



## Media Release

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### **Zavesca® (miglustat) receives EU approval for the treatment of progressive neurological manifestations in patients with Niemann-Pick type C disease**

**ALLSCHWIL/BASEL, SWITZERLAND – 29 January 2009** – Actelion Ltd (SIX: ATLN) announced today that Zavesca® (miglustat) has been approved in the European Union for the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease (NPC). 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.

Zavesca® (100 mg miglustat) is already indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca® may only be used in the treatment of type 1 Gaucher patients for whom enzyme replacement therapy is unsuitable.

Jean-Paul Clozel, M.D. and Chief Executive Officer of Actelion commented: "I am very proud that Actelion – together with the scientific community – has been able to demonstrate the role of Zavesca® in reducing the progression of clinically relevant neurological symptoms in patients with NPC. I would like to thank both the patients and their families who, over the years, have been involved in our clinical program with so much dedication, as well as all the clinical experts for their continuous support. Actelion will continue to support the rare disease community in its efforts to advance science and medicine for the patient".

Ed Wraith, M.D., Royal Manchester Children's Hospital, commented: "For the first time we have an approved therapy for NPC. The data on the effects of treatment with Zavesca® obtained in a clinical trial and in a retrospective cohort study consistently showed a favorable clinical response. As a treating physician I am acutely aware of the importance of reducing progression of neurological symptoms."

Regulatory proceedings to extend the use of miglustat in patients with NPC are ongoing in other territories worldwide.

**About Niemann-Pick type C disease**

NPC is a very rare, fatal, neurodegenerative, genetic condition, primarily affecting children and teenagers but which can strike at any age. The symptoms are caused by the storage of some glycosphingolipids within certain cells in the body, including the brain. It is invariably progressive and most patients die within five to ten years of diagnosis; for the majority the disease is fatal during childhood. Neurological deterioration is the key feature of the disease, and can manifest itself as clumsy body movements, balance problems, slow and slurred speech, difficulty in swallowing, problems with eye movements and seizures. Intellectual decline is also common. In the final stages of the disease the child or young adult is frequently bedridden, has little muscle control and is intellectually impaired. Diagnosis of the disease can be difficult and lengthy due to its rarity and heterogeneity. There is currently no treatment option approved for this condition.

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**Notes to the editor****About Zavesca® and Niemann-Pick type C disease**

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

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 NPC.

The usual dose of Zavesca® in adult NPC patients was 200 mg miglustat three times a day, and was adjusted according to body surface area in pediatric NPC patients.

In the clinical trial OGT918-007, adult and juvenile patients with NPC (n=29, age ≥12 years) were randomized to either miglustat 200 mg t.i.d. (n=20) or standard of care (n=9) for 12 months [1]. In addition, 12 children aged 4-12 years received miglustat at a dose adjusted for body surface area. All patients were then given miglustat for another 12 months. Horizontal saccadic eye movement (HSEM) velocity was the primary endpoint. Other endpoints included swallowing, ambulation, neurological examination, neuropsychological assessment, tremor and quality of life. At 12 months, HSEM velocity had improved in patients treated with miglustat versus those receiving standard care; results were significant when patients taking benzodiazepines were excluded (p=0.028) [1]. Children showed an improvement in HSEM velocity of similar size at 12 months. Improvement in swallowing capacity, stable auditory acuity, and a slower deterioration in ambulatory index were also seen in treated patients older than 12 years [1].

In an uncontrolled extension phase of the OGT918-007 trial, data indicated that treatment with miglustat can provide disease stabilization for important markers of neurological dysfunction in NPC disease, both in the

juvenile/adult and pediatric cohorts, further strengthening the interpretation of a treatment effect of miglustat observed at 12 months in the controlled phase of the trial [2,3].

The safety and tolerability of miglustat 200 mg three times a day in clinical trial participants was consistent with previous trials in type 1 Gaucher disease, where half this dose was used [1, 2, 3].

A first retrospective cohort study was performed in 25 centers in 12 countries to assess data on changes of neurological status and overall utility of treatment with miglustat in 66 NPC patients receiving miglustat outside of the clinical trial OGT918-007 for a mean duration of 1.5 years. A disease-specific disability scale was used to evaluate the severity of dysphagia (swallowing), dystonia (manipulation), ataxia (ambulation) and dysarthria (language articulation) at diagnosis, treatment initiation and last visit [4]. A majority of patients remained at least stable after treatment with regard to the four parameters, indicating that miglustat provides clinically relevant benefits on neurological disease progression in patients with NPC [4].

