

**BioWorld<sup>®</sup>**

TOP 25  
BIOTECHNOLOGY  
DRUGS REPORT

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2007

*By Michael Harris, Senior Managing Editor*

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# CEREZYME

**Proper name:** Imiglucerase

**Type:** Enzyme-replacement therapy

**Drug Developer:** Genzyme Corp.

**Location:** Cambridge, Mass.

**Website:** [www.genzyme.com](http://www.genzyme.com)

**Indication(s):** Type 1 Gaucher's disease

**Approval Date:** May 1994

**2006 Revenue:** \$1 billion

**Percentage of Genzyme's Total Revenue:** 31.38 percent

## **Cerezyme and the orphan drug market**

Cerezyme, the enzyme-replacement therapy for Type I Gaucher's disease, is Genzyme Corp.'s top-selling product. Although the worldwide patient population for the disease is 4,500, with some getting the drug through charities and other Genzyme-supported efforts, its annual cost can exceed \$100,000 in many cases. Cerezyme sold \$1 billion in 2006, and is expected to bring in as much as \$1.075 billion in 2007.

The FDA approved the therapy, which is produced from mammalian cells, in May 1994, when Cambridge, Mass.-based Genzyme predicted revenues to level off at about \$200 million by the year 2000. Instead, Cerezyme has earned the company more than four times that amount, up to \$932 million in 2005 and reaching blockbuster status in 2006.

Orphan drugs like Cerezyme can mean high-risk challenges and years of tough research, but to the investment community they often translate into a big payoff – at least that is the case with enzyme-replacement therapies such as Cerezyme. But does that mean success for new orphan drugs, such as Alexion Inc.'s paroxysmal nocturnal hemoglobinuria (PNH) treatment, Soliris, which won FDA approval in March 2007? "We've been pretty pleased as investors and analysts following this industry over the last decade with the success of drugs for ultra-orphan diseases," said analyst Eric Schmidt, of New York-based Cowen & Co. Case in point: Cerezyme.

In the early 1980s, Genzyme licensed a program from Boston-based Tufts University that eventually led to development and commercialization of both Ceredase and Cerezyme for Gaucher's disease. "We were involved in that disease before there was an Orphan Drug Act," said Dan Quinn, the company's director of corporate communications. The act was established in January 1983 to inspire scientific work for small, financially disadvantageous indications. Companies that develop drugs for diseases affecting less than 200,000 people in the U.S. or that have a prevalence of less than five per 10,000 in a community are rewarded with tax reductions and a monopoly on the market for seven years.

Genzyme's experience in Gaucher's disease eventually led to other orphan products. "We saw hints early on in our clinical trials of the tremendous clinical impact that an enzyme-replacement therapy could have with that disease," Quinn said. "What we have seen with all of these products is if you have a therapy that is effective in a disease area that is not well served, it can create a market in that area," he said.

Orphan drugs are attractive investment opportunities, Schmidt said, because they address markets with few, if any, competitive products, the marketing and other costs typically are low and pricing reimbursement hasn't been a problem. "This has been a gold mine for several biotech companies," Schmidt told *BioWorld Today*. Estimating drug prices, the size of a market and a penetration rate is not an easy task for analysts and investors. The margin of error "surrounding each assumption is typically wide," Schmidt said in a research note, and the outlooks "carry little value." Historically, he said, "The Street is typically too optimistic about the success of a new product launch." Most fail to live up to estimates. But drugs for ultra-orphan disorders "have generally been able to buck this trend," Schmidt said. And that has others following Genzyme's lead. "Clearly, Genzyme being the vanguard here has enticed other companies like Alexion, TKT [Transkaryotic Therapies Inc.] and Biomarin into the market," Schmidt said, "so I think there are more companies than ever focused on these ultra-orphan diseases." Aside from developing Aldurazyme with Genzyme, Biomarin Pharmaceutical Inc. also markets Naglazyme, approved in June 2005 for mucopolysaccharidosis VI.

But there are high risks associated with those small patient populations. It's never easy to develop a potent drug that is well tolerated, and it's difficult to determine the population size for a disease in which there is no current therapy. Genzyme has focused its marketing efforts on educating physicians about the signs and symptoms of the disease, avoiding delays in diagnosis and access to its therapies. Quinn said the number of patients taking Cerezyme, Fabrazyme (for Fabry disease) and Aldurazyme (for mucopolysaccharidosis I) "has grown slowly but steadily over the time that the drugs have been on the market" because of the company's physician education efforts.

In January 2007, Genzyme said a research study published in the January issue of the *Journal of Bone and Mineral Research* demonstrates that long-term use of Cerezyme significantly improves bone mineral density in patients with Type 1 Gaucher's disease in a dose-dependent manner. Cerezyme is the standard of care for patients with Type 1 Gaucher's disease. Because Gaucher patients risk bone complications, the research published in the journal was important, showing long-term use of the compound significantly improved bone mineral density in those afflicted with the disorder.

