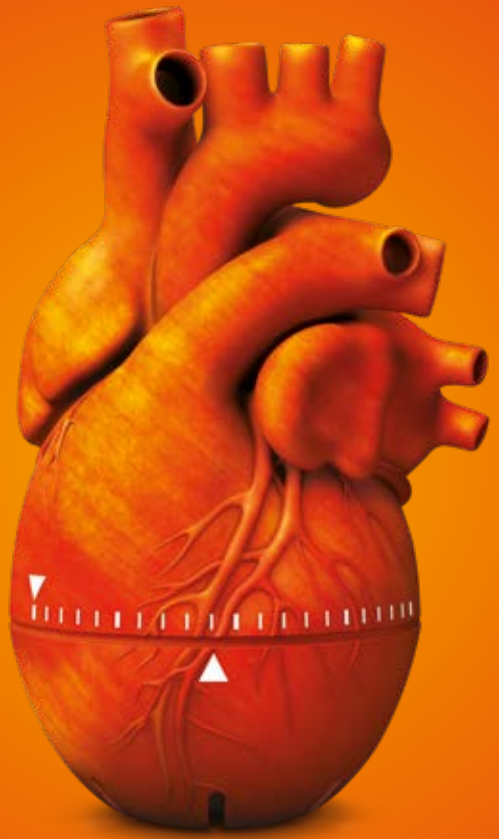
SIMDAX®
levosimendan

EASE THE CHALLENGE OF TREATING THE FAILING HEART

SIMDAX® GIVES YOU TIME WHEN IT'S NEEDED MOST[1]



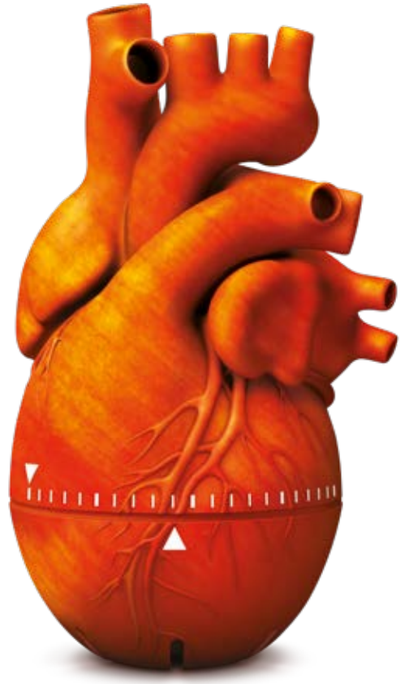
Reference: 1. Nieminen MS et al. Eur Heart J Suppl. 2017;19(suppl_C);C15-C21.

ORION PHARMA
Building well-being

SIMDAX® GIVES YOU TIME WHEN IT'S NEEDED MOST[1]

SIMDAX® is the only inodilator[2,3] to provide sustained hemodynamic benefits[3–8] and symptom control[3–5,9,10] to patients with acute heart failure, and in need of inotropic therapy.

References: 1. Nieminen MS et al. Eur Heart J Suppl. 2017;19(suppl C);C15-C21. **2.** Papp Z et al. Int J Cardiol. 2012; 159:82–87. **3.** Nieminen MS et al. Heart Lung Vessel. 2013;5(4):227–245. **4.** Follath et al. Lancet. 2002;360:196–202. **5.** Slawsky et al. Circulation. 2000;102:2222–2227. **6.** Nieminen et al. J Am Coll Cardiol. 2000;36:1903–1912. **7.** Kivikko et al. Circulation. 2003;107:81–86. **8.** Lilleberg et al. Eur J Heart Fail. 2007;9:75–82. **9.** Mebazaa et al. JAMA. 2007;297:1883–1891. **10.** Packer et al. JACC Heart Fail. 2013;1(2):103–111.



SIMDAX® levosimendan

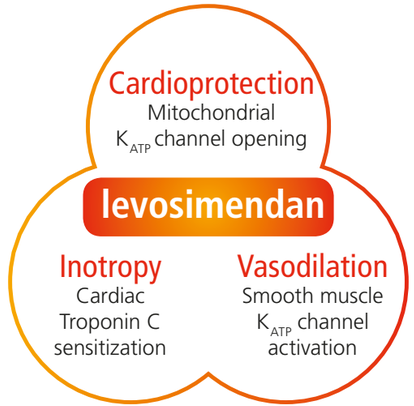
WITH THREE PHARMACOLOGICAL EFFECTS…

The clinical effects of SIMDAX® are mediated through:[1]

- Increased **cardiac contractility** by calcium sensitization of troponin C
- **Vasodilation** through the opening of potassium channels in the vasculature smooth muscle
- **Cardioprotection**, anti-ischemic antistunning effects through the opening of mitochondrial potassium channels in cardiomyocytes

Reference: 1. Papp Z et al. Int J Cardiol. 2012;159:82–87.

