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Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADHF</td>
<td>Acute(ly) decompensated heart failure</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BNP</td>
<td>Brain natriuretic peptide</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval / Cardiac index</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>IABP</td>
<td>Intra-aortic balloon pump</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>K&lt;sub&gt;ATP&lt;/sub&gt; channel</td>
<td>ATP-dependent potassium channel</td>
</tr>
<tr>
<td>LCOS</td>
<td>Low cardiac output syndrome</td>
</tr>
<tr>
<td>LVAD</td>
<td>Left ventricular assist device</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>PDE</td>
<td>Phosphodiesterase</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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</tbody>
</table>

Trial acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALARM-HF</td>
<td>Acute Heart Failure Global Survey of Standard Treatment</td>
</tr>
<tr>
<td>ASCEND-HF</td>
<td>Acute Study of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>Cooperative North Scandinavian Enalapril Survival Study</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol Prospective Randomized Cumulative Survival</td>
</tr>
<tr>
<td>FIRST</td>
<td>Flolan International Randomised Survival Trial</td>
</tr>
<tr>
<td>LIDO</td>
<td>Levosimendan Infusion versus Dobutamine</td>
</tr>
<tr>
<td>LevoRep</td>
<td>Randomised trial investigating the efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure</td>
</tr>
<tr>
<td>OPTIME-HF</td>
<td>Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations - Heart Failure trial</td>
</tr>
<tr>
<td>REVIVE I and II</td>
<td>Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy trials I and II</td>
</tr>
<tr>
<td>RUSSLAN</td>
<td>Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct</td>
</tr>
<tr>
<td>SURVIVE</td>
<td>Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support</td>
</tr>
</tbody>
</table>
Levosimendan - key points

SUMMARY

Levosimendan (SIMDAX®) is a calcium sensitisier developed for intravenous use in hospitalised patients with acutely decompensated heart failure (ADHF). SIMDAX® is proven to be effective and well tolerated in large-scale clinical trials of hospitalised patients with heart failure. Over 500,000 patients worldwide have been treated with SIMDAX®.

Clinical data from heart failure patients showed that SIMDAX® offers:
• Improved haemodynamics\(^1-3\) without a significant increase in oxygen consumption.\(^4, 5\)
• Reduced symptoms of acute heart failure.\(^1, 2, 6, 7\)
• Beneficial effect on neurohormone levels.\(^7, 8\)
• Sustained efficacy due to formation of an active metabolite.\(^8, 9\)
• Additional benefit in patients under beta-blockade.\(^1, 10\)

SIMDAX® is well tolerated and no major interactions with concomitant medications commonly used in heart failure have been reported. SIMDAX® offers:
• A good and predictable safety profile.\(^1-3, 7\)
• No impairment of diastolic function.\(^11, 12\)
• No development of tolerance.\(^9\)
• No adverse effect on survival.\(^1, 7, 13-16\)

The effects of SIMDAX® are mediated through:
• Increased cardiac contractility by calcium sensitisation of troponin C.\(^17-20\)
• Vasodilation through the opening of potassium channels.\(^21-24\)
• Cardioprotection and antiapoptopic effect through the opening of mitochondrial potassium channels.\(^25-28\)

Health economic analyses of the clinical data have shown that SIMDAX® is cost-effective in ADHF patients.\(^6, 28, 30\)
IN ACUTE HEART FAILURE

SIMDAX® (levosimendan) 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. For product details, see the current Summary of Product Characteristics (SPC), page 71.

IN OTHER THERAPEUTIC AREAS

Cardiac surgery
Levosimendan has been studied in four Orion-sponsored clinical trials and in numerous investigator-initiated studies in connection with cardiac surgery. The results of these studies have shown beneficial haemodynamic and cardioprotective effects which suggest a favourable outcome effect.

Repetitive administration in advanced chronic heart failure
Several investigator-initiated studies and case reports with repetitive levosimendan dosing have shown beneficial effects on haemodynamics, neurohormone levels and symptoms in patients suffering from advanced chronic heart failure.

