

Actelion's Marketed Products

Business Strategy & Operations

In an effort to optimize market and customer reach, Actelion has expanded and enhanced its commercial infrastructure and capabilities. At the end of 2009, the company had expanded to 958 sales, marketing and medical professionals based in 28 Actelion country organizations and reaching an additional 36 markets through partner arrangements. This global reach, means that Actelion is fully equipped to optimize returns from current opportunities, as well as launch and commercialize future assets.

Our commercial operations are aligned to:

- Focus on all of Actelion's opportunities and create accountability close to the customer.
- Allow scalability, from both organizational and managerial perspectives to be able to manage growth flexibly.
- Ensure an efficient and effective interaction across functions and with partners.

Business Strategy & Operations has highly experienced people with a proven track record in both specialty and GP markets to compete in an increasingly complex business environment. Together the group is now well placed to not only drive commercial excellence and leverage our unrivalled PAH leadership and orphan drug expertise, but also lead transformational growth initiatives and shape markets and medical utility for the potential which lies ahead.

Actelion Pharmaceuticals Ltd is a global biopharmaceutical company headquartered in Allschwil/Basel, Switzerland. Actelion concentrates on discovering, developing and marketing innovative drugs for high unmet medical needs. The company is quoted on the SIX Swiss Exchange (tickersymbol: ATLN).

Tracleer®



Actelion's lead product is Tracleer® (bosentan), the first and only approved dual endothelin receptor antagonist. Tracleer® was the first oral treatment approved for pulmonary arterial hypertension (PAH), a rare, chronic, life-threatening disorder that severely compromises the functions of the lungs and heart.

Current indications

In the United States, Tracleer® is approved for the treatment of pulmonary arterial hypertension (PAH) Functional Class II - IV to improve exercise capacity and decrease the rate of clinical worsening. Patients with class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in class II patients, which may preclude future use as their disease progresses.

In Europe, Tracleer® is approved for treatment of PAH Functional Class III to improve exercise capacity and symptoms, as well as PAH Functional Class II, where some improvements have also been shown. In the EU, Tracleer® is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Regulatory review and approval for the inclusion of Functional Class II in the Tracleer® label is ongoing on a worldwide basis.

Additionally, a quadrisect, dispersible 32mg tablet formulation of Tracleer® has been approved in the EU for the treatment of PAH in children aged from 2 years.

Product availability

Tracleer® is approved for the treatment of PAH in over 55 countries, including the United States in November 2001, the European Union in May 2002, and Japan in April 2005. For current information please visit our corporate website.

About pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a serious disease of the pulmonary arteries connecting the right side of the heart to the lungs. As PAH develops, blood flow through the pulmonary arteries is restricted and the right side of the heart is put under increasing strain to pump blood through to the lungs. This leads to the main symptoms of PAH - breathlessness, chest tightness, limited exercise capacity and fatigue.

Untreated, PAH is a disease with a very poor prognosis.

The early symptoms of PAH - such as breathlessness, chest tightness and fatigue - can be mild and are common to many other conditions. Reaching the diagnosis can be delayed and as a consequence patients with PAH may first present when the disease has already progressed to a more advanced stage.

Treatment is aimed at improving symptoms, exercise tolerance, long-term outcomes and quality of life. Until the mid-1980s, there were no treatment options for patients and PAH was associated with poor prognosis. Today, treatment options have improved the outlook for patients with this condition.

How is PAH diagnosed?

The early symptoms of pulmonary arterial hypertension (PAH) - such as dyspnea, dizziness and fatigue - are often mild and are common to many other conditions. At rest there are often no symptoms and no apparent signs of illness. As a result, diagnosis can be delayed for months or even years, meaning that PAH is frequently not recognized until the disease is relatively advanced. PAH is often diagnosed only once other conditions have been investigated and ruled out.

The non-specific nature of symptoms associated with PAH means that the diagnosis cannot be made on symptoms alone. A series of investigations are required to make an initial diagnosis, to refine that diagnosis in terms of clinical class of pulmonary hypertension and to evaluate the degree of functional and hemodynamic impairment. Consequently, it can be useful to adopt a four stage approach:

1. Clinical suspicion of pulmonary hypertension

- Breathlessness (dyspnea) without overt signs of specific heart or lung disease.
- Screening of patients with associated conditions (connective tissue disease, congenital heart disease, HIV, sickle cell disease).

