ACTELION’S MARKETED PRODUCTS

As part of the Janssen Group of Pharmaceutical Companies of Johnson & Johnson, Actelion is committed to leverage Johnson & Johnson’s global presence and commercial strength to accelerate growth and patient access to our important therapies.

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.

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.

Actelion is well placed to not only drive commercial excellence and leverage our unrivalled PAH leadership, but also lead transformational growth initiatives and shape markets and medical utility for the potential which lies ahead.

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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.

Uptavi®
Uptavi (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.
**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.

**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**

- Iglarz M et al. Am J Respir Crit Care Med. 2011;183:A6445
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.

On 5 September 2017, the FDA approved a new 32 mg tablet for oral suspension for Tracleer for use in pediatric patients aged three years and older. The new 32 mg dosage of Tracleer features a scored tablet which can be dispersed in a teaspoon of water before oral administration. The lower dosage and score lines on the tablets are designed to allow physicians to vary the prescribed dose by the weight of the patient. Actelion expects to make the 32 mg dosage option of Tracleer available by the fourth quarter of 2017. The existing 62.5 and 125 mg dosages for adult use will remain available.

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).

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, please 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
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 sign 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 over 20 countries, including the US (since January 2016), Germany (since June 2016) and Japan. Submission of the registration dossier to other health authorities is ongoing.

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

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

MILESTONES
2017 Actelion obtained Epoprostenol “ACT” label extension for pediatric PAH patients in Japan
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

MARKETED PRODUCTS

OUR PAH FRANCHISE
UPTRAVI®
TRACLEER®
OFSUMIT®
VELETRI®
VENTAVIS®
OUR SPECIALTY PRODUCT
ZAVESCA®
**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**


**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 NYHA 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 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 ($p = 0.03$).

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
- Hoepner et al. Eur Respir J. 26(5):858-63; 2005

**VENTAVIS®**

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

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 pediatric 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).

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%) are 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
• Giraldo P. et al. Haematologica. 2006; 91:125-8

IN NIEMANN-PICK TYPE C DISEASE
Actelion Pharmaceuticals Ltd. In June 2017, Actelion became part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Actelion’s medicines help expand and strengthen Janssen’s portfolio with leading, differentiated in-market medicines and promising late-stage compounds. Janssen has added Pulmonary Hypertension as a therapeutic area of focus to maintain the leadership position Actelion has built in this important disease area.

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.

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