Orphan Drug Pricing and Payer Management in the United States: Are We Approaching the Tipping Point?

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The Orphan Drug Act of 1983 paved the way for the development of drugs that treat rare diseases, defined in the United States as those affecting fewer than 200,000 patients. Orphan drugs can cost hundreds of thousands of dollars annually, but insurers have traditionally covered these therapies because the small populations involved did not typically lead to significant cost exposure. Payer sensitivity to the cost of orphan drugs is rising, however, with the accelerated rate of new launches of these agents amid intensified economic pressure. Payers are showing increasing levels of concern and scrutiny about coverage of orphan drugs. A new payer survey conducted between February 2008 and March 2009 provides insights on how payers are managing orphan drugs and the way it is likely to evolve in the future. Survey findings show that the patient share of orphan drug costs is rising and is expected to continue to rise, barring sweeping changes in public health policy. This shift in benefit design could affect patient access to orphan agents and, therefore, drug utilization. Manufacturers will have to invest in research to understand payer impact on the uptake of their orphan drugs in development. They will also benefit from being prepared to develop strategies to ensure patient access to and affordability of their orphan agents.

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• Assistance in clinical research study design
• Seven-year period of exclusive marketing after an orphan drug is approved
• Waiver of Prescription Drug User Fee Act filing fees (about $1 million per application for fiscal year 2008)
• Further incentives for development of orphan drugs were incorporated as amendments in 1984, 1985, 1988, and 2007.

The ODA has achieved its goal of increasing the number of drugs available for rare diseases. Before the legislation was signed into law in 1983, 10 orphan drugs came to market, including calcitrol (Rocaltrol, Caligex), for the treatment of hypocalcemia in dialysis patients (1978); metoclopramide (Reglan), a gastric smooth-muscle relaxant for the treatment of gastro-paresis (1979); and alprostadil (Prostin VR), for treating neonates with congenital heart defects before surgery (1981).

As of May 2009, the US Food and Drug Administration (FDA) has designated 2002 drugs for orphan indications. Although a number of agents on the list are either in development or will be once investors can be attracted, a total of 338 agents have been granted marketing approval.

Oncology or oncology support products, such as imatinib mesylate (Gleevec), account for 102 (30%) of the orphan products that have marketing approval. The remaining agents target a wide range of rare conditions from blood disorders (hemophilia, von Willebrand disease, paroxysmal nocturnal hemoglobinuria) and inflammatory conditions (juvenile rheumatoid arthritis, cryopyrin-assisted periodic syndrome) to metabolic disorders (Gaucher disease, Fabry disease, tyrosinemia).3

The rate of orphan product designations has accelerated. In 2008, the FDA’s Office of Orphan Drug Development achieved a record by designating 165 products for orphan diseases and conditions, up from 130 in 2007. Between 1983 and 2003, the greatest number of orphan drug designations for any single year was 95. In 2008, the FDA granted marketing approval for 15 orphan products for the treatment of diseases ranging from leukemia to Huntington disease.

Large Pharmaceutical Companies Fuel Orphan Drug Arena

Large pharmaceutical companies are helping to fuel the growth of orphan drugs, within the increased focus on their biologics sector, which accounts for 60% of the orphan drug market. Globally, it is estimated that large pharmaceutical companies account for 53% of the orphan drug market, and they are well represented in the list of orphan drugs with marketing approval. Each of the following companies sponsors at least 2 products on the list, as of May 2009—Abbott, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Pfizer, and Roche through its acquisitions.

Like biologics that treat diseases such as rheumatoid arthritis, multiple sclerosis, Crohn disease, or hepatitis C, orphan agents command premium prices and offer the potential for revenue growth. The global market for orphan drugs grew an estimated 8% from 2005 to 2006 and is estimated to grow at a compounded annual rate of 7% through 2011. Some biologics, such as imatinib, start as orphan drugs for 1 rare disease but grow by expanding to additional orphan indications. However, other drugs expand into the nonorphan arena or benefit from off-label use. A number of today’s most successful biologics, such as epoetin alfa (Epogen/Procrit), rituximab (Rituxan), infliximab (Remicade), and 5 brand-name human growth hormone products, began life as orphan drugs whose utility expanded through additional indications and/or off-label use.