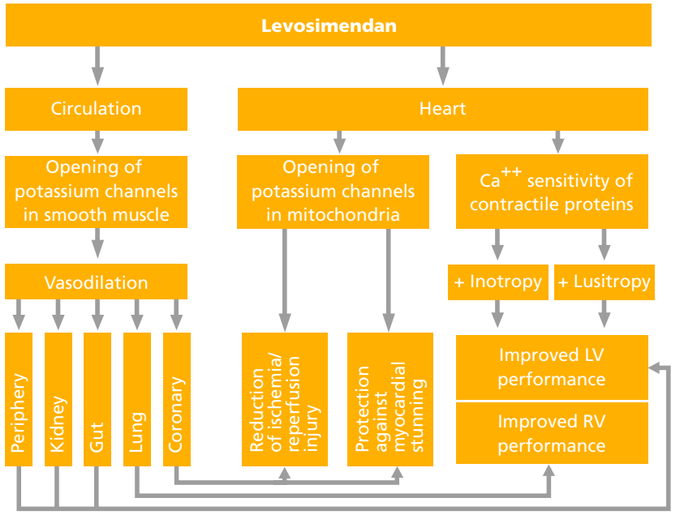
The unique triple mechanism of action of levosimendan[1]



…SIMDAX® PROVIDES MULTIPLE BENEFITS WITHIN AND BEYOND THE HEART

Therapy with SIMDAX®, the first-in-class among the cardio-protective inodilators, brings **multiple beneficial cardiovascular effects.**[1,2]

Multiple action of levosimendan in the cardiovascular system[1]



References:
1. Pinto BB et al. Curr Opin Anaesthesiol. 2008;21:168–177.
2: Farmakis D et al. Int J Cardiol. 2016;222:303-12

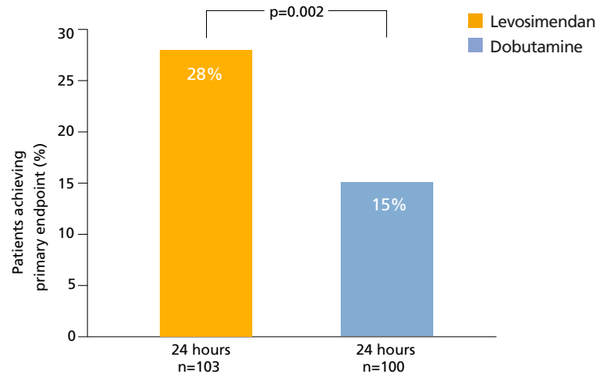
IMPROVING HEMODYNAMICS…

In patients with heart failure, the positive inotropic and vasodilatory actions of SIMDAX® result in an **increased contractile force, and a reduction in both preload and afterload**.[1,2]

SIMDAX® increases cardiac output, stroke volume and ejection fraction, and reduces pulmonary capillary wedge pressure, right atrial pressure, and peripheral vascular resistance.[1,2]

References: 1. Nieminen MS et al. J Am Coll Cardiol. 2000;36:1903–1912.
2. Follath F et al. Lancet. 2002;360:196–202.

Improvement in hemodynamic performance[2]

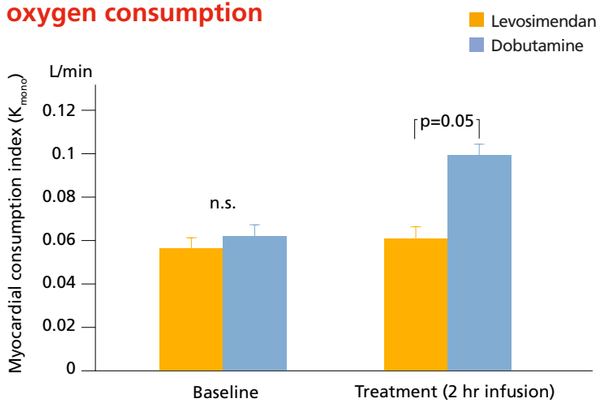


Proportion of patients with hemodynamic improvement after a 24-hour infusion, defined as a 30% or greater increase in cardiac output and a 25% or greater decrease (at least 4 mmHg) in pulmonary capillary wedge pressure.[2]