Other
Levosimendan has also shown preliminary positive effects – mainly in small-scale investigator-initiated studies – in right ventricular failure, cardiogenic shock, septic shock and in other states requiring inotropic support.
Introduction

This monograph focuses on the regulatory studies performed with intravenous levosimendan (SIMDAX®). Most of the studies have been performed in patients with acute worsening of chronic heart failure and, to a lesser extent, in patients with left ventricular failure due to an acute myocardial infarction, cardiac surgery, and other therapeutic use. The clinical programme has included nearly 3,500 patients.

In addition, levosimendan has been assessed in numerous clinical studies by independent investigators throughout the world. The focus of these investigator-initiated studies has lately been on the use of levosimendan in an operative setting and on repetitive dosing of levosimendan in advanced chronic heart failure. Further, smaller scale studies in several other clinical settings have been published. The results of these studies are also presented in this monograph.

Marketing authorisation was first granted for SIMDAX® in 2000 in Sweden. Currently, SIMDAX® has marketing authorisation in over 50 countries world wide and it is estimated that by December 2011, over 500,000 patients had been exposed to SIMDAX® infusion in everyday clinical practice.

ACUTE HEART FAILURE

According to the current European Society of Cardiology (ESC) Guidelines, a patient with acute heart failure presents with the following conditions:

- Worsening or decompensated chronic heart failure
- Pulmonary oedema
- Hypertensive acute heart failure
- Cardiogenic shock
- Heart failure related to acute coronary syndromes
- Isolated right-sided heart failure

The conditions often overlap. In-hospital mortality varies between categories of acute heart failure and is up to 40-60% in patients with cardiogenic shock, but less than 10% in other categories. No single or simple treatment protocol can be recommended for acute heart failure because of the wide range of problems underlying the decompensation episode. Multiple agents are being used to treat acute heart failure, but there is a paucity of clinical studies data and their use is largely empiric.
DRUGS FOR ACUTE HEART FAILURE

Intravenous diuretics and vasodilators
Rapid relief of symptoms can usually be obtained with intravenously-administered morphine followed by intravenous loop diuretics as a bolus or infusion. Initial improvement in congestive symptoms can be accelerated by intravenous vasodilators such as nitroglycerin or sodium nitroprusside. No randomised prospective large-scale trials have been carried out to compare the efficacy and tolerability of various types of diuretics or to compare the efficacy of intravenous diuretics with vasodilator therapy. However, smaller studies indicate that vasodilator-oriented treatment is superior to a diuretic-oriented approach.

The most commonly used intravenous vasodilators are nitroglycerine and sodium nitroprusside. Prolonged infusions of the former, nitroglycerine, may lead to the development of tolerance and of the latter, sodium nitroprusside, to thiocyanate toxicity.

A newer vasodilating agent, a recombinant human brain natriuretic peptide (BNP), nesiritide, was approved by the U.S. Food and Drug Administration (FDA) in 2001 for the treatment of ADHF. In Europe, the drug is only approved for marketing in Switzerland. Recently, the preliminary results of a large-scale placebo-controlled trial, ASCEND-HF, with over 7,000 patients suggested that nesiritide was safe, but ineffective in ADHF.

Intravenous inotropic agents
The current ESC guideline for the treatment of ADHF recommends the use of inotropic agents in patients with low systolic blood pressure or a low cardiac index in the presence of signs of hypoperfusion or congestion. Owing to their suspected detrimental effect on survival, their use is recommended only for the most severe cases and they should be withdrawn as soon as adequate organ perfusion is restored and/or congestion is reduced.

Dobutamine
Dobutamine, a sympathomimetic amine, is the most commonly used intravenous inotropic agent in advanced heart failure patients. Lower doses result in a positive inotropic effect and in vasodilation that reduces aortic impedance and systemic vascular resistance. The adrenergic effects of dobutamine, however, lead to increased levels of intracellular cyclic adenosine monophosphate (cAMP) and calcium and this predisposes patients to arrhythmia and ischaemia. Also, the down-regulation of beta-adrenergic receptors with prolonged dobutamine infusion has clinical implications which lead to the development of tolerance. Due to a competitive effect on beta-receptors, concomitant use of dobutamine with beta-blockers attenuates the haemodynamic effect of dobutamine. Moreover, the systemic vascular resistance may
increase in beta-blocked patients.\textsuperscript{51} The elimination half-life of dobutamine is only a few minutes,\textsuperscript{52-54} which means that the effects of dobutamine rapidly disappear when the infusion is stopped.