Orphan Drugs Rising on Payer Radar

Primed by their experience with the burgeoning growth of biologics, injectables, and other specialty drugs, payers are showing increased concern and scrutiny when it comes to orphan drugs. In an informal member survey at the spring 2006 meeting of the Academy of Managed Care Pharmacy, members listed orphan drugs as one of their top concerns. Citing the rising number of orphan products in the pipeline and new approvals, most survey respondents believed that spending on orphan drugs would continue to increase as a percentage of over-

KEY POINTS

- The Orphan Drug Act of 1983 paved the way for so-called orphan drugs that treat rare diseases, affecting <200,000 persons in the United States.
- As of May 2009, the US Food and Drug Administration has designated 2002 drugs for orphan indications.
- Cost is an issue with orphan drugs, which can amount to hundreds of thousands of dollars annually.
- Traditionally, insurers have covered these drugs, because of the small patient populations involved.
- But current cost concerns in healthcare raise new coverage issues for these expensive agents. The increase in cost-sharing is likely to affect patient access to orphan drugs.
- In 2003, only 4 single-indication orphan drugs were covered by Medicare; that number increased to 12 in 2005. Those with multiple indications are reimbursed by Medicare at various rates.
all drug budgets. Under pressure by patient advocacy groups and physicians to expand access, and plan sponsors to control healthcare spending, payers now see new challenges in the management of orphan drugs.

**Orphan Drug Management by Payers**

To better understand payer sensitivity to orphan drug costs and how insurers manage these costs, Advance Insights, an InVentiv Health company, conducted (from February 2008 to March 2009) a web-based survey of decision makers in 26 payer organizations responsible for 106 million lives across the United States. Two thirds of these lives were covered in commercially sponsored medical or pharmacy plans or both, with the remainder in Medicare or Medicaid plans. Most lives enrolled in pharmacy plans were in 3-tier, open plans (90% for the commercial population and 61% for Medicare), the most common plan design nationally. Four- or 5-tier plans account for 8% of the commercial population and 54% of the Medicare population.

The web survey focused on the current management of 9 orphan agents selected to achieve a mix of oncology and nononcology agents, orphan and ultra-orphan drugs, various modes of administration, existence of treatment alternatives, and multiple indications (Table).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication (US prevalence)</th>
<th>Mode of administration</th>
<th>Therapeutic options available</th>
<th>Annual cost, $ thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib malate (Sutent)*</td>
<td>Advanced renal-cell carcinoma (~90,000) Gastrointestinal stromal tumor (2040)</td>
<td>Oral</td>
<td>X</td>
<td>48,000</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)*</td>
<td>Non–small-cell lung cancer (148,800) Pancreatic cancer (~33,000)</td>
<td>Oral</td>
<td>X</td>
<td>56,000-84,000</td>
</tr>
<tr>
<td>Miglustat (Zavesca)</td>
<td>Gaucher disease type I (~4000)</td>
<td>Oral</td>
<td>X</td>
<td>128,000</td>
</tr>
<tr>
<td>Mecasermin (Increlex)*</td>
<td>Growth failure (~30,000 overall, ~6000 severe form)</td>
<td>Subcutaneous injection</td>
<td>X</td>
<td>12,000-50,000</td>
</tr>
<tr>
<td>Agalsidase beta (Fabrazyme)</td>
<td>Fabry disease (2564)</td>
<td>Infusion</td>
<td>X</td>
<td>239,000</td>
</tr>
<tr>
<td>Idursulfase (Elaprase)</td>
<td>Hunter syndrome (~1500)</td>
<td>Infusion</td>
<td></td>
<td>300,000-500,000</td>
</tr>
<tr>
<td>Galsulfase (Naglazyme)</td>
<td>Mucopolysaccharidosis VI (1200)</td>
<td>Infusion</td>
<td></td>
<td>441,000</td>
</tr>
<tr>
<td>Imiglucerase (Cerezyme)</td>
<td>Gaucher disease type I (~4000)</td>
<td>Infusion</td>
<td>X</td>
<td>442,000-600,000</td>
</tr>
<tr>
<td>Eculizumab (Soliris)</td>
<td>Paroxysmal nocturnal hemoglobinuria (~1050)</td>
<td>Infusion</td>
<td></td>
<td>486,000-508,000</td>
</tr>
</tbody>
</table>

*a Oncology.  
b Pediatric only.  

Source: InVentiv Advance Insights, Somerset, NJ.

Among the most significant findings was that no new management approaches have been developed or appear to be in development specifically for managing unique orphan drugs that treat very small populations. Instead, orphan drugs are likely to be captured in the same net of tools, tactics, and benefit designs already in use or planned for controlling costs of biologics, injectables, or other expensive specialty products used for the treatment of diseases far less rare than most orphan conditions.