- Incidental findings on examination for other clinical reasons.

2. Procedures for detection of pulmonary hypertension

- Electrocardiogram (ECG).
- Chest radiograph, may show evidence of cardiomegaly and enlarged pulmonary arteries.
- Doppler echocardiogram.

3. Identify other clinical aspects/criteria of pulmonary hypertension

- Pulmonary function tests (PFTs) and arterial blood gas samples.
- Ventilation and perfusion lung scan.
- High resolution computed tomography (HRCT).
- Pulmonary angiography.

4. Further pulmonary arterial hypertension evaluation and classification (type, functional capacity, hemodynamics)

- Blood tests and immunology, HIV test, abdominal ultrasound scan.
- 6-minute walk test (6-MWT) and peak VO₂.
- Right heart catheterization and vasoreactivity testing.

How can pulmonary arterial hypertension be treated?

Treatment options have progressed considerably in the last decade, especially those which target the underlying mechanisms of the disease. Recent data have shown that patients in WHO Functional Class II can rapidly deteriorate within six months to more advanced pulmonary arterial hypertension (PAH) as evidenced by progression of the disease.

The main medical treatment options are:

Treatments that are routinely used but with little specific clinically supportive evidence of a positive impact on disease progression.

- Anticoagulants, such as warfarin, to address the observed thrombotic changes and potential predisposition in the pulmonary microcirculation for in-situ thrombosis.
- Calcium-channel blockers (CCBs). Less than 10% of idiopathic PAH patients benefit from CCB therapy. This figure is even lower in other forms of PAH. If not used in appropriate candidates (patients with demonstrated vasoreactivity during right heart catheterization), CCBs can decrease cardiac output and systemic vascular resistance without any improvement

- in PAP and PVR and may therefore be detrimental.
- Diuretics, for treatment of right heart failure.
- Oxygen therapy, to maintain oxygen saturation at >90% at all times.

Treatments that have been specifically studied in PAH.

- **Endothelin receptor antagonists** - endothelin is implicated in the pathogenesis of PAH through actions on the pulmonary vasculature. Endothelin is found to be elevated in patients with PAH and levels of endothelin are directly related to disease severity and prognosis. Endothelin receptor antagonists (ERAs) are oral treatments that either block the ET_A receptor alone, or both the ET_A and ET_B receptors.
- **Phosphodiesterase 5 inhibitors** - oral agents which induce relaxation and antiproliferative effects on vascular smooth muscle cells by preventing the reduction in levels of cGMP.
- **Prostacyclin analogs** - may be delivered by continuous intravenous or subcutaneous infusion or via an intermittent nebulizer.

In very severe cases, surgical options may be considered:

- Balloon atrial septostomy
- Heart and lung transplantation

However, the use of transplantation is constrained by the limited number of donor organs.

About digital ulcers in systemic sclerosis

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease characterized by excessive collagen deposition in the skin and internal organs, such as the gastrointestinal tract, kidney, heart, and lungs. Symptoms result from vascular dysfunction, inflammation, and progressive fibrosis, which lead to occlusion of the microvasculature.

As a result of the vascular injury, complications such as pulmonary arterial hypertension and digital ulcers can occur.

Around 40%-50% of systemic sclerosis patients suffer from digital ulcers (DUs) at least once in their disease history. DUs are very painful and result in difficult-to-heal open sores that occur on fingers and toes. They leave depressed scars and adversely impact the patient's ability to perform work and daily activities, particularly those associated with fingertip functions. In severe cases, infection can become a complication, leading to osteomyelitis and gangrene, for which surgery and even amputation may be required.

Endothelin (ET) plays a key role in the underlying vasculopathy of DUs. The pathway leading to the vasculopathy of DUs is similar to that of PAH, involving excessive vasoconstriction and subsequent vascular remodeling. DUs are visible evidence of vasculopathy in SSc.

How are digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease diagnosed?