Data on the use of intermittent long-term infusions have suggested that dobutamine may have an adverse effect on mortality.\textsuperscript{55, 56} In a retrospective analysis of the data from the FIRST trial, dobutamine-treated patients had increased mortality in comparison with patients not treated with dobutamine.\textsuperscript{57} Additionally, a meta-analysis suggested increased mortality with dobutamine, although the result was not statistically significant; odds ratio 1.47, 95% confidence interval (CI) 0.98–2.21, \( p = 0.06 \).\textsuperscript{58}

\textit{Milrinone}

Milrinone is the most widely used phosphodiesterase (PDE) III inhibitor. By inhibiting the breakdown of cAMP, milrinone enhances contractility in myocytes and relaxation in smooth muscle cells.\textsuperscript{46, 59} In the setting of low-output congestive heart failure, milrinone reduces systemic and pulmonary vascular resistance, decreases diastolic filling pressure, and augments stroke volume and cardiac output. Milrinone also increases ventricular compliance during diastole (lusitropic effect). Similarly to other compounds that increase cAMP concentration, milrinone increases intracellular calcium thus predisposing patients to an increased risk of arrhythmia.\textsuperscript{46} The plasma concentrations of milrinone increase dose-dependently and its elimination half-life is approximately 2 hours.\textsuperscript{60} Due to this relatively long elimination half-life, a loading dose is recommended in order to achieve an immediate haemodynamic response.\textsuperscript{61} Elimination is prolonged in renal impairment and thus caution should be exercised when milrinone is used in patients with renal insufficiency.\textsuperscript{62, 63}

The haemodynamic effects of milrinone on cardiac output, end-diastolic ventricular pressures and systemic vascular resistance have been shown in patients with congestive heart failure.\textsuperscript{64, 65} When compared with dobutamine, milrinone produces similar improvement in cardiac index and exerts stronger vasodilatory effects. A recent meta-analysis\textsuperscript{66} suggested that milrinone might increase mortality in adult patients undergoing cardiac surgery.

A trial to evaluate the effects of intravenous milrinone in 951 patients admitted to hospital with an exacerbation of systolic heart failure not requiring intravenous inotropic support was performed in 78 US sites (OPTIME-HF).\textsuperscript{67} The patients had New York Heart Association (NYHA) class III-IV symptoms and a mean left ventricular ejection fraction (LVEF) of 23%. The trial failed to show any outcome benefit of intravenous milrinone over placebo. On the contrary, adverse events were more frequent with milrinone. Oral milrinone had earlier shown increased mortality and morbidity over placebo.\textsuperscript{68}
Other intravenous inotropic agents

There are several other intravenous inotropic agents in addition to dobutamine and milrinone. Beta-receptor stimulants include dopamine and dopexamine. Their mechanism of action and consequently their clinical effects slightly differ from that of dobutamine. As with dobutamine, the clinical trials performed with these agents are mostly small and were not powered to measure effects on hard endpoints, such as mortality or hospitalisations.69-72

Enoximone, a PDE III inhibitor, has similar haemodynamic effects to milrinone. Unlike the other PDE III inhibitors, enoximone has been shown to have an active metabolite with non-linear pharmacokinetics.73-75 The studies with intravenous enoximone have been too small to give relevant information on their effects on prognosis.

Problems associated with existing intravenous inotropic agents are summarised in Table 1.

Table 1. Detrimental effects associated with traditional intravenous inotropic drugs.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines (e.g. dobutamine)</td>
<td>cAMP ↑, Ca²⁺ ↑</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias ↑, ischaemia ↑</td>
</tr>
<tr>
<td></td>
<td>Development of tolerance</td>
</tr>
<tr>
<td></td>
<td>Beta-blockade attenuates haemodynamic effects</td>
</tr>
<tr>
<td></td>
<td>Possible detrimental effect on mortality</td>
</tr>
<tr>
<td>PDE III Inhibitors (e.g. milrinone)</td>
<td>cAMP ↑, Ca²⁺ ↑</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias ↑</td>
</tr>
<tr>
<td></td>
<td>Hypotension ↑</td>
</tr>
<tr>
<td></td>
<td>Sudden deaths ↑, mortality ↑</td>
</tr>
</tbody>
</table>
Chemistry

