Orphan Drugs Part 1—

Patient Care to the Individual Level

by Denise K. Pierce

What constitutes an orphan disease, and how are treatments developed for such diseases? How do orphan diseases and their associated drugs and biologics impact oncology? What is the payers' perspective on orphan drugs? This article will attempt to answer these and other questions.

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The Orphan Drug Act and Its Impact on Patient Access to Care

The Orphan Drug Act (ODA) of 1983 was created to offset a drug manufacturer's development costs by way of tax credits and grants, and to help motivate research and development of drugs and biologics for diseases or conditions with a prevalence rate of less than 200,000 patients within the United States. The ODA continues to be an extremely important piece of legislation today. It has prompted market entry of treatments that have improved the lives of patients across a variety of rare diseases that may otherwise have no treatment options.

Still, despite the incentives under ODA, only 352 of the total 2,212 orphan applications submitted since the legislation's enactment have actually received FDA approval for their respective orphan diseases, based on efficacy and safety.[1] The FDA's Department of Orphan Products Development has stated that this limited number of novel treatments to help patients with devastating diseases pales in comparison to the unmet need for the nearly 7,000 diseases classified as orphan or ultra-orphan.

Drug development costs are a major hurdle to bringing a drug to market for rare diseases. Looking back to 2003, an analysis estimated a manufacturer's pre-tax total cost of drug development to be $802 million, with $335 million for preclinical testing, and $467 million for clinical trials.[2] Assuming that it takes 15 years from the discovery of a possible product to actual market entry, a tax rate of 35 percent, and 2010 FDA fees, total costs for a drug manufacturer to bring a prospective orphan drug to market today may reach roughly $1.09 billion.[3] Therefore, without the ODA, most treatments to address rare diseases would never be studied due to the high risk that these drug development costs could never be recovered.

Most commonly, the conditions cited as orphan and ultra-orphan diseases and conditions are those that are extremely rare and connote extremely high costs of care. A few examples include:

- Huntington's Disease, which affects 30,000 people in the U.S.[4]
- Gaucher Disease, which affects about 5,440 in the U.S.[5]
- Paroxysmal Nocturnal Hemoglobinuria, which affects between 8,000 to 10,000 people in North America and Western Europe.[6]

Treatment for these conditions is lifelong, and therefore carries a significant cost. The treatments, which include the following examples of Fabrazyme® (agalsidase beta), Cerezyme® (imiglucerase for injection); Elaprase® (idursulfase solution for injection), and Soliris® (eculizumab), can cost between $300,000 and $500,000 per year. These costs take into consideration the drug development cost requirements spread out across the actual number of patients that may present with the rare disease and be prescribed the therapy. Because of the high price tags, the biopharmaceutical manufacturers for these products commonly establish significant patient assistance support programs through foundation programs, such as the National Organization of Rare Disorders (NORD), and have extensive patient and provider coordination services to help ensure access to care.

Orphan Cancer Indications

What may not be as clearly understood is that many cancers also fit into the classification of orphan and ultra-orphan disorders. Accordingly, several drugs and biologics have been approved through the years under the umbrella of the ODA for these disorders. Table 1 provides a small sampling

Table 1. Select Oral and IV Oncology Treatments and Their Orphan Disease Linkage

Drug	Year of Orphan Drug Designation	Orphan Disease Indication
Proleukin® (aldesleukin)	1992	Metastatic Renal Cell Cancer (RCC)
Busulfex® (busulfan)	1997	Stem cell consolidation for Chronic Myelogenous Leukemia (CML)
Trisenox® (arsenic trioxide)	1998	Acute Promyelocytic Leukemia
Temodar® (temozolomide)	1998	Astrocytoma and Glioblastoma
Revlimid® (lenalidomide)	2001	Multiple Myeloma
Avastin® (bevacizumab)	2003	RCC
Treanda ® (bendamustine)	2007	Chronic Lymphocytic Leukemia (CLL)
Folotyn ® (pralatrexate)	2008	Peripheral T-Cell Lymphoma

Source: Food and Drug Administration

of oral and IV oncology treatments and their orphan disease designation, which may have been an initial FDA-approved indication for the particular drug.

These treatments have brought improved clinical outcomes for patients diagnosed with these cancers, and some drugs such as Proleukin®, Trisenox®, and Folotyn®, represent the first FDA-approved treatments in their respective orphan indications. The average cost of cancer-specific orphan therapeutics falls in the range of $48,000 to $100,000 per year, which can be more than the cost for drugs used to treat certain high-volume cancers, but significantly less than the cost to treat other orphan diseases. Novel patient assistance and foundation programs, supported through such organizations as NORD, have been established by the manufacturers of these products to acknowledge the low-volume prevalence of the particular cancers, and to support appropriate patient access. Examples include:

- NORD's Peripheral T-cell Lymphoma Co-Payment Assistance Program
- NORD's Hodgkin Lymphoma Co-Payment Assistance Program
- The Patient Assistance Foundation's Co-Pay Relief Program.