SSc patients with DUs present with necrotic lesions located at the distal digits or bony prominences of the fingers. Insufficient oxygen supply to the fingertips caused by progressive occlusion of the blood vessels results in necrosis and substantial tissue loss. The ulcerations can be extremely painful, unsightly and incapacitating for the patient and in most cases are very slow to heal.

How can digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease be treated?

Therapeutic options for DUs are few, with surgical amputation considered as the only definitive treatment for established DUs. Treatment for the prevention of new ulcers therefore addresses a true unmet medical need.

Treatment of DUs includes frequent local wound care, dressing changes and pain management. DUs are prone to infection and often require prolonged courses of intravenous antibiotics. A delay in treating the infection may lead to bone shortening and deformity.

Until recently, the evidence base for pharmacological treatment of DUs has been limited in both methodology and patient numbers. However, the similarities in the underlying vasculopathy of PAH and DUs provide the rationale for the use of a dual ET antagonist for prevention of DUs in patients with systemic sclerosis.

Results from two large randomized controlled trials support the use of a dual ET antagonist in DUs, showing an effect in reducing the number of new DUs in either patients with existing ulcerations or in patients with a history of DU disease.

Other pharmacological therapies which are routinely used for DUs, but with very limited evidence to support their efficacy are:

- Prostanoid therapy, in particular intravenous iloprost.
- Calcium channel blockers used to help relax the muscles in blood vessel walls

Available clinical data

A comprehensive clinical trial program has been conducted to evaluate the efficacy and safety of Tracleer® across a broad range of PAH patient populations.

The results of clinical studies including two pivotal randomized controlled studies, **Study 351** and **BREATHE-1**, demonstrate the efficacy of Tracleer® in the treatment of patients with idiopathic PAH (where no specific cause can be identified), or PAH secondary to connective tissue diseases such as scleroderma.

The combination of Tracleer® with the initiation of intravenous therapy with epoprostenol in adult patients suffering from PAH is well tolerated, as shown in the randomized controlled **BREATHE-2** study.

The **BREATHE-3** open-label study provided safety and efficacy data in children with PAH treated with Tracleer® with or without concomitant prostanoid therapy. It also provided important information on the dose required in the pediatric formulation.

Results of the open-label **BREATHE-4** study in patients whose PAH is related to their infection with the human immunodeficiency virus (HIV) showed improvement in exercise capacity, WHO functional class, and quality of life, as well as cardiopulmonary hemodynamics, compared to baseline after 16 weeks of treatment with Tracleer®.

The first ever randomized placebo-controlled study in patients with Eisenmenger's syndrome (PAH associated with a congenital heart defect) **BREATHE-5** showed that Tracleer® decreases pulmonary vascular resistance and improves exercise capacity in these patients.

FUTURE-1 (Pediatric Formulation of bosentan in pulmonary arterial hypertension) an open-label study, evaluated the safety and pharmacokinetics of a new dispersible tablet formulation of Tracleer®. This study provided important pharmacokinetic and dosing information using the new pediatric formulation of Tracleer®. In **FUTURE-1**, the observed exposure to Tracleer® was similar to that in children who participated in **BREATHE-3**.

FUTURE-2, an open-label safety extension study, is ongoing to assess long-term safety and outcome data.

The **EARLY** (Endothelin Antagonist Trial in mild to symptomatic PAH patients) study was a randomized, double-blind, placebo-controlled trial and the only randomized controlled trial to study a dedicated early-stage, or WHO Functional Class II, PAH population. Patients were followed for at least 6 months and results showed a signifi-

cant reduction in pulmonary vascular resistance and a delay in time to clinical worsening. A trend towards improvement in exercise capacity was observed.

The multi-center, randomized placebo-controlled study **BENEFIT** evaluated Bosentan in iNoperable Forms of chronic Thromboembolic pulmonary hypertension (CTEPH). The **BENEFIT** study met its primary objective with a significant reduction in pulmonary vascular resistance PVR ($p < 0.0001$). In addition, patients on bosentan showed a significant improvement in breathlessness (Borg dyspnea score) with exercise, and there was a trend in favor of bosentan towards prevention of worsening WHO functional class.