Levosimendan, (-)-(R)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile, belongs to a new class of drugs, the calcium sensitisers. The structural formula of levosimendan is presented in Figure 1. Levosimendan is a moderately lipophilic drug with a molecular weight of 280.3 daltons. It is a weak acid with $\text{pK}_a$ 6.3. Solubility of levosimendan in distilled water and phosphate buffer (pH 8) is poor (0.04 mg/ml and 0.9 mg/ml, respectively). Solubility in ethanol is 7.8 mg/ml and therefore levosimendan in its pharmaceutical composition (levosimendan 2.5 mg/ml infusion concentrate) is diluted in ethanol.76

Figure 1. Structural formula of levosimendan.
Pharmacology

TRIPLE MECHANISM OF ACTION

Levosimendan has three key mechanisms of action: calcium sensitisation and opening of adenosine triphosphate dependent-potassium (K ATP) channels both on the sarcolemma of the smooth muscle cells in the vasculature and in the mitochondria of cardiomyocytes.

1. Calcium sensitisation by selective binding to calcium-saturated cardiac troponin C increases the contractile force of the cardiac myocytes without affecting relaxation.

2. Opening of K ATP channels in vascular smooth muscle cells elicits both arterial and venous vasodilation as well as improvement in coronary artery circulation.

3. Opening of K ATP channels in the mitochondria of cardiomyocytes causes a cardioprotective effect in situations when the heart is subjected to ischemic events.

Through calcium sensitisation, levosimendan improves cardiac contractility in the failing heart without affecting muscle electrophysiology. Through the opening of K ATP channels in vascular smooth muscle cells, levosimendan improves oxygen supply to the myocardium.

Because levosimendan augments myofibril contractions by increasing calcium sensitivity rather than by increasing intracellular calcium, it is not associated with greater myocardial oxygen demand or ischaemia, or tolerance, conditions sometimes incurred with agents traditionally used to treat decompensated heart failure.

In brief, the mechanism of action for levosimendan involves three clinically relevant features that are specific to the cardiovascular system; levosimendan acts on the contractile apparatus of the myocardial cells, on the vascular smooth muscle cells and on the mitochondria of the cardiomyocytes via independent, but complementary, mechanisms.

Calcium sensitisation

The heart muscle consists of cardiac myocytes that show a striated subcellular structure: each cell contains myofibrils with actin and myosin filaments, which form the contractile apparatus. The actin filaments are associated with the regulatory proteins tropomyosin and troponin, the latter being formed from a complex of three smaller proteins (TnC, TnI, and TnT) (Figure 2).

When intracellular Ca2+ concentration increases, troponin C becomes Ca2+ saturated, which triggers the contraction. When calcium is removed from the cytosol, troponin C, now Ca2+ free, triggers the sarcomere relaxation.
Levosimendan selectively binds to calcium-saturated cardiac troponin C (Figure 3).

By binding to troponin C and stabilising the troponin C•Ca$^{2+}$ complex, levosimendan enhances the sensitivity of the myofilament and facilitates the actin-myosin crossbridge formation. The calcium sensitisation effect of levosimendan has been shown in many in vitro models from skinned fibres to isolated hearts. Levosimendan has positive inotropic effects in normal and heart failure models.

The formation of the troponin C•Ca$^{2+}$-levosimendan complex is calcium-dependent and calcium sensitivity is enhanced only when intracellular calcium concentration is elevated. As a result of this unique property, levosimendan increases contractile force during systole when intracellular calcium concentration is increased. Importantly, levosimendan does not impair relaxation during diastole when intracellular calcium concentration is decreased or even improves relaxation. Levosimendan has been shown to increase contractility considerably with only a modest increase in intracellular calcium, even in ventricular muscle strips from end-stage failing human hearts. This finding is significant in relation to clinical effect in that levosimendan does not increase energy consumption and the risk of proarrhythmic events is low. Other agents shown to improve cardiac output, such as milrinone, have different mechanisms of action from levosimendan. In fact, milrinone increases cardiac contractility, but it does so by affecting intracellular calcium concentrations, thereby increasing energy consumption and the potential for arrhythmia.
Calcium sensitisation with levosimendan offers increased cardiac contractility