...WITHOUT AN INCREASE IN OXYGEN CONSUMPTION

The positive inotropic effects of SIMDAX® are achieved without an increase in **oxygen consumption**.[1,2]

No significant increase in oxygen consumption



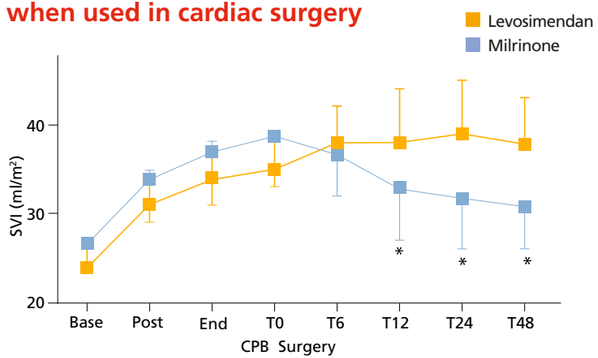
A significant increase in the oxygen consumption is induced by dobutamine while no difference is noticed during treatment with levosimendan.[2]

References:
1. Nieminen MS et al. J Cardiovasc Pharmacol. 2009;53(4):302–310.
2. Ukkonen H et al. Clin Pharmacol Ther. 1997;61:596–607.

THE HEMODYNAMIC BENEFITS OF SIMDAX® ARE SUSTAINED...

After operation, in a comparative study vs milrinone, the positive hemodynamic effects of 19 hours treatment with SIMDAX® lasted much longer than those from 83 hours treatment with milrinone.[1]

Sustained effects of levosimendan when used in cardiac surgery



Stroke volume index (SVI) at the start of surgery (base), 15 min after the end of cardiopulmonary bypass (CPB) (post-CPB), at the end of the operation (end surgery), at arrival in the intensive care unit (T0), and 6 (T6), 12 (T12), 24 (T24), and 48 (T48) hours later in both groups. Data are mean±sd. Levosimendan (orange) vs Milrinone (blue) *p<0.05.[1]

Reference:
1. De Hert SG et al. Anesth Analg. 2007;104:766–773.

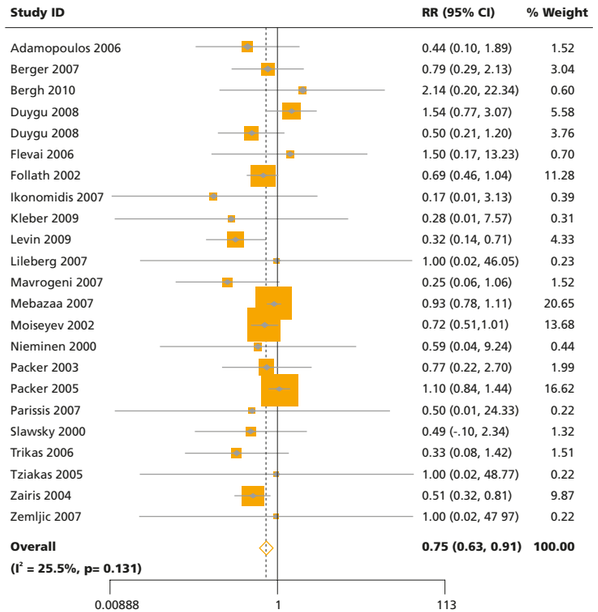
…WITHOUT COMPROMISE ON LONG-TERM SURVIVAL

The use of SIMDAX® **was not associated with a decrease of survival.**

In fact, a meta-analysis of 23 studies describing the use of SIMDAX® in cardiology settings show a **risk reduction** of 0.75 [SIMDAX® 441/2207 (20.0%), control 484/1893 (25.6%), RR=0.75 (95% CI 0.63, 0.91), p for effect: 0.003, p for heterogeneity: 0.131, NNT=18].[1]

Reference:
1. Landoni G et al. Crit Care Med. 2012;40:634–646.

