# ACTELION'S MARKETED PRODUCTS

Actelion has over 1,000 highly experienced sales, marketing and medical professionals with a proven track record in both specialty and GP markets. The company has over 30 operative affiliates and reaches more than 30 additional 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.

## CONTENTS

# OUR PAH FRANCHISE

Pulmonary arterial hypertension (PAH) is a chronic, life-threatening disease characterized by abnormally high blood pressure in the arteries between the heart and lungs of an affected individual.

Actelion's PAH franchise encompasses oral, inhaled and intravenous formulations of compounds, for patients at various stages in the course of this disease (PAH Functional Classes II–IV), enabling Actelion to deliver treatments across the entire continuum of care.


## Opsumit®

Opsumit (macitentan), an orally available endothelin receptor antagonist, resulted from a tailored drug discovery process in Actelion's laboratories.


## Tracleer®

Tracleer (bosentan), an orally available endothelin receptor antagonist, was the first oral treatment approved for PAH.


## Uptravi®

Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, is the only approved oral, selective IP receptor agonist targeting the prostacyclin pathway in PAH.


## Veletri®

Veletri (epoprostenol for injection), an intravenous prostacyclin, is stable at room temperature (77°F/25°C) for up to 24 hours, removing the need for patients to carry ice packs.


## Ventavis®

Ventavis (iloprost), an inhaled formulation of iloprost, is a synthetic compound structurally similar to prostacyclin (PGI2). It is marketed by Actelion in the US and by Bayer Healthcare elsewhere.

# OPSUMIT®

Opsumit (macitentan), an orally available endothelin receptor antagonist, resulted from a tailored drug discovery process in Actelion's laboratories.

## CURRENT INDICATIONS

**In the US, Opsumit is indicated for the treatment of PAH, WHO Group I to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.**

**Effectiveness was established in a long-term study in PAH patients with predominantly WHO FC II-III symptoms treated for an average of 2 years. Patients were treated with Opsumit monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).**

**In Europe, Opsumit is indicated, as monotherapy or in combination, for the long-term treatment of PAH in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.**

**Opsumit is very likely to cause major birth defects. It is contraindicated for use in pregnancy. In the US, Opsumit is distributed under a risk evaluation and mitigation strategy.**

## PRODUCT AVAILABILITY & REGULATORY STATUS

Opsumit is commercially available in over 45 markets, including the US (since November 2013), Germany (since January 2014) and Japan (since June 2015). The registration process for other countries is ongoing.

For the current availability status, visit www.actelion.com.

## AVAILABLE CLINICAL DATA

SERAPHIN, a global, pivotal Phase III study, was designed to evaluate the efficacy and safety of macitentan in patients with symptomatic PAH, through the primary endpoint of time to first morbidity and all-cause mortality event.

A total of 742 patients were randomized to placebo (n=250), macitentan 3 mg (n=250), or macitentan 10 mg (n=242). The primary endpoint occurred in 46.4%, 38.0%, and 31.4% of the patients in these groups, respectively. The hazard ratio for macitentan 3 mg versus placebo was 0.70 (97.5% CI, 0.52 to 0.96; p=0.0108) and the hazard ratio for macitentan 10 mg versus placebo was 0.55 (97.5% CI, 0.39 to 0.76; p<0.0001). Worsening of pulmonary arterial hypertension was the most frequent primary endpoint event. Patients were allowed to receive PAH background therapy throughout the study, either PDE-5 inhibitors or oral/inhaled prostanoids. The effect of macitentan on the endpoint was observed irrespective of background therapy for pulmonary arterial hypertension. The most commonly reported adverse drug reactions with Opsumit were nasopharyngitis (14.0%), headache (13.6%) and anemia (13.2%).