The **RAPIDS** (Randomized Placebo-controlled Investigation of Digital ulcers in Scleroderma) program, consisting of two Phase III clinical trials (**RAPIDS-1** and **RAPIDS-2**), tested the benefits of Tracleer® in ischemic digital ulcers secondary to systemic sclerosis. In both studies, Tracleer® reduced the number of new digital ulcers.

Tracleer® (bosentan) study overview:

Study name	Target patient population	Main result
PAH		
Study 351	Patients with idiopathic PAH and PAH related to connective tissue disease	Tracleer® improved exercise capacity, symptoms, cardiopulmonary hemodynamics, and was associated with the reduction in the rate of clinical worsening
BREATHE-1	Patients with idiopathic PAH and PAH related to connective tissue disease	Tracleer® improved exercise capacity, symptoms, and was associated with the reduction in the rate of clinical worsening
BREATHE-2 (not in USPI)	Patients with idiopathic PAH and PAH related to connective tissue disease and initiated on IV epoprostenol therapy	Combination of bosentan and IV epoprostenol
BREATHE-4	Patients with PAH related to HIV	Tracleer® improved exercise capacity
BREATHE-5	Patients with severe PAH related to congenital heart disease (Eisenmenger's syndrome)	Tracleer® improved cardiopulmonary hemodynamics and improved exercise capacity

Tracleer® (bosentan) study overview continued:

Study name	Target patient population	Main result
PAH		
EARLY	PAH patients in WHO Functional Class II (mildly symptomatic disease)	Tracleer® improved cardiac hemodynamics and was associated with a reduction in the rate of clinical worsening. A trend towards an improvement in exercise capacity was observed
Pediatric program		
BREATHE-3	Children with PAH	Defined the pharmacokinetic profile of Tracleer® in children
FUTURE-1	Children with PAH	Observed exposure to pediatric formulation of Tracleer® was similar to that in children who participated in BREATHE-3
FUTURE-2	Children with PAH	Open-label safety extension study ongoing
SSC - DU		
RAPIDS-1	Patients with digital ulcers secondary to systemic sclerosis	Tracleer® was shown to reduce the number of new digital ulcers
RAPIDS-2	Patients with digital ulcers secondary to systemic sclerosis	Tracleer® was shown to reduce the number of new digital ulcers
CTEPH		
BENEFIT (not stated in USPI or SmPC)	Patients with inoperable chronic thromboembolic pulmonary hypertension	Tracleer® improved cardiopulmonary hemodynamics. No improvement observed in exercise capacity

Milestones

2009	Tracleer indication extended in US to include WHO Functional Class II for the treatment of PAH Tracleer® receives EU approval of pediatric formulation for the treatment of PAH
2008	Tracleer® indication extended in EU to include WHO Functional Class II for the treatment of PAH
2007	Tracleer® indication extended in EU to include reduction of new digital ulcers in systemic sclerosis
2006	Tracleer® indication extended in EU to include Eisenmenger physiology Tracleer® launched in Brazil, China and South Korea
2005	Tracleer® launched in Japan
2003	BREATHE-3 combination study presented BREATHE-4 PAH-HIV study presented
2002	Tracleer® launched in EU and Switzerland
2001	Tracleer® launched in US and Canada
2000	Orphan status granted for Tracleer® in PAH in US
1999	Tracleer® PAH clinical development program initiated

Key scientific literature

Study 351: Channick RN, Simonneau G, Sitbon O, et al. Lancet 2001;358:1119-23.

BREATHE-1: Rubin LJ, Badesch DB, Barst RJ, et al. N Engl J Med 2002;346:896-903.

BREATHE-2: Humbert M, Barst RJ, Robbins IM, et al. Eur Respir J 2004;24:353-9.

BREATHE-3: Barst RJ, Ivy D, Dingemans J, et al. Clin Pharmacol Ther 2003;73:372-82.

BREATHE-4: Sitbon O, Gressin V, Speich R, et al. Am J Respir Crit Care Med 2004;170:1212-17.

BREATHE-5: Galiè N, Beghetti M, Gatzoulis MA, et al. Circulation 2006;114:48-54.

EARLY: Galiè N, Rubin LJ, Hoeper MM, et al. Lancet 2008;371:2093-100.

RAPIDS-1: Korn JH, Mayes M, Matucci Cerinic M, et al. Arthritis Rheum 2004;50:3985-93.

