Orphan medicines: the high cost of hope

SARAH HOULTON

Orphan drugs can transform the lives of patients with rare diseases, but they often come at an extremely high cost. Sarah Houlton discusses the incentives that are encouraging pharma investment in orphan drug research and the steps that NICE and the NHS are taking to budget for these treatments as they come to market.

Some of the most expensive drugs on the market are designed to treat rare diseases that affect only a handful of people. These medicines, termed orphan drugs, provide a lifeline to extremely sick people, but the cost implications for the NHS budget can be significant.

The patient organisation EURORDIS – Rare Diseases Europe estimates that there are between 6000 and 8000 rare diseases. About 80% of these are genetic in origin, and three-quarters affect children. Tragically, 30% of those with a rare disease will not reach their fifth birthday, and many of the rest will have a significantly impaired quality of life as the diseases are often chronic, degenerative, progressive, disabling and, all too frequently, life-threatening. Most are currently incurable.

While rare diseases represent serious unmet medical need, developing treatments is not easy. The underlying cause of the disease may be unknown, and there is often no obvious target for a drug to act at in the body. The small target populations make recruiting patients to run clinical trials a challenge. And, for better or worse, drugs are developed by pharmaceutical companies, who need to make a profit by selling the drugs to pay for the research and reward their investors. To put it bluntly, diseases that only affect a handful of people around the world will not generate the revenues that underpin the drug development process.

Orphan drug legislation
This is why the concept of the orphan drug was introduced in the USA back in 1983. The US Orphan Drug Act encourages investment in rare disease research by giving a product an additional seven years of market exclusivity, as well as tax credits and other incentives for spending money on this type of research. To qualify, the disease must affect fewer than 200,000 Americans.

It was some years before Europe caught up, and similar legislation did...
not appear until 2000 when the ‘orphan medicinal product’ category was introduced. This encompasses a broader spread of conditions than the US definition, including a number of tropical diseases.

A product given orphan designation by the European Commission will gain 10 years of market exclusivity if it is approved. To be considered rare, a disease must be life-threatening or chronically debilitating, and affect fewer than five in 10,000 EU citizens. Table 1, which shows the orphan medications that were given marketing authorisation by the European Commission in 2017, gives an idea of the breadth of indications for which orphan drugs are being developed.

There is some overlap with drugs that are intended for non-rare diseases, often in the cancer sector, that may also have value in treating a form of the disease that is classified as rare. Orphan designation encourages pharma companies to run clinical trials in those more unusual cancers too, despite the greater difficulty in patient recruitment. Figure 1 breaks down the number of drugs in development in 2016 by therapeutic category; cancers and genetic conditions predominate.

A growing market
There has been a steady increase in the number of potential medicines being investigated to treat rare diseases. According to the 2017 Orphan Drug Report from EvaluatePharma, new orphan designations in Europe hit a peak of 208 in 2016; a decade earlier, in 2006, this figure was 82. Unsurprisingly, sales have been rising too, as the chart in Figure 2 shows.

“It is definitely growing at a much faster rate than the overall prescription market,” says the report’s author, EvaluatePharma senior analyst Andreas Hadjivasiliou. “There has been a lot of interest, going back quite a number of years now, from both big and small pharmaceutical companies. Early innovators in the space have already proved that the business model can work, and that it is attractive.”

The number of drugs being approved is rising, too. “It is not just highly targeted drugs for rare diseases; we now see drugs that treat larger indications being awarded orphan designation,” Hadjivasiliou adds. “This is another interesting development in this space and I think this is how it will continue to develop.”