## MILESTONES

- **2014** Opsumit launched in the EU
- **2013** Opsumit launched in the US
- **2013** FDA approval & EMA market authorization of Opsumit in PAH
- **2012** SERAPHIN outcome study meets the primary endpoint
- **2007** Initiation of Phase III SERAPHIN study in PAH patients

## KEY SCIENTIFIC LITERATURE


- Pulido T et al. N Engl J Med. 2013;369:809-18
- Sidharta PN et al. Eur J Clin Pharmacol. 2011;67(10):977-84
- Gatfield J et al. PloS ONE. 2012;7(10):e47662
- Iglarz M et al. J Pharmacol Exp Ther. 2008;327(3):736-45

# TRACLEER®

Tracleer (bosentan), an orally available endothelin receptor antagonist, was the first oral treatment approved for PAH.

## CURRENT INDICATIONS

**In the US, Tracleer is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and to decrease clinical worsening.**

**Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Considerations for use: Patients with WHO 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 WHO 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.**

**A quadrisect, dispersible 32 mg tablet formulation of Tracleer has been approved in the EU for children. In addition, Tracleer is approved for the treatment of PAH in children aged from 1 year old.**

**Tracleer can cause serious liver damage, including in rare cases liver failure, and is very likely to cause major birth defects. It is contraindicated for use with cyclosporine A, glyburide, and in pregnancy and breast feeding. In the US, Tracleer is distributed under a risk evaluation and mitigation strategy.**

## PRODUCT AVAILABILITY & REGULATORY STATUS

Tracleer is commercially available in over 60 markets, including the US (since November 2001), the European Union (since May 2002), and Japan (since April 2005).

For the current availability status, visit www.actelion.com.

## 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.

For a detailed analysis of the study results, refer to the scientific publications - reference information is given in the key scientific literature section.

## MILESTONES

**2015** Additional pediatric data included in the Tracleer European Product Information

**2009** Tracleer receives EU approval of pediatric formulation for the treatment of PAH

**2005** Tracleer launched in Japan

**2002** Tracleer launched in the EU

**2001** Tracleer launched in US

## KEY SCIENTIFIC LITERATURE


- **Study 351:** Channick RN et al. Lancet. 2001;358:1119-23
- **Breathe-1:** Rubin LJ et al. N Engl J Med. 2002;346:896-903
- **Breathe-2:** Humbert M et al. Eur Respir J. 2004;24:353-9
- **Breathe-3:** Barst RJ et al. Clin Pharmacol Ther. 2003;73:372-82
- **Breathe-4:** Sitbon O et al. Am J Respir Crit Care Med. 2004;170:1212-17
- **Breathe-5:** Galiè N et al. Circulation. 2006;114:48-54
- **Early:** Galiè N et al. Lancet. 2008;371:2093-100
- **Rapids-1:** Korn JH et al. Arthritis Rheum. 2004;50:3985-93
- **Future-1:** Beghetti M et al. Br J Clin Pharmacol. 2009;68(6): 948-55

# UPTRAVI®

Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, is the only approved oral selective IP receptor agonist targeting the prostacyclin pathway in PAH.

## CURRENT INDICATIONS

**In the US, Uptravi is indicated for the treatment of PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).**

**In Europe, Uptravi is indicated for the long-term treatment of PAH in adult patients with WHO functional class II-III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.**

As with other therapies targeting the prostacyclin pathway, hyperthyroidism has been observed with Uptravi. If there are any signs of pulmonary edema, the possibility of pulmonary veno-occlusive disease should be considered and, if confirmed, Uptravi should be discontinued. Other adverse events observed with Uptravi usage were similar in nature to those expected with prostacyclin receptor agonists.

## PRODUCT AVAILABILITY & REGULATORY STATUS

Uptravi is commercially available in 9 countries, including the US (since January 2016), and Germany (since June 2016).

Market authorization has been received in Australia, Canada, the European Union, Japan, New Zealand, South Korea, Switzerland and the US.

Submission of the registration dossier to other health authorities is ongoing.

For current information, visit www.actelion.com.

## AVAILABLE CLINICAL DATA

GRIPHON, a global, pivotal Phase III study, was designed to demonstrate a prolongation of time to the first morbidity/mortality event for selexipag compared to placebo and to evaluate the safety of selexipag in PAH patients.

