Perspective

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# A Corporate View of Rare Drugs and the Story of Miglustat – A Perspective

**Natasha D'Souza***

Narsee Monjee Institute of Management Studies, Mumbai, India

***Corresponding author:** Natasha D'Souza

natz.anisha213@gmail.com

**Tel:** + 919978627569

Narsee Monjee Institute of Management Studies, Mumbai, India.

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## Abstract

To be rare is a gift. It makes you stand out from the crowd, defining you with qualities that most people don't seem to have. But in the medical world, it may not be a boon after all. To have a rare disease means to have unique health issues, often a lifetime of medication which is moreover difficult to find and at times not being able to live a normal life. The toughest challenge here is your disease being recognized enough to have a decent population base which prompts pharmaceuticals players to invest research in a drug thereby putting the product on pharmacy shelves. In addition to this, rare drugs are often viewed as an opportunity to make the drug a cash cow due to fewer players in the market thus making affordability a prime concern to patients.

**Keywords:** Rare diseases; Miglustat; Gaucher's disease; Regulatory approval

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## Introduction

The European Union considers a disease as rare when it disturbs less than 1 in 2,000 citizens. Rare diseases presently affect 3.5% to 5.9% of the worldwide population, an estimated 30 million people in Europe and 300 million worldwide. Over 6,000 different rare diseases have been branded to date. 72% of rare diseases are genetic though others are the result of infections (bacterial or viral), allergies and environmental causes. 70% of those heritable rare diseases start in childhood. The pool is enormous but what makes companies hesitant to invest is the fact that besides the low prevalence of each disease, medical expertise is rare, knowledge is scarce and research limited. Hundreds of billions are raked in by pharma giants each year to fund research in the quest for a newer drug or for improvement of an existing drug. The choice of the drug however is purely made based on the ROI it stands to offer. The lack of a clear meaning and therefore regulatory approval process for rare diseases has, until now, de-incentivized pharmaceutical companies to pursue rare disease drug development in countries like China. Most people living in such countries pay out of pocket for their treatment or therapy as the typical insurance umbrella does not cover rare diseases. The government often intervenes and comes to the aid of such patients by allowing a special import permit through which orphan drugs can be imported under "unlicensed supply" or by asking a certain drug maker to manufacture the drug intended for the disorder. Worldwide sales for orphan drugs is projected to be $176 billion by the year 2020, which will comprise almost 20% of total drug sales.

The first country to implement a policy for the development of drugs to treat rare diseases with the Orphan Drug Act of 1983 is the United States and has since approved the most drugs via this pathway. The US FDA defines an orphan drug as one treating a disease affecting less than 200,000 strength in the United States, or one that will not be profitable within 7 years following FDA approval. Thus, drugs for economically limiting tropical diseases are also managed. Orphan drugs receive 7 years of market exclusivity beginning after drug approval, which is independent of patient status. Even after this 7-year monopoly expires, new competitors cannot enter the market without proving that their drug is superior to the existing one. Up to one half of research and development costs can be recouped through tax credits, with up to $30 million per year in R&D grants provided for phase I through III clinical trials. These incentives also include a 15-year carry forward provision and 3-year carry back that can be applied once the drug is profitable. In addition, Federal Food, Drug, and Cosmetic Act (FFDCA) Section 526 allows Prescription Medicine User Fee Act (PDUFA) user fees to be waives, which results in an average savings of $2 million for companies with less than $50 M in revenue. This provides an incentive for start-up companies to develop novel treatments for rare diseases. Section 505A under the FDA Modernization Act of 1997 also grants an additional 6 months of patent exclusivity for drugs that serve the paediatric population, which comprise 50% of the rare disease population.

Being in the pharmaceutical industry myself, I have been closely

 

associated with rare drugs and watched the magic of having the drug in our list and the queue of interested clients lining up. It would be a lie to say that drug makers choose to invest in orphan drugs solely for the benefit of society. The incentives in store are lucrative and the crown of monopoly in the market on successful development is the highlight. History is proof that this has often proved to be detrimental to the healthcare system with patients being tossed like puppets in a play. Valent Pharmaceuticals hiked the price of their rare drug Trientine Hydrochloride, used for the treatment of patients with Wilson's disease up to 1,700% over 6 years. Wilson's disease is a rare inherited disorder that effects copper to accumulate in your liver, brain and other vital organs. Most people with Wilson's disease are treated between the ages of 5 and 35, but it can affect younger and older people, as well. The distinct characteristic of this disease is the Kayser-Fleischer ring in the eyes of the patient seen as a golden brown discoloration. The primary action of the treatment is to chelate the excessive copper accumulated. Wilson's disease is inherited as an autosomal recessive trait which makes it difficult to end with just one patient in a family. Although estimates vary, it is believed that Wilson's disease occurs in approximately one in 30,000 to 40,000 people worldwide. Approximately one in 90 people may be features of the disease gene. While cheaper alternatives like Penicillamine are available, Trientine triumphs owing to way lesser side effects and more efficacy. The entry of many generic players for this drug has managed to slide down the prices due to competition while more companies gear up to launch the drug which will ultimately be a ray of hope for patients. In such diseases where drugs are used as lifelong therapy and not just a treatment plan, the average patient is left with the burden of the disease as insurance plans only cover a portion of the drug cost. In most patients with rare diseases, drugs are essential for mere survival.