### **About Gaucher's disease**

Gaucher's disease, a lysosomal storage disorders (LSD), affects about 30,000 people worldwide. Characterized by a lysosomal accumulation of glucocerebroside inside cells, Gaucher's disease is an inherited genetic condition caused by a deficiency in the Glucocerebrosidase (GCase) enzyme. GCase usually breaks down lipid molecules that build up in organs and tissues. In Gaucher patients, fatty deposits can develop, which may cause serious and life-threatening symptoms.

### **Competition**

Amicus Therapeutics Inc., a Cranbury, N.J.,-based company that filed for an IPO in March 2007, has lead products targeting Gaucher's, Fabry's and Pompe diseases. Existing therapy for those conditions from Genzyme involves enzyme replacement therapy, but Amicus' approach is designed to work by restoring enzyme function. Its Gaucher's disease product, Plicera (isofagomine tartrate), is in two Phase II trials, with preliminary results expected by year-end 2007. Plicera aims to facilitate proper trafficking of the GCase enzyme to the lysosomes to break down the glucocerebroside. The company, which retains all rights to its compounds, plans to fund them all the way through development before establishing its own commercial operations and sales force to market at least some of the products. Rather than simply replace missing lysosomal enzymes, Amicus makes oral small molecules to restore the function of a patient's own, using a pharmacological chaperone that binds to the target protein, for a correct fold that boosts activity.

John Crowley, Amicus' president and CEO, went into biotechnology in a quest to save his two children, afflicted with Pompe disease. Crowley put his life savings into co-founding Novazyme Pharmaceuticals Inc., of Oklahoma City, which Genzyme bought during the fall of 2001 in a stock deal originally valued at about \$137.5 million. He worked at Genzyme for about a year and a half, then went on to found the obesity firm Orexigen Therapeutics Inc., of San Diego. Crowley left the CEO job there in 2005 to assume his current post at Amicus, having served as a director since 2004.

Also exploring the LSD space is Zystor Therapeutics Inc., of Milwaukee, Wis., which deploys what the firm calls Glycosylation Independent Lysosomal Targeting technology licensed from St. Louis-based Symbionics Inc. Zystor's approach enhances the binding ability of replacement enzymes by attaching to the enzyme a peptide tag that targets receptors on cell surfaces. The method is carefully targeted, Zystor's president and CEO Loren Peterson told *BioWorld Today*, noting that Crowley served briefly on his firm's board.

The appeal of LSDs, despite Genzyme's established products and sales force, has to do with relatively low cost of developing a drug for a well-identified niche patient population, Peterson said. "I could get [a drug candidate] into the clinic on

another \$15 million,” he said. “You’re not talking about huge sums of money, and pivotal trials are done with as few as 43 patients.”

In addition, Protalix Biotherapeutics Inc., created from the merger of Orthodontix Inc. and Protalix Ltd., has a Phase III-ready drug for Gaucher’s disease. Protalix’s lead compound for the enzyme-shortage disease, glucocerebrosidase, is made differently from Cerezyme, “and it’s a slightly different isoform,” said Curt Lockshin, the former chairman and director of Orthodontix.

### **About Genzyme**

The victory – dubious in some quarters – by Genzyme over Millennium Pharmaceuticals Inc. at the finish of last year’s bidding war for AnorMED Inc. is water under the bridge, but the cost of the win flooded Genzyme’s bottom line, leaving the company with a net loss of \$17 million for fiscal 2006 despite record revenues. Vancouver, British Columbia-based AnorMED agreed to let Genzyme take over the firm for \$13.50 per outstanding share shortly after Millennium refused to go higher than its \$12-per-share offer. Genzyme earlier had proposed \$8.55 per share. In the end, AnorMED and Genzyme entered a mutually beneficial support agreement regarding the acquisition at the higher price – a 168 percent premium – and Millennium, of Cambridge, Mass., walked away with a \$19.5 million termination fee.

“Revenues were right on the guidance,” noted Henri Termeer, chairman and CEO of Genzyme, during a conference call. The fourth quarter, he added, was even stronger than company officials expected. Specifically, the firm drew \$3.2 billion in revenue for 2006, up from \$2.7 billion in 2005, but lost \$16.8 million, compared to \$441.5 million in net income reported the prior year. For the fourth quarter 2006, revenue hit an all-time high of \$854.2 million, up from \$728.7 million during the same period the year before. Net loss totaled \$286.2 million, or \$1.02 per share, during the quarter, compared to \$106.6 million, or 39 cents per share, in net income during 2005. Still, after various costs were taken out of the equation, Genzyme beat analysts’ estimates by 2 cents.