Sensitivity to drug cost ranges considerably among surveyed plans, but for 54%, scrutiny increases when a drug is priced ≤$50,000 per patient per year. The remaining respondents cite thresholds ≥$50,001 per patient per year, with 2 plans indicating that the drug cost must exceed $250,000 per patient per year for greater scrutiny (Figure 1).

Not surprisingly, clinical data associated with an orphan drug are ranked highest among the factors that drive benefit design or restrictions for orphan drugs in most plans, followed closely by overall cost exposure (Figure 2). Clinical data—FDA-approved indication, trial design and results, formulation, and requirements for administration—provide the basis for prior authorization and continued use. Overall cost exposure—a
function of disease prevalence, number of indications, potential for off-label use, and the availability of less expensive treatment options—serves to further raise the visibility of an orphan drug and to guide management.

Most of the plans surveyed require prior authorization to ensure that the proposed use matches the FDA-approved indication for each of the orphan drugs (Figure 3). Payers, however, are likely to vary significantly in how they use clinical information and FDA labeling to restrict access to orphan products as illustrated by 2 cases involving eculizumab (Soliris), a product for treatment of paroxysmal nocturnal hemoglobinuria.

Health plan A is a regional affiliate of a national plan, with 1.9 million members. Health plan B is a 2.4-million-member independent regional plan. Both required prior authorization to obtain coverage for eculizumab. For plan A, this meant confirmation of diagnosis by a specialist, which led to the approval of the product. In contrast, plan B had a formal medical policy in place, with criteria for use based on FDA-approved labeling and patient selection criteria and end points used in the clinical trials conducted to gain product FDA approval. Plan B’s approach resulted in denial of coverage for eculizumab for 1 patient in 2008, because clinical measure did not meet policy criteria. The respondent for plan A indicated a price sensitivity threshold of $100,001 to $150,000 per patient per year, whereas plan B indicated increased scrutiny of orphan drugs at pricing from $25,001 to $50,000—both well below the estimated annual drug cost associated with eculizumab, but perhaps reflective of the difference in plan sensitivities and philosophies that exist among those administering health plans.
Although most of the respondents surveyed reported using less restrictive prior authorization policies similar to that described for plan A, a significant number reported tighter policies for each of the drugs in the study (Figure 4). These more restrictive approaches may include genetic testing to confirm a diagnosis or step therapy, if appropriate. In plans with formal policies, it is common to incorporate periodic reevaluation of patient status against measures based on clinical trial results to determine if a treatment is effective.

**Access Does Not Guarantee Affordability**

Benefit design does not distinguish between orphan and nonorphan drugs. Following patterns in the nonorphan drug arena, oral products are usually covered under the pharmacy benefit, whereas infused agents are normally covered under the medical benefit. Injectable coverage varies between the two. Where patient cost-sharing for drugs is used, the patterns mirror those used in the nonorphan environment. Copayments are often used in conjunction with oral agents, whereas coinsurance, defined as percent-based cost-sharing, is more common for infused drugs.

As a result, coverage scenarios for orphan drugs vary widely, as illustrated by galsulfase (Naglazyme), a treatment for the enzyme-deficiency disease mucopolysaccharidosis VI, one of the drugs that was included in the current survey. A commercially insured patient receiving galsulfase under the medical benefit in 1 of the 5 plans that cover the drug under the medical benefit (Figure 4) pays only a typical office copayment, ranging from $25 to $40 each time the drug is administered in the clinic.

A commercially insured patient receiving the same drug under the pharmacy benefit (20 plans in the survey) typically pays the office copay along with drug copays up to $25 per prescription or coinsurance, which ranges from $25 to $150 per prescription.
from 11% to 20% of the cost per prescription. Under a coinsurance scenario, for a patient taking galsulfase, the annual out-of-pocket (OOP) drug costs would range between $48,500 and $88,200 per year, in the absence of a plan-imposed cap or maximum.6

Although annual OOP maximums help to mitigate these expenses, some 29% of plans surveyed by the Kaiser Family Foundation and the Health Research & Educational Trust in 2007 do not offer them and use of those that do varies widely.8 In single coverage plans, 22% of insured employees were in plans that capped annual OOP expenditures at $3000 or more and 28% were in plans with maximums of <$1500 a year. Of those enrolled in family coverage plans, 24% had annual OOP maximums of $2000 to $6000 and 10% had maximums <$2000.8

Regardless of caps on OOP maximums, copayments and coinsurance represent only 1 form of cost-sharing, with the potential to impact orphan drug use as it does for many patients with serious illnesses. Rising premiums, deductibles, variations in coverage based on plan type, and limits on benefits combine to create significant economic hardship for many with serious illnesses. For example, 22% of the employed population opts for policies that limit lifetime medical benefits to between $1 million and $2 million.9 Patients using orphan drugs generating costs between $50,000 and $100,000 per year plus costs associated with administration and ancillary care can rapidly reach these maximums.