- without increasing intracellular calcium\(^9\), \(^9\)
- without increasing oxygen consumption\(^5\), \(^9\), \(^7\), \(^10\), \(^12\), \(^13\)
- without affecting cardiac rhythm\(^9\), \(^2\), \(^14\) and relaxation\(^1\), \(^15\), \(^17\)

Opening of \(K\text{ATP}\) channels in the vascular smooth muscle cells

Vasodilation with levosimendan results from the opening of \(K\text{ATP}\) channels; it reduces preload and afterload, and improves oxygen supply to the myocardium. Vasodilation with levosimendan has been demonstrated in both arterial\(^2\) and venous\(^2\) vascular beds, and in the coronary arteries.\(^2\) Opening of \(K\text{ATP}\) channels has also been observed in ventricular myocytes - an effect that may help to protect ischaemic myocardium.\(^1\)

The opening of \(K\text{ATP}\) channels by levosimendan has been both electrophysiologically\(^2\) and pharmacologically\(^2\) demonstrated in arterial and venous preparations and in coronary arteries.\(^1\) It has also been shown that the venodilatory effect of levosimendan on the norepinephrine-constricted human portal vein\(^2\) or serotonin-constricted human saphenous vein\(^2\) is also mediated by the opening of \(K\text{ATP}\) channels.

In addition, some pharmacological findings indicate that levosimendan may open the calcium-dependent potassium channels in arteries and veins\(^2\) as well as voltage-dependent potassium channels in coronary arteries.\(^2\)

In light of the above-mentioned studies, it seems that levosimendan may preferentially stimulate \(K\text{ATP}\) channels in small resistance vessels.\(^2\)

In large conductance vessels the vasodilatation appears to be mediated mainly through opening of voltage- as well as calcium-dependent potassium channels.
Opening of $K_{\text{ATP}}$ channels in the cardiomyocyte mitochondria

By opening mitochondrial adenosine triphosphate-dependent potassium (mito$K_{\text{ATP}}$) channels, levosimendan protects the heart against ischaemia-reperfusion damage. The fact that levosimendan can prevent or limit myocyte apoptosis via the activation of mito$K_{\text{ATP}}$ channels provides a potential mechanism whereby this agent might protect cardiac myocytes during episodes of acute heart failure as well as in chronic heart failure situation.

Additional in vitro results

In vitro studies indicate that levosimendan is a highly selective PDE III inhibitor compared to other PDE isoenzymes. The PDE III inhibition alone is not sufficient to increase the cAMP intracellular level. Hence, this mechanism of action does not contribute significantly to the contractility-enhancing and vasodilatory effects of levosimendan in isolated guinea-pig heart and, therefore, probably not in clinical practice either. It has been shown that the inotropic effect of levosimendan cannot be blocked by a protein kinase inhibitor that is known to prevent the activity of PDE-inhibiting drugs. Simultaneous inhibition of both PDE III and PDE IV is needed to increase cAMP and intracellular calcium, which is seen with non-selective PDE inhibitors (such as enoximone and milrinone).
PHARMACOKINETICS

General pharmacokinetics
Levosimendan is extensively metabolised before excretion into urine and faeces. The main pathway is conjugation with glutathione to form inactive metabolites. The minor pathway (approximately 6% of the total levosimendan dose) is reduction in the intestine to an intermediate metabolite (OR-1855), which is further acetylated to the active metabolite, OR-1896. Levosimendan is excreted as conjugates via the urine and faeces and only traces of unchanged levosimendan are found in experimental animals and in man. Levosimendan metabolism is illustrated in Figure 4.

The metabolite OR-1896 has been shown to have haemodynamic and pharmacologic properties similar to those of the parent drug in pre-clinical models.