A total of 1'156 patients were randomized to receive placebo or selexipag. Utilizing a dosing scheme that titrated patients up to their individualized doses, dosing in GRIPHON was initiated at 200 micrograms (mcg) twice daily (b.i.d) and increased weekly in steps of 200 mcg up to a maximum of 1600 mcg b.i.d. If patients were unable to tolerate a dose, the dose was reduced to previously tolerated dose. A primary endpoint event occurred in 397 patients – 41.6% of those in the placebo group and 27.0% of those in the selexipag group (hazard ratio in the selexipag group as compared with the placebo group, 0.60; 99% confidence interval, 0.46 to 0.78; P<0.0001). Disease progression and hospitalization accounted for 81.9% of the events. At baseline, 80% of patients were receiving oral medication specific for PAH: either an ERA, a PDE-5 inhibitor, or a combination of the two.

The effect of selexipag with respect to the primary endpoint was similar in the subgroup of patients who were not receiving treatment for the disease at baseline and in the subgroup of patients who were already receiving PAH-specific treatment at baseline (including those who were receiving a combination of both ERA and PDE-5 inhibitor). Adverse reactions occurring more frequently on Uptravi compared to placebo by ≥3%, over the course of the study, were headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia, anemia, decreased appetite and rash. These adverse reactions were more frequent during the dose titration phase. Hyperthyroidism was observed in 1% (n=8) of patients on selexipag and in none of the patients on placebo.

## MILESTONES

**2016** Market authorization for Uptravi in the EU
**2016** Uptravi launched in the US
**2015** Uptravi approved by US FDA
**2014** GRIPHON outcome study meets the primary endpoint
**2008** Actelion in-licensed selexipag from Nippon Shinyaku

## KEY SCIENTIFIC LITERATURE


- Sitbon O et al. N Engl J Med. 2015; 373:2522-33.
- Simonneau G, et al. Eur Respir J. 2012; 40: 874-880.
- Kuwano et al. J Pharmacol Exp Ther. 2008;326:691-699.
- Tetsuo Asaki et al. J. Med. Chem. 2015, 58 (18), pp 7128–7137.
- Morrison et al. J Pharmacol Exp Ther. 2012;343:547-555.

# VELETRI®

Veletri (epoprostenol for injection), an intravenous prostacyclin, is stable at room temperature (77°F/25°C) for up to 24 hours, removing the need for patients to carry ice packs.

## CURRENT INDICATIONS

**In the US, Veletri is indicated for the treatment of PAH (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.**

**In some EU countries, Veletri is indicated for the treatment of PAH (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III–IV symptoms to improve exercise capacity. Veletri is also indicated for use in haemodialysis in emergency situations, when the use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated.**

Veletri must be reconstituted and diluted only as directed using Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Veletri must not be reconstituted or mixed with any other intravenous medications or solutions prior to or during administration. Most common side effects include headache, jaw pain, flushing, diarrhea, nausea and vomiting, hypotension, abdominal pain, arthralgia, flu-like symptoms, decreased platelet count, bleeding, tachycardia, bradycardia, chest pain, rash, pain, and anxiety/nervousness. Sepsis and septicemia, mostly related to delivery system for Veletri were commonly reported. In order to reduce the risk of catheter related blood stream infections, the care of the central venous catheter and the catheter exit site should follow established medical principles. Excessive doses of Veletri may acutely result in systemic low blood pressure, rapid heartbeat, jaw pain, headache, flushing, nausea and vomiting, diarrhea, flu-like symptoms, or anxiety; excessive doses administered continuously can lead to extreme restlessness and high-output cardiac failure.

Abrupt withdrawal or sudden large reductions in dosage of Veletri may result in symptoms associated with rebound pulmonary hypertension, including dyspnea, dizziness, and asthenia and may result in death. Therefore abrupt withdrawal should be avoided.