RAPIDS-2: Seibold JR, Denton CP, Furst DE et al. [abstract]. ACR; San Diego, USA; 2005.

BENEFIT: Jaïs X., D'Armimi A., et al. J Am Coll Cardiol 2008; 52 (25), 2127.



Ventavis®

Ventavis®
(iloprost) INHALATION SOLUTION

Ventavis® (iloprost) is an inhaled synthetic analog of prostacyclin (PGI₂) that produces potent pulmonary vasodilation and inhibits platelet aggregation, among other benefits. Prostacyclin functions as a hormone, binding to receptors on smooth muscle cells, thereby affecting their function. Prostacyclin has multiple physiological effects, including vasodilation, inhibition of platelet aggregation, antiproliferation, anti-inflammation, and enhanced cardiac contractility. Ventavis® is an inhaled synthetic prostacyclin which has been shown to:

- Significantly increase (p = 0.0033) patient improvement after 12 weeks of treatment compared to baseline on a composite endpoint of improved exercise capacity 30 minutes after dosing, improvement of at least one NYHA class and no clinical deterioration.
- Significantly improve 6-minute walk distance at week 12 with a 10% or greater increase in individual walk distance (p < 0.01).
- Significantly improve patients' functional class at week 12 (p = 0.03).

For patients with PAH (WHO Group 1) with NYHA Class III or IV symptoms.

Current indications

Ventavis® is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with NYHA Class III or IV symptoms.

Product availability

In January 2007, Actelion announced the successful completion of its cash tender offer for shares of CoTherix, Inc., thereby strengthening its PAH franchise by adding Ventavis® to its product offerings in the United States. Bayer Schering Pharma currently markets Ventavis® as the first inhaled prostacyclin in countries outside the US.

About pulmonary arterial hypertension

For information on pulmonary arterial hypertension, diagnosis of PAH and treatment of PAH please see the Tracleer® section of this Fact Sheet.

Available clinical data

In controlled clinical trials, Ventavis® improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and the absence of clinical deterioration.

In December 2006, data from the Phase II/III clinical trial STEP, evaluating the safety and added benefit of using Ventavis® (iloprost) inhalation solution therapy in patients with PAH already undergoing treatment with bosentan, were published. The analysis of this study showed that the combination of Ventavis® added to bosentan therapy was well tolerated, and was consistent with the safety profile observed in patients receiving only iloprost.

Currently, Actelion continues to support Ventavis® with initiatives to further improve its convenience, such as reducing inhalation time.

Milestones

- 2009 Ventavis® receives US approval for increased 20 mcg/ml strength formulation
- 2007 Actelion acquired CoTherix Inc, adding Ventavis® to its product offerings
- 2004 FDA approved inhaled iloprost for treatment of PAH in the US

Key scientific literature

Ivy et al. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. *J Am Coll Cardiol.* 51(2):161-9; 2008.

McLaughlin et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 174(11):1257-63; 2006.

Hoeper et al. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J.* 26(5):858-63; 2005.

Hossein A. et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Card.* 42 (1): 158-64; 2003.

Olschewski et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med.* 1;347(5):322-9; 2002.



Zavesca®



Zavesca® (miglustat) is a low-molecular-weight inhibitor which competitively and reversibly inhibits glucosylceramide synthase and α -glucosidase. With its unique physico-chemical properties, miglustat exhibits a large volume of distribution and has the capacity to access deep organs such as bone, brain and lung.

Current indications

Zavesca® (miglustat) is the first and only oral medication approved for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease, and it may only be used in those patients for whom enzyme replacement therapy is unsuitable.

Zavesca® is also approved in the European Union for the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease (NP-C). Zavesca® is the first treatment to be approved for patients with Niemann-Pick type C disease, a very rare, invariably progressive and eventually fatal neurodegenerative genetic disorder affecting both children and adults.

Product availability

Zavesca® is approved for the treatment of type 1 Gaucher disease in over 35 countries, including the United States and the European Union since 2003.

Zavesca® is approved for the treatment of Niemann-Pick type C disease in the European Union.

For full availability listing please visit our corporate website.