A second retrospective cohort study was performed in 7 centers in 6 countries to assess data on changes in neurological status in 57 patients not treated with miglustat during the natural course of the disease for a mean duration of 5.5 years. The same disease-specific disability scale was used to evaluate the severity of dysphagia, dystonia, ataxia and dysarthria at the time of diagnosis until the last visit. The results will be presented in the first half of 2009.

The benefit of treatment with Zavesca® for neurological manifestations in patients with Niemann-Pick type C disease should be evaluated on a regular basis, e.g. every 6 months; continuation of therapy should be re-appraised after at least 1 year of treatment with Zavesca®.

#### **About Zavesca® and type 1 Gaucher disease**

Zavesca® (100 mg miglustat capsule) is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca® may only be used in the treatment of type 1 Gaucher patients for whom enzyme replacement therapy is unsuitable. It is approved in the European Union, the United States, Canada, Switzerland, Brazil, Australia, Turkey and Israel.

#### **Zavesca® safety information**

Gastrointestinal events, mainly diarrhea, have been observed in more than 80% of patients treated with Zavesca®, either at the onset of treatment or intermittently during treatment. The majority of cases are mild and are expected to resolve after the first weeks on therapy. In clinical practice, diarrhea has been observed to respond to diet modification (reduction of lactose and other carbohydrate intake), to taking Zavesca® away from meals, and/or to antidiarrheal medicinal products such as loperamide. In some patients, temporary dose reduction may be necessary. Patients with chronic diarrhea or other persistent gastrointestinal events that do not respond to these interventions should be investigated according to clinical practice. Zavesca® has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease.

Cases of peripheral neuropathy have been reported in patients treated with Zavesca®. Peripheral neuropathy seems to be more common in patients with type 1 Gaucher disease compared to the general population. All patients should undergo baseline and repeat neurological evaluation. Patients who develop symptoms such as numbness and tingling should have a careful re-assessment of risk benefit.

Zavesca® may cause fetal harm if administered to a pregnant woman and is contraindicated in women who are or who may become pregnant; patients should be informed of the potential hazard to the fetus. There is a risk of impaired fertility in men. Men should maintain reliable contraceptive methods and not plan to conceive while taking Zavesca® and for three months thereafter.

Reduced growth has been reported in some pediatric patients with Niemann-Pick type C disease in the early phase of treatment with Zavesca® where the initial reduced weight gain may be accompanied or followed by reduced height gain. Growth should be monitored in pediatric and adolescent patients during treatment with Zavesca®; the benefit/risk balance should be re-assessed on an individual basis for continuation of therapy.

Mild reductions in platelet counts without association to bleeding were observed in some patients with Niemann-Pick type C disease treated with Zavesca®. In patients included in the clinical trial, 40%-50% of patients had platelet counts below the lower limit of normal at baseline. Monitoring of platelet counts is recommended in these patients.

#### References

1. Patterson MC, Vecchio D, Prady H, Abel L and Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol* 2007; 6:765-772.
2. Patterson MC, Vecchio D, Prady H, Abel L and Wraith JE. 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.*
3. Patterson MC, Vecchio D, Jacklin E and Wraith JE. Miglustat in Niemann-Pick disease Type C (NPC): long-term data from a clinical trial. *Proceedings of 58th Annual meeting of the American Society of Human Genetics, 2008; abstract # 766.*
4. 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* 2008; 31(Suppl 1) 98. Note: this abstract describes the results of the survey with the first 44 cases collected.

#### Actelion Ltd

Actelion Ltd is a biopharmaceutical company with its corporate headquarters in Allschwil/Basel, Switzerland. Actelion's first drug Tracleer®, an orally available dual endothelin receptor antagonist, has been approved as a therapy for pulmonary arterial hypertension. Actelion markets Tracleer® through its own subsidiaries in key markets worldwide, including the United States (based in South San Francisco), the European Union, Japan, Canada, Australia and Switzerland. Actelion, founded in late 1997, is a leading player in innovative science related to the endothelium – the single layer of cells separating every blood vessel from the blood stream. Actelion's over 1900 employees focus on the discovery, development and marketing of innovative drugs for significant unmet medical needs. Actelion shares are traded on the SIX Swiss Exchange (ticker symbol: ATLN) as part of the Swiss blue-chip index SMI (Swiss Market Index SMI®)

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