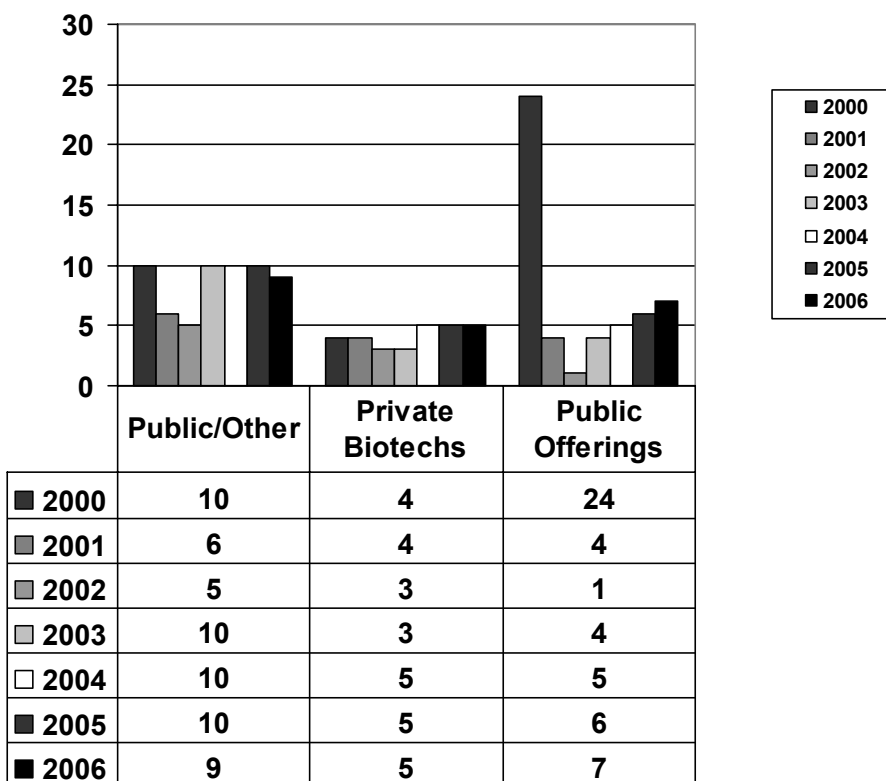
Genzyme had forecast total 2007 sales of \$3.6 billion to \$3.8 billion, and now aims for 2007 net income of \$1.90 to \$2 per share. Taking away the costs of the AnorMED buyout, the firm said 2007’s earnings per share should reach between \$3.20 and \$3.30 per share, higher than the \$3.10 to \$3.20 range offered near the start of this year.

## Biotech Product Approvals, 1982 to April 2007

<i>Company</i>	<i>Company</i>	<i>Company</i>	<i>Company</i>
<b>2005</b>			
American Pharmaceutical Partners Inc.*	Abraxane	American Pharmaceutical Partners Inc.	For use after failure of chemotherapy in metastatic breast cancer (1/05)
DVC LLC (unit of Computer Sciences Corp.)	VIGIV	DVC LLC	Treating adverse reactions to smallpox vaccination (2/05)
Nastech Pharmaceutical Co. Inc.	Nascobal	Questcor Pharmaceuticals Inc.	Vitamin B-12 deficiency (2/05)
Amylin Pharmaceuticals Inc.	Symlin	Amylin Pharmaceuticals Inc.	For use with insulin to treat Types I and II diabetics who are not achieving desired glucose control with insulin therapy (3/05)
ISTA Pharmaceuticals Inc.	Xibrom	ISTA Pharmaceuticals Inc.	Ocular inflammation following cataract surgery (3/05)
Amylin Pharmaceuticals Inc.	Byetta (exenatide)	Amylin Pharmaceuticals Inc. and Eli Lilly and Co.	For use as an adjunctive therapy to improve blood sugar control in Type II diabetes (4/05); expanded label to improve blood sugar control in Type II diabetics who have not achieved adequate control on a thiazolidinedione (12/06)
Halozyme Therapeutics Inc.	Cumulase	Cook Ob/Gyn Inc., MediCult A/S and MidAtlantic Diagnostics Inc.	Treatment of oocytes to facilitate certain <i>in vitro</i> fertilization procedures (4/05)
Cangene Corp.	Vaccinia immune globulin (VIG)	Cangene Corp.	For use in counteracting certain adverse reactions to smallpox vaccination (5/05)
Depomed Inc.	Proquin XR	Partner was being finalized	Uncomplicated urinary tract infections (5/05)
BioMarin Pharmaceutical Inc.	Naglazyme	BioMarin Pharmaceutical Inc.	Mucopolysaccharidosis VI (6/05)
Depomed Inc.	Glumetza	Biovail Corp.	Type II diabetes (6/05)
NitroMed Inc.	BiDil	NitroMed Inc.	Heart failure in African-Americans (6/05)
Tercica Inc.	Increlex	Tercica Inc.	Long-term treatment of growth failure in children with severe primary IGF-1 deficiency (8/05)

## Money Raised By Biotech, 2000-2006

(in billions of rounded U.S. dollars)



SOURCE: *BioWorld Financial Watch*

Money Raised By Biotech, 2000-2006 (in billions of U.S. dollars)			
	Public/Other	Private Biotechs	Public Offerings
<b>2000</b>	10.09	3.94	23.64
<b>2001</b>	6.12	3.75	4.49
<b>2002</b>	5.33	3.23	1.39
<b>2003</b>	9.46	3.33	3.63
<b>2004</b>	10.46	4.89	5.46
<b>2005</b>	9.73	4.81	5.58
<b>2006</b>	8.53	5.13	6.63

SOURCE: *BioWorld Financial Watch*