**Medicare Reimbursement Policies**

Medicaid coverage and reimbursement policies for orphan drugs vary from state to state. Medicare patients seeking orphan drugs face limitations on reimbursement and potentially high OOP costs.

Under provisions in the Medicare Modernization Act (MMA) of 2003, OOP costs typically reach $5700 per patient per year before catastrophic coverage kicks in for patients covered under Medicare Part D. The Centers for Medicare & Medicaid Services (CMS) has the ability to raise this maximum annually. Patients receiving care through Medicare Part B or the medical benefit may encounter reimbursement or access hurdles based on whether the drug meets Medicare’s criteria for a single-indication orphan drug.

These criteria require drugs to be (1) designated as orphan drugs and approved by the FDA for the treatment of ≥1 orphan conditions, and (2) listed in the current US Pharmacopoeia Drug Quality and Information only for the orphan indication, with no
other approved indication or off-label use.9 This policy is based on the assumption that nonorphan indications or off-label use expand income available to manufacturers, and, because they are used by a larger patient population, providers and suppliers are more motivated to supply them.

Single-Indication Orphan Drugs

When this rule was passed as part of the MMA, 4 drugs were on the list of single-indication orphan drugs. The list was expanded to 12 drugs in 2005 with the input of provider groups or patient advocacy groups, such as the National Organization for Rare Diseases (NORD).

The list of single-indication orphan drugs includes imiglucerase (Cerezyme) and interferon gamma 1-b (Actimmune) but not epoetin alfa, which has a number of indications that CMS considers outside the orphan arena, and botulinum toxin type A (Botox), which generates far more income from cosmetic use than it does from its orphan indications, including the treatment of dystonia.9

Single-indication orphan drugs receive special payment consideration through the Medicare’s Hospital Outpatient Prospective Payment System (OPPS). They were also excluded from the Competitive Acquisition Program (CAP) vendor program, which, until it was postponed in September 2008, supplied a list of specialty drugs and biologics to physicians as part of the MMA. This means that CAP vendors were not required to carry and provide the 12 products, forcing providers or patients to find other pathways for acquiring and obtaining reimbursement for the drug. These included arranging for administration of the drug in a hospital or hospital outpatient clinic, working with specialty pharmacy providers that are focused on orphan drug or other rare disease markets, and patching together reimbursement from Medicare and manufacturer patient-assistance programs, all of which they now do in the absence of the CAP.

Orphan Drugs Not on Single-Indication List

Orphan drugs that are not on the single-indication list are reimbursed by Medicare at various rates. Reimbursement under OPPS depends on whether the drugs are enfolded into a procedure or are reimbursed separately. Reimbursement rates within these groups may vary from drug to drug based on clinical and access considerations.10 For drugs administered by physicians in the office, Medicare Part B generally pays 80% of medical benefit costs, which can include the cost of infused drugs along with administration and other ancillary costs associated with the drug and patient care. For patients taking orphan drugs, the remaining 20% can amount to thousands of dollars a month, according to patient advocates.11

Patient-Assistance Programs Are Key

Patient-assistance programs are a resource for many patients and form the cornerstone of manufacturer marketing programs for orphan drugs. The amount of financial assistance varies based on individual patient income and may involve other organizations. Genzyme Corporation, for example, offers the Charitable Access Program for patients using imiglucerase, alg glucerase (Ceredase), laronidase (Aldurazyme), agalsidase beta (Fabrazyme), and alglucosidase alfa (Myozyme).11 These programs offer free drugs in limited amounts to qualified patients.

Other programs, such as that offered and administered by NORD, assist insured patients with insurance premiums and copayments. On its website, NORD lists 34 different patient-assistance programs that it administers on behalf of orphan drug manufacturers.12

Future Developments

Over the next 3 to 5 years, insurers who participated in the present survey expect to see increasing budget pressure from orphan products, citing new launches, price increases, and new indications for existing products. A few of them expect some of these launches to provide therapeutic alternatives or potential biosimilars that would allow contracting or the development of step edits. The majority of respondents, however, expect that commercial insurers will continue to shift more cost to patients through mechanisms such as opt-in riders for expensive drugs and increased reliance on drug health plans with fourth and fifth tiers, which are comprised of expensive injectables and/or infused drugs.13

This finding is reinforced by the recently published results of the Benefit Design Index conducted by the Zitter Group in 2008.14 Among other measures, the Benefit Design Index highlights employer and insurer satisfaction with cost-sharing. In the 12 months leading up to that study, nearly 70% of insurers increased copayments/coinsurance rates for prescription drugs. Payers in this study indicate that they can shift to patients from $354 to $377 per month in OOP costs without the member foregoing medically necessary care.14

Patient advocates view this trend with alarm, fearing that higher OOP expenses will inhibit or prevent patients from using needed medications.2 Furthermore, increased drug cost-sharing does not take into account the impact of cumulative OOP healthcare costs stemming from serious illnesses which, at the very least, can result in gaps in care.