The terminal elimination half-life (t\text{1/2 el}) of levosimendan is about 1 hour both in healthy volunteers and in patients with heart failure (Table 2) and it rapidly disappears from the circulation after the infusion is stopped (Figure 5). Levosimendan is highly bound to plasma proteins (97-98%). The plasma concentrations of levosimendan increase dose-proportionally.
The mean elimination half-life values for the levosimendan metabolite OR-1896 is approximately 80 hours and its plasma protein binding is about 40% (Table 2).\textsuperscript{137, 138}

Table 2. Pharmacokinetic variables of levosimendan and its active metabolite OR-1896 in patients with NYHA III-IV heart failure.\textsuperscript{137-139}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan</th>
<th>Metabolite OR-1896</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2el}$ (h)</td>
<td>1.1 - 1.4</td>
<td>77.4 - 81.3</td>
</tr>
<tr>
<td>$CL_{tot}$ (l/h/kg)</td>
<td>0.18 - 0.22</td>
<td>na</td>
</tr>
<tr>
<td>$V_c$ (l/kg)</td>
<td>0.33 - 0.39</td>
<td>na</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>97</td>
<td>42</td>
</tr>
</tbody>
</table>

$t_{1/2el} =$ terminal elimination half-life, $CL_{tot} =$ total clearance, $V_c =$ volume of distribution based on area under the curve (AUC), na = not assessed.

The activity of the enzyme responsible for the acetylation, the N-acetyltransferase, is known to differ considerably in man. Most Caucasian populations in Europe and North America have 40\% to 70\% slow acetylators, whereas most Asian populations have only 10\% to 30\% slow acetylators.\textsuperscript{140} The acetylator status of a patient affects the pharmacokinetics of levosimendan metabolites, but not that of the parent drug. In rapid acetylators, the OR-1896 levels were significantly higher and OR-1855 significantly lower; in slow acetylators the opposite was seen. However, the haemodynamic effects on heart rate, blood pressure, pulmonary capillary wedge pressure and cardiac output were similar in the two acetylator types. These findings could be explained either by assuming that both metabolites are active in man or by the fact that the differences in OR-1896 levels seen in the study were too small to produce different haemodynamic responses.\textsuperscript{141}
Pharmacokinetics in special populations

Population pharmacokinetic analysis has shown no effects of age, ethnic origin (Caucasians vs. African Americans) or gender on the pharmacokinetics of levosimendan.\textsuperscript{142}

The pharmacokinetic profile of levosimendan in paediatric patients with congenital heart disease was similar to that of adult patients after a single intravenous infusion of levosimendan (12 μg/kg).\textsuperscript{143} The pharmacokinetics of the active metabolite has not been investigated in children.

The pharmacokinetics of levosimendan in patients with severe renal impairment or undergoing chronic haemodialysis revealed that the elimination of the metabolite OR-1896 was prolonged 1.5-fold compared with healthy subjects and the exposure to the metabolites (area under the curve [AUC]) was up to 170% higher.\textsuperscript{144} However, no clinically relevant differences in the pharmacokinetics of the parent drug were observed. The metabolites were dialyzable, but the parent drug seemed not to transfer to dialysate. The probable explanation is the lower plasma protein binding of the metabolites compared to the parent drug.

In patients with moderate hepatic impairment the elimination of the metabolite OR-1896 was also prolonged 1.5-fold, but exposure to the metabolites was not significantly altered.\textsuperscript{145} Similarly to renal impairment, the pharmacokinetics of levosimendan itself was not altered in hepatic impairment.

In patients undergoing cardiac surgery, the formation of the metabolites OR-1855 and OR-1896 was delayed compared to patients with chronic heart failure. In chronic heart failure, the peak concentrations of the metabolites were seen 2-4 days after starting the infusion,\textsuperscript{138} compared to 6 days\textsuperscript{146} in patients undergoing cardiac surgery. The reason is not fully known, but may be related to initiation of therapy following a fasting state and the use of broad-spectrum antibiotics. These conditions reduce populations of intestinal bacteria involved in the acetylation of levosimendan, leading to reduced/delayed formation of metabolites OR-1855 and OR-1896. The steady state plasma concentrations of the parent drug were somewhat lower in cardiac surgery patients than in chronic heart failure with the AUC 14% lower with similar dosing (approximately 1200 vs. 1400 h × ng/ml, respectively).\textsuperscript{146}

Interactions

Preclinical findings suggest that cytochrome P450 (CYP) enzymes do not play any role in the metabolism of levosimendan or OR-1896.\textsuperscript{146}

Several clinical interaction studies with levosimendan have been performed. In pharmacokinetic interaction studies between intravenous or oral levosimendan and itraconazole,\textsuperscript{135} warfarin,\textsuperscript{147} captopril,\textsuperscript{148}
isosorbide mononitrate or alcohol, no clinically significant effects of concomitant administration on levosimendan pharmacokinetics were found. Furthermore, studies with felodipine and carvedilol have revealed no relevant haemodynamic or pharmacokinetic interactions.