The advent of personalised medicine is also encouraging research into new orphan drugs, Hadjivasiliou says. As therapies have become more specific to individual patients by targeting specific gene mutations, that lends itself in a big way to developing orphan drugs where there is a small population size.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>INN</th>
<th>Therapeutic indication</th>
<th>Date of authorisation</th>
</tr>
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<tbody>
<tr>
<td>Cystadrops</td>
<td>mercaptamine hydrochloride</td>
<td>cystinosis</td>
<td>19/1/2017</td>
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<tr>
<td>Ledaga</td>
<td>chlormethine</td>
<td>mycosis fungoides</td>
<td>3/3/2017</td>
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<tr>
<td>Chenodeoxycholic acid Leadiant</td>
<td>chenodeoxycholic acid</td>
<td>inborn errors of metabolism, cerebrotendinous xanthomatosis</td>
<td>10/4/2017</td>
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<tr>
<td>Natpar</td>
<td>parathyroid hormone</td>
<td>hypoparathyroidism</td>
<td>24/4/2017</td>
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<tr>
<td>Dinutuximab beta EUSA</td>
<td>dinutuximab beta</td>
<td>neuroblastoma</td>
<td>8/5/2017</td>
</tr>
<tr>
<td>Spinraza</td>
<td>nusinersen sodium</td>
<td>spinal muscular atrophy</td>
<td>30/5/2017</td>
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<tr>
<td>Brineura</td>
<td>cerliponase alfa</td>
<td>neuronal ceroid-lipofuscinoses</td>
<td>30/5/2017</td>
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<tr>
<td>Besponsa</td>
<td>inotuzumab ozogamicin</td>
<td>precursor cell lymphoblastic leukaemia-lymphoma</td>
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<td>Oxervate</td>
<td>recombinant human nerve growth factor</td>
<td>neurotrophic keratitis</td>
<td>6/7/2017</td>
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<tr>
<td>Xermelo</td>
<td>telotristat etiprate</td>
<td>carcinoid tumours, neuroendocrine tumours</td>
<td>18/9/2017</td>
</tr>
<tr>
<td>Rydapt</td>
<td>midostaurin</td>
<td>acute myeloid leukaemia, mastocytosis</td>
<td>18/9/2017</td>
</tr>
<tr>
<td>Bavencio</td>
<td>avelumab</td>
<td>neuroendocrine tumours</td>
<td>18/9/2017</td>
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<tr>
<td>Zejula</td>
<td>niraparib tosylate monohydrate</td>
<td>fallopian tube neoplasms, ovarian neoplasms, peritoneal neoplasms</td>
<td>16/11/2017</td>
</tr>
</tbody>
</table>

Table 1. Orphan medicines authorised by the European Commission in 2017. Source: European Medicines Agency (www.ema.europa.eu/ema)
Prescribing and reimbursement

By their very nature, orphan medicines are usually prescribed by specialists, who may know every person with the disease in the whole country by name. With such a small number of patients, it is easier to engage with them on a more personal level and enrol them into clinical trials, so it reduces the cost of development.

However, these drugs don’t come cheap. Pricing analysis from EvaluatePharma shows that, in general, the smaller the number of people a drug is treating, the higher the price is likely to be. “There is always a lot of discussion around the appropriate price for medicines, but until recently, I don’t think there has been as much focus on orphan products because of the very, very small number of people involved,” Hadjivasiliou remarks. “A lot of these people are in a life-or-death situation, so there is a very strong incentive to provide the drug, whatever the cost.”

Table 2 shows the prices of the eight most expensive drugs, according to EvaluatePharma’s research. All are orphan medicines. Although these are the US prices, and prices paid in the UK are usually lower, the price differential tends to be smaller for orphan drugs.4

However, very high-cost drugs can have distorting effects on the health budget, and this is now drawing attention, even within the orphan sector. “If you look at the absolute numbers, these drugs aren’t necessarily causing the same budget impact as some of the other drugs that are prescribed more widely to a larger number of people, but [payers] are now looking closely at these drugs and asking if they demonstrate enough benefit to the patient to justify the price,” Hadjivasiliou says. “These questions, even five years ago, might not have been asked. When people start to ask these questions, it’s not under the radar anymore.”

Of course, in the UK, NICE evaluates drugs, determining cost-effectiveness using quality-adjusted life years (QALYs) and acting as a ‘gatekeeper’ to the system. “My view is that it is perfectly sensible to measure cost-effectiveness in exactly the same way, whether a drug is to treat a common disease or a rare one,” says Allen Wailoo, professor of health economics at the University of Sheffield. “One may then wish to apply different thresholds, though even that is debatable. The cost of saying ‘yes’ to these treatments is less money for people receiving other kinds of services in the NHS, less money for the salaries of NHS workers. But orphan drugs are tricky because, although the cost per patient can be extremely high, the very small numbers involved mean it is often not a vast amount of money relative to the overall budget of the NHS.”