About type 1 Gaucher disease

Gaucher disease is one of the many glycosphingolipid (GSL) storage disorders. These rare diseases are genetic conditions characterized by an imbalance between the rate of synthesis and the rate of degradation or recycling through trafficking of specific GSL substrates leading to their cytotoxic accumulation.

The first clinical description of Gaucher disease was made in 1882 by the French dermatologist Dr Phillippe Gaucher, who described a female patient with massive spleen enlargement, which he mistakenly took to be due to a malignancy.

Today it is known that the disease he identified, now called Gaucher disease, is an inherited metabolic lysosomal storage disorder in which harmful amounts of fatty substances called glycosphingolipids accumulate in tissues.

This accumulation leads to multiple clinical manifestations, typically affecting liver, spleen, blood, bones and CNS.

Traditionally, Gaucher disease has been classified into three types. Type 1 is the most common non-neuronopathic form, affecting adults with an average age of onset of 20 to 40 years; mutations and combinations of mutations seem to determine the age of onset. Type 2 is an acute infantile neuronopathic form, whereas Type 3 is a juvenile neuronopathic form (Norrbottnian).

How is type 1 Gaucher disease diagnosed?

Type 1 Gaucher disease is a heterogeneous disorder – with some patients being without clinical manifestations (asymptomatic), others being mildly affected, while others can be severely affected.

The reason for this heterogeneity is the fact that Gaucher disease can affect many different systems of the body, and to varying degrees of severity.

In addition, the time to development of clinical symptoms can vary significantly between patients – some with a rapid onset of clinically relevant symptoms and others with much slower progression.

Indeed, some Gaucher patients will never develop clinically visible symptoms, whilst in others (such as infants) the progression of disease can be very rapid.

A diagnosis of Gaucher disease is made by a combination of assessments:

Based on clinical suspicion (an assessment of a patient's clinical symptoms and manifestations) the diagnosis is confirmed by enzymatic measurement of the glucocerebrosidase activity in the patient's cells and genetic analyses.

In the past, Gaucher cell counts in bone marrow biopsies were used to confirm diagnosis, but this procedure is now obsolete.

Bone assessment (X-rays, MRI and Dexa), is extremely important, as bone manifestations are one of the most painful and debilitating manifestations of the disease.

How can type 1 Gaucher disease be treated?

The goal of an effective type 1 Gaucher disease treatment is the reduction of glucosylceramide accumulation in the tissue and macrophages, with subsequent improvement of the main disease symptoms: organomegaly, thrombocytopenia, anemia and bone manifestations.

This can be achieved in two ways: replacing the missing or defective glucocerebrosidase with a genetically engineered enzyme, or reducing the synthesis of the substrate glucosylceramide. The first approach is called enzyme replacement therapy (ERT), the second substrate reduction therapy (SRT).

For many years ERT with intravenous imiglucerase has been the only available therapy. The introduction of SRT with oral miglustat (Zavesca®) has offered a new, oral treatment option for patients living with type 1 Gaucher disease.

About Niemann-Pick type C disease

Niemann-Pick type C disease is a rare genetic lysosomal storage disorder that causes severe, progressive neurological symptoms. It is a very serious, life-threatening condition that can affect infants, children and adults. NP-C is characterized by cellular accumulation of lipids, in particular unesterified cholesterol and glycosphingolipids, in many parts of the body including brain, liver and spleen.

The symptoms of NP-C are highly variable and classically present in mid-to-late childhood. Symptoms become progressively more severe and include: disturbance of voluntary rapid eye movements (supranuclear gaze palsy); difficulty in swallowing (dysphagia); slurred and irregular speech (dysarthria); lack of muscle control (ataxia); cognitive dysfunction with associated dementia and in some cases seizures, and sudden muscle weakness during moments of strong emotion such as laughter (gelastic cataplexy). Lipid accumulation can also lead to an enlarged liver and/or spleen (hepatosplenomegaly).

How is Niemann-Pick type C disease diagnosed?

Diagnosing NP-C is complicated and the highly varied pattern of symptoms combined with the rarity of the disease means it is often misdiagnosed or goes undetected. Consequently, the true incidence of NP-C is likely to be underestimated. Despite this, it is still possible to make a definite diagnosis of NP-C using current techniques. New diagnostic techniques are currently being developed that will make it easier to diagnose NP-C.

