SIMDAX® GIVES YOU TIME WHEN IT’S NEEDED MOST¹

SIMDAX® is the only inodilator to provide sustained hemodynamic benefits and symptom control to patients with acute heart failure, and in need of inotropic therapy.

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The clinical effects of SIMDAX® are mediated through:
- 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

The unique triple mechanism of action of levosimendan

With three pharmacological effects...

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

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:

Multiple action of levosimendan in the cardiovascular system1

References:

Improvement in hemodynamic performance2

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

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

**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

**Sustained effects of levosimendan when used in cardiac surgery**

Sustained effects of levosimendan when used in cardiac surgery

References:

Reference:
...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].

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.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamopoulos 2006</td>
<td>0.69 (0.50, 1.00)</td>
<td>1.00</td>
</tr>
<tr>
<td>Berger 2007</td>
<td>0.79 (0.76, 0.82)</td>
<td>3.04</td>
</tr>
<tr>
<td>Bergh 2010</td>
<td>2.14 (0.20, 22.34)</td>
<td>0.49</td>
</tr>
<tr>
<td>Duygu 2008</td>
<td>1.14 (0.77, 1.70)</td>
<td>5.58</td>
</tr>
<tr>
<td>Duygu 2008</td>
<td>0.59 (0.21, 1.20)</td>
<td>3.76</td>
</tr>
<tr>
<td>Follath 2002</td>
<td>1.50 (0.17, 0.13)</td>
<td>0.70</td>
</tr>
<tr>
<td>Flottmann 2002</td>
<td>0.63 (0.46, 0.96)</td>
<td>11.28</td>
</tr>
<tr>
<td>Hornikx 2007</td>
<td>0.17 (0.11, 1.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>Kieber 2009</td>
<td>0.28 (0.15, 0.57)</td>
<td>0.31</td>
</tr>
<tr>
<td>Lewis 2009</td>
<td>0.32 (0.14, 0.71)</td>
<td>4.33</td>
</tr>
<tr>
<td>Liebich 2007</td>
<td>1.69 (0.02, 46.05)</td>
<td>23.04</td>
</tr>
<tr>
<td>Marzullo 2007</td>
<td>0.33 (0.06, 1.96)</td>
<td>1.52</td>
</tr>
<tr>
<td>Mehra 2007</td>
<td>0.93 (0.76, 1.11)</td>
<td>28.65</td>
</tr>
<tr>
<td>Molnar 2008</td>
<td>0.73 (0.21, 2.41)</td>
<td>13.68</td>
</tr>
<tr>
<td>Rinne 2006</td>
<td>0.59 (0.04, 22.48)</td>
<td>0.44</td>
</tr>
<tr>
<td>Parodi 2003</td>
<td>0.77 (0.22, 2.78)</td>
<td>1.98</td>
</tr>
<tr>
<td>Parodi 2005</td>
<td>1.10 (0.36, 3.44)</td>
<td>14.42</td>
</tr>
<tr>
<td>Perthes 2007</td>
<td>0.55 (0.01, 28.33)</td>
<td>0.22</td>
</tr>
<tr>
<td>Stovall 2000</td>
<td>0.69 (0.16, 2.34)</td>
<td>1.32</td>
</tr>
<tr>
<td>Tzikas 2006</td>
<td>0.83 (0.06, 1.42)</td>
<td>1.51</td>
</tr>
<tr>
<td>Tzikas 2006</td>
<td>0.48 (0.02, 46.77)</td>
<td>0.22</td>
</tr>
<tr>
<td>Zarkas 2004</td>
<td>0.81 (0.02, 31.02)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Overall: DF = 20.0%, p = 0.003


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.

Current data suggest that SIMDAX® also diminishes myocardial injury.¹²

Troponin T levels up to 48 hours in cardiac surgery patients. Levosimendan (orange) vs placebo (grey). *p=0.032.¹

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

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### Meta-analysis of the levosimendan effects on length of stay in hospital¹

<table>
<thead>
<tr>
<th>Study ID</th>
<th>WMD (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergh CH 2010</td>
<td>-1.40 (-9.00, 6.20)</td>
<td>0.92</td>
</tr>
<tr>
<td>Duygu H 2008a</td>
<td>0.00 (-1.10, 1.10)</td>
<td>17.48</td>
</tr>
<tr>
<td>Duygu H 2008b</td>
<td>-2.00 (-3.62, -1.38)</td>
<td>23.69</td>
</tr>
<tr>
<td>Follath F 2002</td>
<td>0.80 (-2.59, 4.19)</td>
<td>4.09</td>
</tr>
<tr>
<td>Mebazaa A 2007</td>
<td>-2.50 (-5.51, 0.51)</td>
<td>4.99</td>
</tr>
<tr>
<td>Packer M 2013</td>
<td>-1.50 (-2.56, -0.54)</td>
<td>19.28</td>
</tr>
<tr>
<td>Parissis JT 2007</td>
<td>-2.60 (-3.63, -1.57)</td>
<td>18.28</td>
</tr>
<tr>
<td>Trikas A 2006</td>
<td>-2.00 (-3.71, -0.29)</td>
<td>11.27</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>-1.59 (-2.33, -0.85)</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis.

References:
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 tract, 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 of 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.

Severe hypotension and tachycardia. Significant prolongation of the QTc interval.

**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.

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.

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