Meta-analysis on mortality of levosimendan clinical trials in cardiology settings[1]

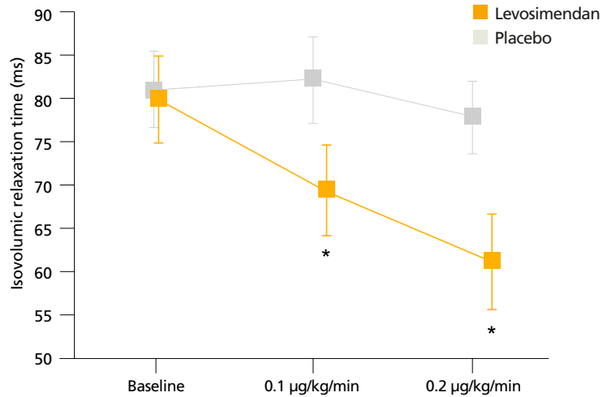


SIMDAX® DOES NOT DISTURB RELAXATION…

In a study by Jörgenssen et al. SIMDAX® not only improved contractility whilst maintaining constant heart rate and blood pressure, but also decreased isovolumic relaxation time.[1]

Reference:
1. Jörgensen K et al. Circulation. 2008;117(8):1075–1081.

Effects of levosimendan on relaxation time

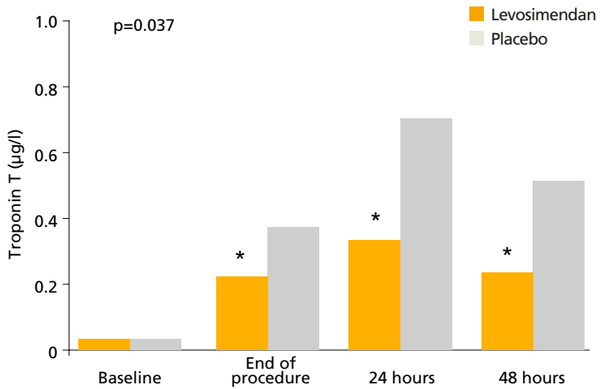


Effect of levosimendan vs placebo on Isovolumic relaxation time (IVRT) (mean±SEM) at maintained preload and afterload conditions after aortic valve replacement for aortic stenosis. *p<0.05.[1]

...REDUCES MYOCARDIAL INJURY...

Current data suggest that SIMDAX® also **diminishes myocardial injury.**[1,2]

Effects of levosimendan on release of troponin T during cardiac surgery



Troponin T levels up to 48 hours in cardiac surgery patients. Levosimendan (orange) vs placebo (grey). *p=0.032.[2]

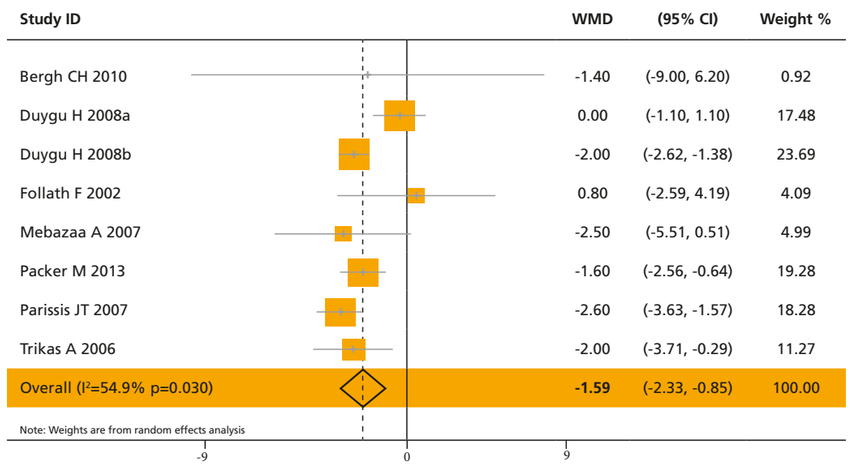
References:
1. Zangrillo A et al. J Cardiothorac Vasc Anesth. 2009;23:474–478.
2. Eriksson H et al. Ann Thor Surg. 2009;87:448.

...AND REDUCES HOSPITAL STAY

These results are corroborated by a meta-analysis of 8 studies in which SIMDAX® was used in cardiology settings:

Length of stay in hospital was decreased by 1.59 days in SIMDAX® treated patients in addition to a significant reduction in mortality.[1]

Meta-analysis of the levosimendan effects on length of stay in hospital[1]



Reference: 1. Landoni G *et al. Crit Care Med.* 2012;40:634–646 (electronic supplementary material).

PRODUCT INFORMATION: Simdax 2.5 mg/ml concentrate for solution for infusion.

Therapeutic indications
Simdax is indicated for the short-term treatment of acutely decompensated severe chronic heart failure (ADHF) in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate.