How can Niemann-Pick type C disease be treated?

There is no cure for NP-C and until recently, management strategies for the disease were based on non-specific, symptomatic treatments. These therapies may be at least partially successful in treating some symptoms of NP-C, but have no impact on disease progression or long-term outcomes. Symptoms that can be treated with general therapies include, but are not limited to:

- Gelastic cataplexy - can be treated by using tricyclic antidepressants or CNS stimulants
- Dystonia - can be treated by using anti-cholinergic drugs
- Movement restrictions - can be treated by using physical therapy
- Seizures - can be controlled by using anti-epileptic drugs
- Feeding problems resulting from difficulty in swallowing - can be managed with a feeding tube

Zavesca® is approved in the EU for the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease.

Available clinical data

Zavesca® (miglustat) 100 mg is the only oral drug available for the treatment of type 1 Gaucher disease, and was approved on the basis of three international open-label clinical trials. The rationale for the use of miglustat in type 1 Gaucher disease is to help balance the overall level of glucosylceramide by reducing its production to a level compatible with breakdown by residual glucocerebrosidase activity, a unique mode of action known as "substrate reduction therapy". Results from a pooled analysis of the three open-label clinical trials have recently shown that Zavesca® monotherapy may reduce the incidence of bone crisis and improve bone mineral density in type 1 Gaucher disease patients, including those with a history of splenectomy and/or osteoporosis.

In order to gain approval for Zavesca® in Niemann-Pick type C disease, a set of clinical data were obtained from one clinical trial OGT918-007 and two multicenter retrospective cohort studies in patients with NP-C. In both the clinical trial and the case series, miglustat was associated with clinically relevant stabilization or improvement in neurological manifestations of the disease. For more information on these studies please visit our corporate website.

Milestones

- 2009 Zavesca® receives EU approval for Niemann-Pick type C disease
- 2008 EU approval for a type II variation for Zavesca® and bone disease in type 1 Gaucher disease
Zavesca® approved in Turkey
- 2007 Zavesca® approved and launched in Australia and Brazil
- 2005 Zavesca® approved and launched in Canada
- 2004 Zavesca® launched in the US;
approved and launched in Switzerland
- 2003 Zavesca® approved and launched in the EU;
approved in the US
- 2002 Zavesca® in-licensed; marketing authorization granted by European Commission

Key scientific literature

In type 1 Gaucher disease

Pastores G.M. et al. Effect of miglustat on bone disease in adult patients with type 1 Gaucher disease: a pooled analysis of three multinational open-label studies. *Clinical Therapeutics*. 29: 1645-53; 2007.

Elstein D. et al. Oral maintenance clinical trial with miglustat for type 1 Gaucher disease: switch from or combination with intravenous enzyme replacement. *Blood*. 110: 2296-2301; 2007.

Giraldo P. et al. Short-term effect of miglustat in every day clinical use in treatment-naïve or previously treated patients with type 1 Gaucher's disease. *Haematologica*. 91:125-8; 2006.

Elstein D. et al. Sustained therapeutic effects of oral miglustat (Zavesca®, N-butyldeoxynojirimycin, OGT 918) in type 1 Gaucher disease. *J Inherit Metab Dis* 27: 757-66; 2004.

In Niemann-Pick type C disease

Patterson M.C., Vecchio D., Prady H., Abel L., Wraith J.E. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol* 6,765-772; 2007.

Patterson M.C., Vecchio D., Prady H., Abel L., Wraith J.E. Miglustat for treatment of Niemann-Pick C disease: results of 24 month's treatment. *Proceedings of 57th Annual meeting of the American Society of Human Genetics*, 2007; abstract # 2253.

Pineda M, Wraith JE, Sedel F, et al. Miglustat in patients with Niemann-Pick type C disease (NPC): a multicentre retrospective survey. *Journal of Inherited Metabolic Disease* 31(Suppl 1) 98; 2008.

Disclaimer:

This fact sheet has the sole purpose to provide members of the public with general information about the activities of Actelion Ltd and its associated companies. The forward-looking statements in this fact sheet are based on current expectations and belief of company management, which are subject to numerous risks and uncertainties.

Latest update: February 2010