Another rare disease that has an interesting evolution of therapy is Gaucher's disease. First described by Dr. Philippe Gaucher in 1882, Gaucher (go-SHAY) disease is a lysosomal storage disorder that is caused by the deficiency of glucocerebrosidase, and is characterized by the accumulation of glycosylceramide that leads to dysfunction in multiple organ systems. Three types of Gaucher disease have been described, but, actually, these represent different degrees of severity along a spectrum. The clinical features of type I Gaucher disease, the non-neuronopathic form, are splenomegaly, which is more prominent than the hepatomegaly, anemia, thrombocytopenia, and bone lesions. Occurring in up to 1 in 40,000 live births in the general population, Gaucher's disease is more common among Jews of Ashkenazi (Eastern European) descent, occurring in approximately 1 in 450 within this population.

## Pre-Miglustat Era

In 1991, the advent of targeted enzyme replacement therapy (ERT) using algucerase (Ceredase®; Genzyme Corporation) followed by the introduction of imiglucerase (Cerezyme®; Genzyme Corporation) resulted in huge improvements in the treatment of patients with Gaucher's disease. Imiglucerase is a changed form of glucocerebrosidase, created using recombinant DNA technology, and is given as intravenous infusions, usually every other week. Imiglucerase acts like the naturally occurring enzyme glucocerebrosidase to break down the glucosylceramide that has accumulated in Gaucher cells.

## Introduction of Miglustat

N-butyldeoxynojirimycin (NB-DNJ) i.e. Miglustat one of the N-alkylated iminosugars extracted from plants and microorganisms, is a substrate reduction agent developed by Oxford GlycoSciences and marketed by Actelion Pharmaceuticals with the brand name Zavesca®, approved by EPAR (2002) and FDA (2003) as a treatment option for type I Gaucher disease.

## MOA

Miglustat (administered as 100 mg capsules) inhibits glycosylceramide synthase, which catalyzes the transfer of glucose from UDP-glucose to ceramide to form glucosylceramide (GlcCer). The aim is to decrease the biosynthesis of GlcCer so that patients with significant residual enzyme activity can break down GlcCer more efficiently and thus allow clearance of GlcCer from lysosomes. Imino sugars such as NB-DNJ can also target the protein folding and trafficking pathways of glycosidase to assist correction of lysosomal enzyme activity (chaperone mediated therapy). A partial increase in enzyme activity may be sufficient to initiate the metabolic breakdown of glycosphyngolipids (GSL) and decrease the GSL storage in lysosomes. The efficacy of Miglustat in Gaucher's disease type I probably results from both a decrease in the biosynthesis of GlcCer and an increase in the activity of glucocerebrosidase.

## Miglustat *vs.* ERT

In majority of patients (>90%), ERT has been effective in reducing many of the signs and symptoms of type I Gaucher disease but has no or limited effect on the neurologic findings of type II and III Gaucher disease because of its inability to cross the blood – brain barrier. Life-long intravenous infusion every 2 weeks can be a burden for some patients, particularly in those with poor venous access. The high cost of ERT also precludes its use in some countries and burdens health care cost. Unlike ERT, Miglustat is a small molecule and can pass the blood – brain barrier and has the potential to be effective in treating lysosomal storage disorders with neurologic manifestations. In addition, the oral Additional dosage form offers a painless non- invasive treatment option.

## Additional Indications: Niemann Pick Type C Disease, Tay-Sachs and Fabry disease

On 19 February 2008, Actelion Registration Ltd. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its usage for a new indication for Zavesca, in the treatment of neurological manifestations in patients with Niemann Pick type C disorder (a rare inherited disease where fatty substances such as 'glycosphingolipids' build up within cells in the brain, as well as elsewhere in the body). It was concerned that a

usage of Zavesca in the treatment of the neurological symptoms of Niemann Pick type C disease had not been sufficiently demonstrated. The medicine showed a very limited usage in the main study: there was only a marginal difference in the change in the speed of eye movements between the patients taking Zavesca and those receiving standard protection, and there were uncertainties over whether looking at eye movements was the best way to measure the medicine's effectiveness. Zavesca was also linked to side effects affecting the intestinal and gut, as well as cases of weight loss and thrombocytopenia (low blood platelet counts).

## Discussion and Conclusion

Miglustat therapy has been unsuccessful in halting the progress of infantile-onset Tay-Sachs disease (a genetic disorder that results in the destruction of nerve cells in the brain and spinal cord). Oral administration of Miglustat leads to a significant increase of endogenous enzymatic function and thus can replace previous intravenous enzyme replacement therapy, leading to improved quality of life in patients with amenable Fabry disease (rare genetic disease due to a deficiency of the enzyme alpha-galactosidase A (a-Gal A) that causes a buildup of a type of fat called globotriaosylceramide (Gb3, or GL-3) in the body) mutations.

With the advance of technology and science, there are an increasing number of rare diseases being added to the list. Sadly, while more than 7,000 rare diseases have been identified, only 5 percent have treatments. We as a society are challenged to accelerate progress so that no disease and no patient is, ultimately, left behind in getting access to safe and effective therapeutics. This significantly unmet need makes it imperative that we find ways to accelerate the therapy development process so that we can help the many patients and families who are in search of better treatments.