## PRODUCT AVAILABILITY & REGULATORY STATUS

Veletri is commercially available in 17 markets, including the US (since 2010), Switzerland and Canada - marketed as Caripul® - (since 2012), Japan - marketed as Epoprostenol "ACT" - and some European markets (since 2013).The registration process for other countries is ongoing.

For current availability status, visit www.actelion.com

## MILESTONES

**2013** Veletri launched in some European markets and Japan (marketed as Epoprostenol "ACT")

**2012** Veletri launched in Switzerland and Canada (marketed as Caripul)

**2010** Veletri launched in the US

**2009** Actelion acquired Veletri from GeneraMedix Inc.

**2008** FDA approved epoprostenol for injection for treatment of primary pulmonary hypertension in the US

## KEY SCIENTIFIC LITERATURE


- Lambert O et al. Drug Design Dev Ther. 2012;6:235-244
- Sitbon O, et al. Am J Respir Crit Care Med. 2012;185:A2500
- Tamura Y, et al. Adv Ther. 2013;30:459-71
- Nicolas LB, et al. Clin Ther. 2013;35:440-49

# VENTAVIS®

Ventavis (iloprost), an inhaled formulation of iloprost, is a synthetic compound structurally similar to prostacyclin (PGI2).

## CURRENT INDICATIONS

**In the US, Ventavis is indicated for the treatment of PAH (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration.**

**Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).**

## PRODUCT AVAILABILITY & REGULATORY STATUS

Actelion has marketed Ventavis in the US since 2007. Bayer Healthcare markets Ventavis elsewhere.

## AVAILABLE CLINICAL DATA

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

For patients with PAH (WHO Group 1) with NHYA Class III or IV symptoms, Ventavis 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 NHYA 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).

Most common (>3% placebo adjusted) adverse reactions are vasodilation (flushing), cough increased, headache, trismus, insomnia, nausea, hypotension, vomiting, alkaline phosphatase increased, flu syndrome, back pain, tongue pain, palpitations, syncope, GGT increased, muscle cramps, hemoptysis, and pneumonia.

In December 2006, data from the Phase II/III clinical trial STEP, evaluating the use of 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.

## MILESTONES

**2009** Ventavis receives US approval for increased 20 mcg/ml strength formulation

**2007** Actelion acquires 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 J Am Coll Cardiol. 51(2):161-9; 2008
- McLaughlin et al. Am J Respir Crit Care Med. 174(11): 1257-63; 2006
- Hoeper et al. Eur Respir J. 26(5):858-63; 2005
- Hossein A. et al. J Am Coll Card. 42 (1): 158-64; 2003
- Olschewski et alN Engl J Med. 1;347(5):322-9; 2002

# OUR SPECIALTY PRODUCTS

Actelion is creating specialty franchises alongside PAH – discovering, developing and/or in-licensing/acquiring products in new therapeutic areas.

## Valchlor®

Valchlor (mechlorethamine) 0.016% gel is applied topically once daily to affected areas of the skin. Valchlor is currently only available in the US and is approved for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy.

## Zavesca®)

Zavesca (miglustat) available as oral capsules, is a glucosylceramide synthase inhibitor indicated as monotherapy for the treatment of adult patients with mild to moderate type I Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.

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

# VALCHLOR®

Valchlor (mechlorethamine) gel 0.016% is applied topically once a day to affected areas of the skin. Valchlor is the first and only FDA-approved topical formulation of mechlorethamine.

## CURRENT INDICATIONS

**In the US, Valchlor gel 0.016% is indicated for the topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in patients who have received prior skin-directed therapy.**

## PRODUCT AVAILABILITY & REGULATORY STATUS

Valchlor is commercially available in the US (since 2013) and in Israel through special import authorization procedure (since 2016). In France, patients benefit from the drug under a temporary authorization for use ("ATU") program initiated during the second half of 2014.

In March 2017, the European Commission has granted marketing authorization for the use of the active ingredient of Valchlor under the brand name Ledaga® (chlormethine gel) 160 micrograms/g for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL). Subject to fulfilling the agreed commitments and achieving market access in various countries, a potential first European launch of Ledaga is not expected before H1 2018.