Dosage and administration
Simdax is for in-hospital use only. It should be administered in a hospital setting where adequate monitoring facilities and expertise with the use of inotropic agents are available.

Simdax is to be diluted prior to administration. The infusion is for intravenous use only and can be administered by the peripheral or central route.

Dosage: The dose and duration of treatment should be individualised according to the patient's clinical condition and response.

The recommended duration of infusion in patients with acute decompensation of severe chronic heart failure is 24 hours. No signs of development of tolerance or rebound phenomena have been observed following discontinuation of Simdax infusion. Haemodynamic effects persist for at least 24 hours and may be seen up to 9 days after discontinuation of a 24-hour infusion.

Experience of repeated administration of Simdax is limited. Experience with concomitant use of vasoactive agents, including inotropic agents (except digoxin) is limited.

Monitoring of treatment: Consistent with current medical practice, ECG, blood pressure and heart rate must be monitored during treatment and the urine output measured. Monitoring of these parameters for at least 3 days after the end of infusion or until the patient is clinically stable is recommended. In patients with mild to moderate renal or mild to moderate hepatic impairment monitoring is recommended for at least 5 days.

Elderly: No dose adjustment is required for elderly patients.

Renal impairment: Simdax must be used with caution in patients with mild to moderate renal impairment. Simdax should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min).

Hepatic impairment: Simdax must be used with caution in patients with mild to moderate hepatic impairment although no dose adjustment appears necessary for these patients. Simdax should not be used in patients with severe hepatic impairment.

Children: Simdax should not be administered to children and adolescents under 18 years of age.

Contraindications
Hypersensitivity to levosimendan or to any of the excipients. Severe hypotension and tachycardia. Significant mechanical obstructions affecting ventricular filling or outflow or both. Severe renal impairment (creatinine clearance <30 ml/min) and severe hepatic impairment. History of Torsades de Pointes.

Special warnings and special precautions for use
An initial haemodynamic effect of levosimendan may be a decrease in systolic and diastolic blood pressure, therefore, levosimendan should be used with caution in patients with low baseline systolic or diastolic blood pressure or those at risk for a hypotensive episode. More conservative dosing regimens are recommended for these patients. Physicians should tailor the dose and duration of therapy to the condition and response of the patient.

Severe hypovolaemia should be corrected prior to levosimendan infusion. If excessive changes in blood pressure or heart rate are observed, the rate of infusion should be reduced or the infusion discontinued.

The exact duration of all haemodynamic effects has not been determined, however, the haemodynamic effects, generally last for 7-10 days. This is partly due to the presence of active metabolites, which reach their maximum plasma concentrations about 48 hours after the infusion has been stopped. Non-invasive monitoring for at least 4-5 days after the end of infusion is recommended. Monitoring is recommended to continue until the blood pressure reduction has reached its maximum and the blood pressure starts to increase again, and may need to be longer than 5 days if there are any signs of continuing blood pressure decrease, but can be shorter than 5 days if the patient is clinically stable. In patients with mild to moderate renal or mild to moderate hepatic impairment an extended period of monitoring maybe needed.

Simdax infusion should be used cautiously in patients with tachycardia atrial fibrillation with rapid ventricular response or potentially life-threatening arrhythmias.

Interaction with other medicinal products and other forms of interaction
Consistent with current medical practice, levosimendan should be used with caution when used with other intravenous vasoactive medicinal products due to a potentially increased risk of hypotension.

No pharmacokinetic interactions have been observed in a population analysis of patients receiving digoxin and Simdax infusion. Simdax infusion can be used in patients receiving beta-blocking agents without loss of efficacy. Co-administration of isosorbide mononitrate and levosimendan in healthy volunteers resulted in significant potentiation of the orthostatic hypotensive response.

Undesirable effects
The most commonly (>1/10) reported adverse reactions include headache, hypotension and ventricular tachycardia.

Overdose
Overdose of Simdax may induce hypotension and tachycardia. High doses (at or above 0.4 microgram/kg/min) and infusions over 24 hours increase the heart rate and are sometimes associated with prolongation of the QTc interval. Simdax overdose leads to increased plasma concentrations of the active metabolite, which may lead to a more pronounced and prolonged effect on heart rate requiring a corresponding extension of the observation period.

Storage
Store at 2°C-8°C (in a refrigerator). Do not freeze.

ORION PHARMA
Building well-being

CONTACT INFORMATION: Orion Corporation, Orion Pharma, PO Box 65, FI-02101 ESPOO, FINLAND. Tel. +358 10 4261

sim1217