Another issue, especially with some of the newer gene therapy products, is – at what point is a cure a cure? “Is there a potential for relapse maybe five or 10 years in the future, and what are the costs associated with that?” asks Hadjivasiliou. This is going to force regulators to change the way they behave, he says, and perhaps try to consider some of these additional questions, and think about how we deal with these products.

“Should products that give different benefits to people be treated and classed in the same way, in terms of just how long they extend your life? Or is there more to it? Should we be asking patients what a meaningful improvement to their condition would be, and what is the value to them? And does it have an associated cost saving that will provide benefits to the overall health system?”

Ultra-rare diseases

Ultra-rare diseases pose an even bigger issue for drug development and reimbursement – they are conditions that affect fewer than one person in 50,000, which equates to a EU patient population of under 10,000. NICE’s highly specialised technologies (HST) programme, prior to April 2017, used to analyse cost-effectiveness of these products without any threshold or framework to hang it on, according to the programme’s associate director, Sheela Upadhyaya. “We have now decided to introduce a cost-effectiveness threshold into the methodology, so we can help the NHS manage the fiscal challenge,” she says. “This is no mean feat.”

The old process, she says, was very judgmental, and committees spent a huge amount of time debating where the benefit would be seen. A new system has now been developed that involves considering anecdotal evidence alongside information presented by companies. “The problem was reconciling the committee’s thoughts with what the NHS is able to bear financially. With such a small number of patients, making this work is challenging,” Upadhyaya explains. A lot of the technologies they have assessed, she says, have delivered in excess of 15–20 QALYs, and they felt the system would be willing to pay more for the magnitude of the benefit they give. But the


CAGR = compound annual growth rate
small patient populations pose real challenges in terms of trying to demonstrate benefit.

The independent evidence review group will then assess all of the information, and may come up with a different number of QALYs. “They may come back and say they think it’s 11, not 15, and the committee will then have to make a judgment call on where it fits,” Upadhyaya says. “It may go down the middle, and put it at, say, 13.” That decision will be underpinned by evidence gleaned from both clinical and patient experts. These data are particularly important for such small patient populations, she says, and have to be relied on far more than is the case for a standard technology appraisal.

NICE’s new fast-track option for appraisal of treatments that offer exceptional value for money, introduced in April 2017, also covers HSTs. These will be evaluated against a sliding scale, meaning the more the treatment costs, the greater health benefit it must provide to patients. The maximum QALY threshold for HSTs is set at £300,000, three times higher than the figure in the original proposal. This is an order of magnitude higher than the upper end of the standard threshold range, and reflects the transformational health benefits they can offer patients, NICE says.

Managing the budget
Reconciling the NHS’s multiple funding commitments with HST guidance is always going to be a challenge. “The prices of these drugs are high, and the budget impact, even if the population is extremely small, can be huge for the NHS to manage,” Upadhyaya says.

NICE recently introduced a budget impact test across its entire technology appraisals programme, including HST. “For any new technology that has the potential for a budget impact above £20 million in the first three years, we ask the company to liaise with NHS England and come up with a commercial deal that reduces the budget impact, or some form of phased entry into the market that allows NHS England to manage its budget without having to displace other commitments,” explains Upadhyaya. “I think very few products will hit this figure for the HST programme, but it is possible as, although the patient numbers are very small, the cost of the technology can be very high.” The aim is to allow access to the drug as its cost-effectiveness is being established.

At the end of the agreement period, the evidence for a technology will be re-reviewed by NICE, and a decision made about whether the NHS will continue to provide it. “This allows ample time for the company, with clinicians and patients, to collect data to demonstrate whether the product is actually working,” she says. “If it doesn’t work, or works less effectively than anticipated, then the recommendation can be changed.” This is also of benefit to patients, as resources are not being spent on expensive treatments that do not work, diverting funding to newer treatments that might be more effective.

Professor Wailoo says that some people might argue that we should be prepared to pay more for something that is rare than for something that is common.

