disease is particularly serious, it may be unethical to conduct a placebo-controlled trial, so sometimes the Phase 3 trials for an orphan drug may actually be single arm, which can lead to questions about the comparative efficacy versus standard of care. Indirect treatment comparisons can be used to identify the comparative effectiveness, but that also can be a challenge to find the right trials to undertake that type of analysis because there may be very few prospectively designed trials in an orphan indication.

Payer leniency for these challenges

PAYERS ARE BECOMING MORE AWARE OF THE OVERALL IMPACT OF ORPHAN DRUGS ON THEIR BUDGETS.

"Nobody understands how companies come to such high prices for orphan drugs… **if the manufacturer thinks this product could be this price (€300K), then this is crazy!** If you can demonstrate life extended by 10 years, then maybe." –France

"€50K is the maximum they can hope for… **the health system cannot afford these kind of prices anymore.**" –Italy

"Just thinking from the economic standpoint—and the fact that the **G-BA are required to save €2 billion in the next year**—the major restriction for this drug may be its cost. If it's too expensive then it would be used later in therapy algorithm." –Germany

"€300K per year is very, very expensive. Depends on the number of patients per region in terms of what kinds of restrictions will be placed. **The restrictions would be heavy, but patients would probably receive the treatment.**" –Spain

varies from country to country, but the key is to be very upfront about the appropriateness of the trial or trials that have been conducted for the orphan drug. Confidence that the trial was conducted in the most appropriate, ethical, and clinically sound way is critical, while keeping the message focused on the product's key efficacy benefits in this disease that has substantial burden and unmet needs.

Economic and outcomes value

As mentioned previously, patients and their families and caregivers can experience quite a significant impact on quality of life as a result of having an orphan disease. They spend a lot of time being patients and suffering the consequences of a disease that has often very little visibility and awareness. Particularly in diseases that have this kind of substantial humanistic burden, such as genetic diseases that start in infancy and are chronic and often result in a very shortened life span, quality of life and patient-reported outcome (PRO) data can very much bolster that core efficacy message.

Having surrogate endpoints showing that a biomarker is improved, and to then have immediate evidence showing patients and/or families reporting better outcomes and quality of life, can help to support the core efficacy message. A potential pitfall, however, is that often it seems easier to use the generic quality of life or PRO scales or ones created for a similar disease, but that does not always capture the true impact of a new product for a very specific orphan disease. Therefore, validating a PRO scale or a quality of life questionnaire specifically for the disease that is being studied can be helpful. It is also important to note that quality of life/PRO data are generally seen as a secondary consideration by payers with efficacy and safety being the key product attributes. There may actually be a requirement for quality of life data for rare diseases, but specifying use of disease-specific measurement tools (or at least the data is considered more relevant when disease-specific tools are used). These tools should address any unusual circumstances that patients face with the particular disease, such as travelling long distances for treatment because that is the only treatment option available or measuring psychosocial concerns arising from having a low visibility condition. The recommendation is that these measurements are tested and discussed with payers before developing and finalizing the final PRO and quality of life (QOL) tools.

Perhaps the most hotly discussed aspect of value in orphan drugs is economic value, and this is a challenging issue. As previously established, most orphan drugs are not cheap, and if looking at traditional incremental cost-effectiveness ratio thresholds, most orphan drugs are not seen as cost effective. Different countries are evolving in terms of how they approach economic evaluation for orphan drugs. As noted, budget impact arguments can be more effective than cost-effectiveness analysis simply because, with a rare disease, the overall budget impact is going to be relatively low. Budget impact is also improved by the fact that generally a life-changing, disease-modifying treatment is going to be associated with some cost offsets, such as patients not being hospitalized as often or not having to undergo surgeries and other procedures if their disease is being well controlled on pharmacologic therapy.

In markets that do require cost-effectiveness analysis, there are a few issues to consider in terms of the goals and outputs of economic modeling. So an economic model, even if it does not show that something is cost effective according to traditional thresholds, will be able to provide a framework for capturing health gains and for allowing someone to vary assumptions and then to be able to project the product's clinical value in this burdensome disease.

When planning the evidence to

support health technology assessments, a budget impact assessment tool and a cost-effectiveness analysis are always considered. However, there is often a role for epidemiology forecasting, and developing models earlier in the drug development process may be helpful. A few examples illustrating how models can inform evidence generation plans are provided below.

Epidemiology forecasting

- Assess impact of individual characteristics on number of cases eligible for therapy
- Explore impact of diagnostic, genetic, or biomarker tests
- Inform understanding of disease progression, mortality, and established heterogeneity or predictors of outcomes

"Early" models

- Aid decision-making on further studies, prioritize data collection to address gaps
- Use early or proxy data on intervention to understand impact of improving surrogate endpoint(s) on long-term outcomes
- Explore heterogeneity, key outcome drivers, pricing scenarios
- Clinical trial simulation

Economic modeling (CEA/CUA)

- HTA submissions often predict clinical benefits beyond trial period
- Explore economic and health impact
  - Treatment stopping rules to maintain treatment benefit while minimizing cost
  - Subgroups, other scenarios to demonstrate value of therapy

Budget impact assessment

- Forecast budget impact of therapy
- Explore impact of patient access schemes
- Epidemiology inputs key to credible budget impact assessments

A key component of evidence-generation planning includes an assessment of the extent of the data available to populate the models developed to support HTA submissions. Credible inputs are necessary for the model results to impact payer decisions. The relevant scenarios to consider may become quite complex, for example when exploring the potential impact of using a new treatment in combination with diagnostic tests, monitoring biomarkers and treatment stopping rules. For a budget impact assessment, payers will certainly be interested in how many patients will be eligible for treatment with this new product and the quality of the evidence available to support this estimate.

Generally, we can anticipate limited data will be available and there will typically be substantial uncertainty when projecting long-term outcomes. If the model design discussions are initiated early, this can sometimes facilitate identifying the key data gaps to address and allow us to explore the feasibility of conducting additional studies to support the HTA submissions.

CONCLUSION

There has been tremendous scientific and clinical innovation that has driven a remarkable uptake in the number of orphan drugs coming to market in the past decade, and this has offered tremendous clinical, humanistic benefits to patients and families. So now the job of those who are working in market access is to be equally innovative and creative in order to develop the evidence to support value propositions and communications with healthcare decision makers to maximize patient access to these potentially transformative therapies.

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