Many drug manufacturers also offer their own patient assistance programs. Examples include:

- Allos Support for Assisting Patients (ASAP) Program (Folotyn)
- Celgene Patient Support Program (Revlimid)
- CephalonCares Foundation Patient Assistant Program (Treanda)
- Genentech's Access Solutions (Avastin).

Orphan Disease Treatment Costs from the Payer Perspective

Orphan oncology drugs and biologics undergo payer coverage decision processes similar to any other oncology agent. Proven medical necessity must be present to warrant coverage, which conventionally comes in the form of FDA approval for the indication and support in clinical compendia, such as the National Comprehensive Cancer Network's (NCCN's) *Drugs & Biologics Compendium*™, Thomson Reuters *DrugDex*®, Gold Standard/Elsevier's *Clinical Pharmacology*, and the American Hospital Formulary Service *Drug Information (AHFS-DI)* published by the American Society of Health-System Pharmacists. Additionally, there must be clear understanding of the appropriate patient selection for the treatment. Historically, orphan drugs gained little attention from payers after a coverage decision was made, due to the extremely low likelihood of the payer seeing a claim for that orphan disease. Over time, however, payers have increased their sensitivity to orphan oncology drug costs and their impact to the healthcare plan, and have begun implementing more utilization management criteria. A study that assessed payer levels of scrutiny on higher cost drugs concluded that 54 percent of payers surveyed apply scrutiny and utilization management for drugs with an annual patient cost greater than $50,000.[7]

For example, many payers have developed prior authorization requirements for use of an orphan treatment, place quantity limits (especially for oral orphan drugs), or place the drug on a specialty tier related to patient cost share. These mechanisms are applied to non-orphan oncology drugs and biologics as well. An analysis conducted in 2009 of healthcare plan utilization restrictions on orphan drugs

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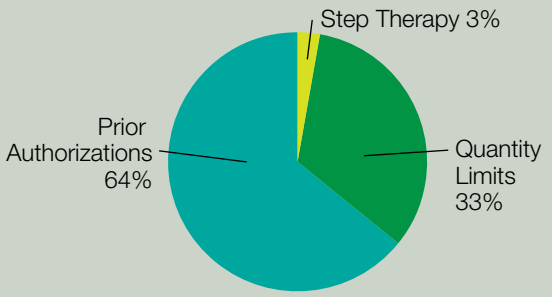
(not limited to oncology) found that about 64 percent of healthcare plans require a prior authorization procedure for orphan drugs (see Figure 1, at right).[8]

Occasionally, a payer will publish a specific policy or guideline that deals directly with orphan drugs. For example, WellPoint has a published clinical guideline on orphan drugs, which simply states that: *Use of an orphan drug is considered* ***medically necessary*** *when it receives FDA Orphan Drug designation and approval ("Designated/Approved").*[9]

Payers become most concerned when a drug or biologic first enters the market for an orphan indication, and then later expands into non-orphan indications. In these cases, the payer applies much greater scrutiny to the cost of care and the patient cost share component—especially if the drug's cost is not modified to align with the new indication's prevalence, or to the comparative cost of other treatment options (if available).

Figure 1. Payer and Healthcare Plan Orphan Drug Coverage Requirements



Source: Quintiles Consulting. *Orphan Drug Market Access in the U.S. May, 2009.*

Orphan Drugs and the Oncology Practice

There is no question that payers are concerned about overall oncology drug costs, with orphan drugs being a part of that cost. However, payers do not question the value of treatments approved for unmet needs in diseases where the patient population may not have the voice or influence as in other, more prevalent diseases. What is expected is that payers will continue to apply scrutiny to orphan drugs—and oncology drugs and biologics overall—and will expect providers to ensure appropriate patient selection and documentation of medical necessity. To assist in this effort, the following steps can be taken to help ensure consistent patient access and physician prescribing discretion for these agents:

1. Check payer requirements for potential prior authorization processes.
2. Document. Document. Document. Ensure that the patient record reflects documentation of the medical necessity for the treatment decision.
3. Contact the drug or biologics manufacturer for clinical documentation that will support medical necessity. This action is often accomplished by contacting the manufacturer's reimbursement support services, medical affairs department, or field sales representative.
4. Make sure the appropriate codes are used (ICD-9 diagnosis codes, HCPCS drug codes, CPT procedure codes) and the established billing unit of use that aligns with the HCPCS code. Avoiding errors in initial billing may help reduce any subsequent claim questions about coding or medical necessity.

By instituting a consistent process for managing orphan oncology drugs in your practice, the likelihood of payer scrutiny goes down over time, and consistent access to care goes up for patients. Manufacturers will continue to develop drugs and biologics for the many orphan indications with unmet needs. That type of investment brings hope and opportunity for many patients across the U.S., but requires careful documentation and medical necessity support to ensure these patients maintain access to care.

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