Table 2. The eight most expensive drugs in the USA in 2016. Source: EvaluatePharma® (April 2017), ©Evaluate, www.evaluate.com

<table>
<thead>
<tr>
<th>Brand name</th>
<th>INN</th>
<th>2016 cost PPHY, * USA, in $</th>
<th>Product type</th>
<th>Therapeutic area</th>
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<tbody>
<tr>
<td>Soliris</td>
<td>eculizumab</td>
<td>599,842</td>
<td>antibody</td>
<td>paroxysmal nocturnal haemoglobinuria, atypical haemolytic uraemic syndrome</td>
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<tr>
<td>Naglazyme</td>
<td>galsulfase</td>
<td>492,213</td>
<td>enzyme replacement therapy</td>
<td>mucopolysaccharidosis VI</td>
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<td>Eloctate (Elocta in UK)</td>
<td>anti-haemophilic factor (recombinant) Fc fusion protein</td>
<td>459,332</td>
<td>recombinant protein</td>
<td>recombinant factor VIII to treat haemophilia A</td>
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<td>Cerezyme</td>
<td>imiglucerase</td>
<td>457,930</td>
<td>enzyme replacement therapy</td>
<td>Type I Gaucher disease</td>
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<td>Gazyva (Gazyvaro in UK)</td>
<td>obinutuzumab</td>
<td>449,984</td>
<td>antibody</td>
<td>follicular lymphoma and chronic lymphocytic leukaemia</td>
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<td>Cinryze</td>
<td>C1 esterase inhibitor</td>
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<td>blood product</td>
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<td>NovoSeven</td>
<td>epptacog alfa</td>
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<td>recombinant protein</td>
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<td>agalsidase beta</td>
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</table>

*PPPY: per patient per year
The humanised monoclonal antibody drug eculizumab, developed by US-based biotech company Alexion and sold under the brand name Soliris, currently tops the list of the world’s most expensive drugs. The typical cost of the drug is $600,000 per patient per year. It’s not a cure – patients will require infusions every two weeks for life.

But behind the eye-watering costs lie very sick patients and a chance for a more healthy life. It was first approved in 2007 to treat paroxysmal nocturnal haemoglobinuria (PNH), in which the body’s own immune system destroys the red blood cells, which affects just one to two patients per million.5 Before eculizumab reached the market, bone marrow transplants were commonly given. While the drug does not cure the disease, it does reduce the need for ongoing blood transfusions and improves patients’ quality of life.

Four years later, it was approved for a second orphan disease, atypical haemolytic uraemic syndrome (aHUS). Like PNH, this is a disease of the complement system, which is the immune system’s mechanism of destroying foreign particles. The prognosis is poor, and kidney failure is common. Eculizumab represents an alternative to plasma exchange/infusion or dialysis. aHUS is so rare that it was approved on the basis of two tiny trials, one in 20 patients and the other in 17.6

NICE gave eculizumab the go-ahead for aHUS in 2014 via the highly specialised technologies programme.7 It has to be prescribed through an expert centre, its use must be monitored and a national protocol for starting and stopping treatment developed, as well as a research programme to evaluate when treatment should be stopped or the dose adjusted. NICE estimated that the total cost to the NHS would be more than £60m in the first year; the company’s estimate was more conservative, at £36m.

Although exact figures for the development costs of eculizumab are not available, Alexion told International Business Times that it cost “nearly $1 billion over 15 years” to develop the drug. With fewer than 10,000 PNH patients in the USA and Europe, and a similar number with aHUS, recouping these costs, plus those involved in manufacturing and distributing it, means the drug is never going to be cheap. NICE urged NHS England and Alexion to look at how that cost might be reduced.

Box 1. Eculizumab – the world’s most expensive drug

common. “The patients are very identifiable – some conditions may have only tens of patients in the country,” he remarks. “It’s a very difficult value judgment, but some of the arguments about why we should be prepared to pay more reflect the idea that everyone should have an equal chance of being treated, and many of these conditions affect children and are very severe. Many arguments are not really about rarity per se but could equally apply to severe but common conditions.”

On a personal level, Upadhyaya feels we owe it to these patients, who equally pay into the system, to offer the hope of treatment that comes with encouraging innovation. “Whatever we do, it is not necessarily going to be the right answer,” she concludes. “We are trying to find a path that allows innovation to come through to set the scene for what might be possible in future – but not at any cost. We have to be seen to be fair.”

References

Declaration of interests
None to declare.

Sarah Houlton is a freelance science journalist