

SIMDAX[®] (levosimendan)

Levosimendan is an Orion-originated innovative NCE (new chemical entity), the active substance in Simdax[®], for acutely decompensated heart failure.

Indication of Simdax

The i.v. (intravenously administered) formulation of levosimendan, trade name Simdax[®], is indicated for the short-term treatment of acutely decompensated severe chronic heart failure in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate.

Mechanism of action

Levosimendan is a calcium sensitizer that works through a dual mechanism of action:

- 1) **Calcium sensitization**, which makes the heart pump stronger
By binding to troponin C, a critical protein that affects heart muscle contraction, levosimendan increases the contractile force of the heart without building up of excessive calcium, which could cause arrhythmia.
- 2) **Potassium channel opening**, which improves vasodilation (widening of the blood vessels)
Levosimendan enhances vasodilation by opening potassium channels in vascular smooth muscle that eases the burden of delivering oxygen-rich blood to the body and to the heart itself.

Adverse reactions in the SPC

The most common adverse reactions in clinical trials have been headache, dizziness, hypotension, ventricular tachycardia, atrial fibrillation, tachycardia, ventricular extrasystoles, cardiac failure, myocardial ischaemia, extrasystoles, nausea, vomiting, constipation, diarrhea, insomnia, decreased haemoglobin and hypokalaemia.

Levosimendan patent

The compound patent of levosimendan is valid until 2013 in the USA and until 2015 in those key European markets where the product is available.

About Heart Failure (HF)

Heart failure is a condition in which the heart's ability to pump blood is insufficient to meet the body's normal requirements for oxygen and nutrients. The most common underlying reasons for heart failure are ischemic heart disease (especially earlier myocardial infarction), high blood pressure, valvular heart disease and dilated cardiomyopathy.

Several factors - including ischemia, arrhythmias and infections - may suddenly worsen patient's condition. In acutely decompensated heart failure, the patient suffers from severe shortness of breath due to accumulation of fluid in the lungs. Poor blood flow to other organs, such as the brains, kidneys, intestines and liver causes further serious consequences.

Some 15 million people worldwide suffer from heart failure. Half of the patients with a diagnosis of heart failure die within five years, and approximately 40 percent of patients who experience an episode of acutely decompensated heart failure die within one year.

About Stage III and Stage IV heart failure patients

- Stage III and IV heart failure patient population is significant: about 3.5 million people.
- Patients with most severe/progressed disease; greatest number of hospitalizations a year about 3 – so they are the easiest to access. Typical patient admitted due to shortness of breath.
 - Stage IV: patients have shortness of breath at rest
 - Stage III: patients have shortness of breath at minimal activity
 - Stages III and IV: patient population of about 3.5 million people. About 1 million people receive primary diagnosis of CHF; 2.5 million people receive secondary diagnosis of CHF (secondary diagnosis meaning that they come into hospital for something else and are diagnosed with CHF)

US market of heart failure

- About 6 million Americans are diagnosed with HF; about 550,000 new cases are diagnosed every year.
- Heart failure is the most frequent cause of hospitalization for patients over the age of 65.
- Costs associated with HF are in excess of USD 25 bn/year; related primarily to inpatient hospitalizations.
- 50% of patients are readmitted within six months after their initial discharge.
- Mortality remains high with over 50% of patients dying within five years of diagnosis.
- Despite the fact that six million people are impacted by heart failure in the United States, there have been few advances in treating the disease within the past years.

Treatment of acutely decompensated heart failure and the role of Simdax

The treatment of acutely decompensated heart failure depends on the severity of the symptoms and patients characteristics. The initial treatment usually consists of oxygen supply and administration of i.v. diuretics. Most patients have adequate blood pressure and should be treated with i.v. vasodilators, such as i.v. nitrates. With lower blood pressure and with more severe symptoms, inotropic agents can be added to the treatment. The most commonly used inotropic agent is currently dobutamine, a beta-receptor agonist. As a drawback, the inotropes may increase the heart's oxygen consumption and increase the amount of intracellular calcium and therefore lead to myocardial ischaemia and arrhythmias.

Simdax has both vasodilator and inotropic properties. The latest European Society of Cardiology Guidelines (2008), accordingly, recommend Simdax to be used both in cases where classical vasodilators and in cases where inotropes are indicated.

Clinical data

Clinical trials before the REVIVE II and SURVIVE studies demonstrated an improvement in hemodynamics and outcomes:

- Statistically significant hemodynamic and symptomatic improvement.
- Statistically significant improvement in survival compared to both dobutamine (LIDO trial) and placebo (RUSSLAN trial)

REVIVE II (U.S.) in 2003-2005

- A placebo-controlled randomized trial; conducted primarily in the U.S.
- 600 patients with acutely decompensated heart failure were included.
- Simdax or placebo was administered on top of the standard of care.
- Enrollment criteria: patient needed to have been treated with a diuretic, but still have shortness of breath at rest in order to be included in the trial
- The primary endpoint of the study was a composite of clinical signs and symptoms over five days as assessed by patients and their physicians. More patients improved and fewer patients worsened when treated with Simdax than with placebo ($p=0.015$). Simdax-treated patients also had a reduced average length of initial hospital stay.
- REVIVE II was not primarily designed to assess mortality. A secondary endpoint was mortality at 90 days for which there was no statistically significant difference between the treatment arms, although there were a greater number of deaths in the Simdax arm.

SURVIVE (primarily in Europe) in 2003-2005

- The first prospective mortality trial in acutely decompensated heart failure.
- Approximately 1,300 patients were randomized to Simdax or dobutamine.
- Primary endpoint was mortality at 180 days.
- Enrollment criteria: patient required to be in clinical need of an inotrope as evidenced by inadequate response to diuretics and/or vasodilators.
- The results showed that levosimendan resulted in numerically, but statistically not significantly lower mortality compared with dobutamine through the six months of follow up. The benefit of Simdax was emphasized in patients with concomitant beta-blocker treatment.

Past regulatory history of Simdax i.v.

- Orion originally filed a US NDA (New Drug Application) in late 1998. The FDA wanted an additional trial, so Orion withdrew the NDA in November 1999.
- An EU NDA was filed in late 1999 via the Mutual Recognition Procedure (MPR) with Sweden as the reference member state
- Simdax i.v. was first approved in Sweden in 2000 and since then is available in about 40 countries (South-European countries, Scandinavia, Russia and several markets in South America). Major EU countries did not recognize the Swedish MA.

Licensing relationships with Abbott

Orion entered in to partnership with Abbott under a marketing agreement for Simdax in February 1998. In April 2004, Abbott gained worldwide rights to further develop and commercialize the iv. product and assumed clinical and financial responsibility for in-process research and development programs. Orion retained the rights to market i.v. Simdax in Finland, Sweden, Norway, Iceland and Denmark, and co-promotion rights in Hungary, Russia and Ukraine. Orion also retained the patent rights to levosimendan, as well as all rights to veterinary applications and non-injectable formulations, including orally administered levosimendan. All the rights for i.v. levosimendan were reacquired by Orion in May 2009, with the exception of Latin America, where Abbott retains the marketing rights.