What to expect?

Haemodynamic and neurohormonal effects
Pulmonary capillary wedge pressure ↓↓↓
Cardiac output (index) ↑↑
Stroke volume ↑
Systemic vascular resistance ↓↓
Pulmonary vascular resistance ↓↓
Natriuretic peptide levels ↓↓↓

↓ = decrease, ↑ = increase

Other clinical effects
Relief of symptoms of heart failure
Effects maintained also with beta-blockers
Sustained effects due to an active metabolite
No development of tolerance
No increase in myocardial oxygen consumption
Anti-ischemic effect
No impairment of diastolic function

SIMDAX® levosimendan

Detailed infusion rates for loading dose and continuous infusion of a 0.05 mg/ml SIMDAX solution for infusion:

Patient weight kg	Loading dose (ml/hr) to be administered during 10 min		Continuous infusion rate (ml/hr)		
	6 µg/kg	12 µg/kg	0,05 µg/kg/min	0,1 µg/kg/min	0,2 µg/kg/min
40	29	58	2	**5**	10
50	36	72	3	**6**	12
60	43	86	4	**7**	14
70	50	101	4	**8**	17
80	58	115	5	**10**	19
90	65	130	5	**11**	22
100	72	144	6	**12**	24
110	79	158	7	**13**	26
120	86	173	7	**14**	29

Further readings

More detailed recommendations are available in literature on the use of SIMDAX in acute heart failure,[3] advanced heart failure,[4] and perioperative settings.[5]

3. Tavares M et al. Arq Bras Cardiol. 2008;90(3):211-5
4. Nieminen MS et al. Int J Cardiol. 2014;174(2):360-7
5. Toller W et al. J Cardiothorac Vasc Anesth. 2013;27(2):361-6

sim0417

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.

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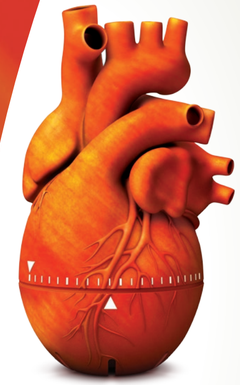
Building well-being

SIMDAX® levosimendan

EASE THE CHALLENGE OF TREATING THE FAILING HEART

SIMDAX® STARTER'S GUIDANCE



ORION PHARMA
Building well-being

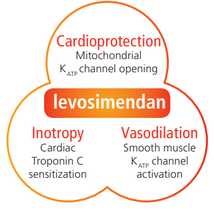
What is SIMDAX (levosimendan i.v.)

SIMDAX

- is a cardioprotective inodilator with a unique triple mechanism of action.[1]

SIMDAX

- improves hemodynamics without significant increase in oxygen consumption.[2]
- reduces symptoms of acute heart failure.[2]
- has a sustained effect[2]



Triple mechanism of action of levosimendan.[1]

SIMDAX in clinical practice

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 considerate appropriate.

SIMDAX improves myocardial contractility without increasing oxygen requirements and induces peripheral and coronary vasodilation with a potential anti-stunning and anti-ischaemic effect. Clinical trials data from heart failure patients showed that SIMDAX offers:

- improved hemodynamic without a significant increase in oxygen consumption
- reduced symptoms of acute heart failure
- beneficial effect on neurohormone levels
- sustained efficacy due to formation of an active metabolite
- additional benefit in patients under beta-blockade
- a good and predictable safety profile
- no impairment of diastolic function
- no development of tolerance

1. Papp Z et al. Int J Cardiol. 2012;159(2):82-7
2. Nieminen MS et al. Heart Lung Vessel. 2013;5(4):227-45

SIMDAX® levosimendan

Introduction to SIMDAX

If SIMDAX (levosimendan i.v.) has not been used earlier in your institution or if you do not have direct experience with this drug, we suggest you to treat some patients according to the following guidance. These "first SIMDAX patients" will have all the characteristics for receiving the most of the benefits from levosimendan.

Overall characteristics of the patients

Your first SIMDAX patients will have an existing chronic heart failure with a left ventricular ejection fraction below 40%, assessed within 12 months before the dosing of SIMDAX.

In this document we describe examples of both patients who fall in the category of acutely decompensated heart failure (cardiology setting) and patients who undergo coronary artery bypass grafting (cardiac surgery settings).

The following exclusion criteria will apply for both categories:

- severe hypotension and/or tachycardia
- severe renal impairment
- severe hepatic impairment
- history of Torsades de Pointes

Acute decompensated heart failure (use in cardiology settings)

AHF patients with the following characteristics may be considered for SIMDAX treatment:

- signs of hypoperfusion, i.e. cool extremities, oliguria
- severe pulmonary oedema
- unadequate response to traditional treatment (However, the start of the SIMDAX infusion should not be unnecessarily delayed.)

Coronary Artery Bypass Grafting (use in cardiac surgery settings)

Cardiac surgery patients with the following characteristics may be considered for levosimendan treatment:

- planned coronary artery bypass operation
- signs of decompensation before the planned operation
- and/or failure to wean from cardiopulmonary bypass (CPB)
- and/or postoperative low cardiac output syndrome
- scheduled for mechanical assist device (IABP/LVAD)
- patients with signs of right ventricular dysfunction

Dosing

Dosing of levosimendan will be according to the SPC. However, the bolus dose should only be given if immediate effects are needed and the baseline blood pressure is > 120 mmHg. Thus, in most cases:

- SIMDAX-infusion will be started with an infusion rate of 0.1 mcg/kg/min.
- The rate can be increased to 0.2 mcg/kg/min if further effect is warranted or decreased to 0.05 mcg/kg/min if adverse effects (e.g. hypotension) occurs.
- The maximum duration of the infusion should not exceed 24 hours.

Timing of the infusion

SIMDAX infusion should be started as soon as the treating physician finds a clinical need for its use. In case of cardiac surgery, the infusion should preferably be started before the operation (up to 24 h before the planned operation), while, in case of failure to wean from CPB or post-operative low cardiac output syndrome, the infusion is started later.

Measures during the treatment

- Hypovolemia and hypotension should be corrected before the initiation and during the levosimendan infusion, with colloids and/or vasoconstrictors (e.g. norepinephrine).
- The dosing of i.v. diuretics should be temporarily interrupted or their dose reduced.
- An existing beta-blockade should be continued, whenever possible.
- Potassium levels should be followed regularly and supplemented as needed; serum potassium should preferably be kept > 4.0 mmol/l.