Oncology provides good examples for this. A February 2009 report by the Kaiser Family Foundation and the American Cancer Society cited cases of patients with cancer, including 1 who amassed $100,000 in med-
The continued application of traditional patient cost-sharing strategies in the orphan drug arena is likely to have far-reaching effects not only for patients but also for providers and for drug manufacturers.

Conclusions

It is difficult to envision a scenario in which orphan drugs will be denied coverage; however, payer scrutiny is likely to increase as new products enter the market and budgets contract in a weakening economic environment. Responses will vary by payer and plan based not only on cost exposure but also on payer resources, philosophies, and available benefit design options, all of which can affect patient access. Responses are also likely to be affected by any changes that may come in public policy through healthcare reform. A clear understanding of the clinical and economic value of the drugs will play an increasingly important role in decision-making.

The continued application of traditional patient cost-sharing strategies in the orphan drug arena is likely to have far-reaching effects not only for patients but also for providers and for drug manufacturers. For plans with formal medical policies, specialists must be prepared to document that patients meet specified clinical guidelines to receive drugs. Increasingly, manufacturers will have to invest in research to understand payer impact on uptake of their orphan drugs in development. They must also be prepared to develop strategies to ensure that payers truly understand the value of their therapy and tactics to ensure that patients will be able to access and afford the orphan agents they develop.

References

6. Hyde R, Dobrovolny D. Orphan drug pricing: have we reached the tipping point? Presented at the 26th Annual Meeting and Showcase of the Academy of Managed Care Pharmacists. San Francisco, CA; April 16-19, 2008.
Currently, Representative Henry Waxman, Chairman of the House Energy and Commerce Committee, along with the Obama administration, are proposing legislation to allow brand-name biologics used for orphan drugs to be subject to generic competition in the United States after 7 years of patent exclusivity. This proposed legislation is significant for the orphan drug market, as biotechnology drugs are key drivers of this market, which is estimated to reach $82 billion by 2011. Biologics account for approximately 60% of the global orphan drug market today. Promising categories within biologics are monoclonal antibodies, interferons/interleukins, growth hormones, and plasma products.

What would the potential impact of this legislation be? First, it could increase access to affordable treatments for orphan drugs to payers, providers, and patients. Approximately 5000 of the 6000 orphan diseases involve genetic disorders, and many will need enzyme, hormone, and protein therapies, which require biologics rather than traditional small-molecule drugs. If approved, generic biologics could be sold at a 10% to 30% discount, allowing for “substantial consumer savings,” without eroding market share for brand-name pharmaceutical companies, according to a recent Federal Trade Commission report.¹

Second, the physical availability of orphan drugs for patients and providers may also be influenced by the presence of generic biologics, according to NORD. Most orphan biologics are made by only 1 manufacturer, and yet providers are experiencing critical shortages of lifesaving biologic treatments (eg, recombinant factor VIII for hemophilia and Prolastin for alpha-1 antitrypsin deficiency). This shortage leads to rationing of orphan drugs, thereby limiting much-needed access for patients.

Third, a lack of competition in biologics may also impede new treatment advances for orphan diseases. Without competition from generic manufacturers, there may be little incentive for biotechnology manufacturers to continue to innovate for orphan biologics. The Drug Price Competition Act has resulted in brand-name manufacturers innovating to make newer delivery/dosage forms of their products. But without competition for biologics there is no incentive for manufacturers to continue to innovate in developing biologics for orphan diseases.

Despite the concerns about the feasibility of generic biologics (ie, can they be developed; will they be therapeutically equivalent to brand-name biologics), the future of the orphan drug industry will significantly be influenced by the entry of generic biologics. Globally, countries such as Australia, Japan, Singapore, Taiwan, and Korea have already implemented legislation for promoting research on orphan drugs. If current efforts in the United States take a similar direction, patients, providers, and payers can only stand to benefit from these advances.

Reference

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