## AVAILABLE CLINICAL DATA

The efficacy of Valchlor was assessed in a randomized, multicenter, observer-blind, non-inferiority trial of 260 patients. Patients were stratified based on Stage (IA vs IB and IIA) and then randomized to receive Valchlor gel 0.016% w/w of mechlorethamine (equivalent to 0.02% mechlorethamine HCl) or Aquaphor®-based mechlorethamine HCl 0.02% ointment (compounded mechlorethamine). Patients had received at least one prior skin-directed therapy. Qualifying prior therapies included topical corticosteroids, phototherapy, Targretin® gel, and topical nitrogen mustard. Patients were not required to be refractory to or intolerant of prior therapies. Treatments were applied topically on a daily basis for 12 months.

60% of the patients on the Valchlor arm and 48% of patients on the comparator arm achieved a response based on the Composite Assessment of Index Lesion Severity (CAILS) score. Valchlor was non-inferior to the comparator based on a CAILS overall response rate ratio of 1.24 (95% CI 0.98, 1.58). Complete responses constituted a minority of the CAILS or Severity Weighted Assessment Tool (SWAT) overall responses. The onset of CAILS overall response for both treatment arms showed a wide range from 1 to 11 months.

The most common adverse reactions (≥5%) were dermatitis (56%), pruritus (20%), bacterial skin infection (11%), skin ulceration or blistering (6%), and skin hyperpigmentation (5%). These reactions may be moderately severe or severe. Elderly patients aged 65 and older may be more susceptible. Depending on severity, treatment reduction, suspension, or discontinuation may be required.

## MILESTONES

**2017** European Commission grants marketing authorization for Ledaga

**2013** Valchlor launched in the US

**2013** Actelion acquires Ceptaris Therapeutics, Inc., adding Valchlor to its specialty product offerings in the US

**2013** Valchlor approved in the US

## KEY SCIENTIFIC LITERATURE


- Lessin SR, et al. JAMA Dermatol. 2013;149(1):25-32

# LEDAGA®

Ledaga (chlormethine) is an alkylating drug indicated for the treatment of mycosis fungoides-type cutaneous T-Cell lymphoma (MF-CTCL) formulated as a topical, once-daily, colorless gel.

## CURRENT INDICATIONS

**Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF type CTCL) in adult patients.**

## PRODUCT AVAILABILITY & REGULATORY STATUS

In March 2017, the European Commission has granted marketing authorization for the use of Ledaga (chlormethine gel) 160 micrograms/g for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL). Subject to fulfilling the agreed commitments and achieving market access in various countries, a potential first European launch of Ledaga is not expected before H1 2018.

Chlormethine gel, under the brand name Valchlor® (mechlorethamine), is commercially available in the US (since 2013) and in Israel through special import authorization procedure (since 2016). In France, patients benefit from the drug under a temporary authorization for use ("ATU") program initiated during the second half of 2014.

## AVAILABLE CLINICAL DATA

The market authorization for Ledaga is based on the results of the pivotal 201 study, the largest randomized controlled study ever conducted in early stage MF-CTCL, involving 260 patients. In this study, within the efficacy evaluable (EE) population, 77% of patients who were treated for at least 6 months with chlormethine gel achieved a clinical response in the Composite Assessment of Index Lesion Severity (CAILS) score, while 59% of those treated with the compounded control had a clinical response. A response was defined as at least a 50% improvement in the baseline CAILS score. Complete response was achieved in 19% of patients treated with chlormethine gel in the EE population versus 15% of patients treated with the compounded control. Reductions in mean CAILS scores were seen as early as four weeks into the study, with further reductions observed with continuing therapy.

In the 201 study, the most frequent adverse reactions reported with chlormethine gel were skin related: dermatitis (54.7%; e.g., skin irritation, erythema, rash, urticaria, skin-burning sensation, pain of the skin), pruritus (20.3%), skin infections (11.7%), skin ulceration and blistering (6.3%), and skin hyperpigmentation (5.5%). No evidence of systemic absorption of chlormethine was observed with the treatment.

## MILESTONES

**2017** European Commission grants marketing authorization for Ledaga

**2013** Valchlor launched in the US

**2013** Actelion acquires Ceptaris Therapeutics, Inc., adding Valchlor to its specialty product offerings in the US

**2013** Valchlor approved in the US

## KEY SCIENTIFIC LITERATURE


- Lessin SR, et al. JAMA Dermatol. 2013;149(1):25-32

# ZAVESCA®

Zavesca (miglustat) is an orally active competitive, reversible inhibitor of glucosylceramide synthase.

## CURRENT INDICATIONS

**In the US, Zavesca is indicated as monotherapy for the treatment of adult patients with mild to moderate type 1 Gaucher disease (GD-1) for whom enzyme replacement therapy is not a therapeutic option (e.g. due to allergy, hypersensitivity, or poor venous access).**

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

## PRODUCT AVAILABILITY & REGULATORY STATUS

Zavesca is commercially available for the treatment of mild to moderate type 1 Gaucher disease in 47 countries, including the US and the European Union since 2003.

Outside of the US, Zavesca is commercially available for the treatment of Niemann-Pick type C disease in 46 countries, including the European Union since 2009 and Japan since 2012.

For full availability listing, visit www.actelion.com

## AVAILABLE CLINICAL DATA

The approval for Zavesca in type 1 Gaucher disease was based on 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 mode of action known as "substrate reduction therapy". Results from a pooled analysis of the three open-label clinical trials have 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.

The most common adverse reactions (incidence ≥5%) diarrhea, weight loss, stomach pain, gas, nausea and vomiting headache including migraine, tremor, leg cramps, dizziness, weakness, vision problems, thrombocytopenia, muscle cramps, back pain, constipation, dry mouth, heaviness in arms and legs, memory loss, unsteady walking, anorexia, indigestion, paresthesia, stomach bloating, stomach pain not related to food, and menstrual changes.

Outside of the US, the approval for Zavesca in Niemann-Pick type C disease was based on a set of clinical data 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.

## MILESTONES

**2012** Miglustat approved and launched for NP-C in Japan (marketed as Brazaves®)
**2009** Zavesca approved and launched for NP-C in the EU
**2004** Zavesca launched for GD-1 in the US
**2003** Zavesca approved and launched for GD-1 in the EU; approved for GD-1 in the US
**2002** Zavesca in-licensed

## KEY SCIENTIFIC LITERATURE


**IN TYPE 1 GAUCHER DISEASE**

- Pastores G.M. et al. Clinical Therapeutics. 2007; 29: 1645-53
- Elstein D. et al. Blood. 2007; 110: 2296-2301
- Giraldo P. et al. Haematologica. 2006; 91:125-8
- Elstein D. et al. J Inherit Metab Dis. 2004; 27: 757-66

**IN NIEMANN-PICK TYPE C DISEASE**

- Wraith JE, et al. Mol Genet Metab. 2010; 99:351-357
- Patterson MC, et al. J Child Neurol. 2010 ;25(3):300-5
- Pineda M, et al. Mol Genet Metab. 2009; 98:243-9
- Patterson MC, et al. Lancet Neurol. 2007; 6:765-772

**Actelion Pharmaceuticals Ltd** is a leading biopharmaceutical company focused on the discovery, development and commercialization of innovative drugs for diseases with significant unmet medical needs. The company is headquartered in Allschwil/Basel, Switzerland and is quoted on the SIX Swiss Exchange (tickersymbol: ATLN). All trademarks are legally protected.

**Latest Update:** February 2017



**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.

**Actelion Pharmaceuticals Ltd** Gewerbestrasse 16 / CH-4123 Allschwil
Switzerland / investor.relations@actelion.com / Phone +41 61 565 62 62
Fax +41 61 565 65 07 / www.actelion.com