**PHARMACODYNAMICS**

**Haemodynamics**

The haemodynamic effects of levosimendan are thoroughly presented on pages 24-27. Briefly, levosimendan produces dose-dependent increases in cardiac output, stroke volume and heart rate, and decreases in pulmonary capillary wedge pressure, mean blood pressure, mean pulmonary artery pressure, mean right atrial pressure and total peripheral resistance. The effects are seen in minutes if a loading dose is used. There is no sign of development of tolerance even with a prolonged infusion up to 48 hours. Due to the formation of an active metabolite, the haemodynamic effects are maintained several days after stopping levosimendan infusion.

**Myocardial energy and oxygen consumption**

The beneficial effects of levosimendan on haemodynamics are not associated with any significant increase in myocardial energy consumption, as evidenced using dynamic positron emission tomography (PET) in hospitalised patients with heart failure (NYHA III-IV) (Figure 6). The patients were given levosimendan (18 µg/kg as a loading dose followed by a continuous infusion of 0.3 µg/kg/min for about 5 hours) and placebo in a crossover fashion. Despite increases in both cardiac output and stroke volume, myocardial oxygen consumption was unaltered by levosimendan.

Similarly, bolus doses of 8 µg/kg or 24 µg/kg did not increase myocardial oxygen consumption in postoperative patients, although cardiac function markedly improved.

Figure 6. Myocardial oxygen consumption in postoperative patients.
Anti-stunning
Levosimendan also possesses anti-stunning effects. This was shown in a randomised, double-blind study in patients with an acute myocardial infarction who had undergone percutaneous transluminal coronary angioplasty (PTCA). The patients received levosimendan 24 µg/kg as a bolus dose (n=16) or corresponding placebo (n=8) 10 minutes after completion of the successful PTCA. The study showed that levosimendan clearly improved the function of stunned myocardium, as shown by a substantial reduction in the number of hypokinetic segments in the left ventricular wall (-2.4) compared with placebo (which showed an increase of 0.8, p=0.016).

Diastolic function
The same study also showed that diastolic function was not worsened by levosimendan; end diastolic pressure-volume ratio and chamber compliance during late diastole changed similarly with levosimendan and placebo. In addition, the index of isovolumic relaxation (Tau) was improved in the levosimendan group and impaired in the placebo group, which suggests improved diastolic function. A similar finding was observed in a study using intracoronary infusions. Ten patients with heart failure received two intracoronary doses of levosimendan without systemic effects (3.75 and 12.5 µg/min and dextrose [control] as bolus doses). In this study Tau was improved with the higher dose, but was unaffected with the lower dose of levosimendan. Levosimendan also increased left ventricular +dP/dt dose-dependently at various paced heart rates, indicating a direct contractility enhancing effect with levosimendan.
Main clinical trials

TRIALS

Levosimendan has been studied in nearly 3,500 patients in sponsored clinical trials. The design of the most important studies is described in the following sections and summarised in Table 3.

Table 3. Trials with levosimendan.

<table>
<thead>
<tr>
<th>Study</th>
<th>N (total/LS)</th>
<th>Dose (mg/kg/min), duration of LS infusion (h)*</th>
<th>Comparator</th>
<th>Diagnosis/NYHA class</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-ranging</td>
<td>151/95</td>
<td>0.05-0.6, 24</td>
<td>Placebo/dobutamine</td>
<td>CHF/III</td>
<td>Invasive haemodynamics</td>
</tr>
<tr>
<td>Dose-escalation and withdrawal</td>
<td>146/98</td>
<td>0.1-0.4, 24 or 48</td>
<td>Placebo</td>
<td>CHF/III-IV</td>
<td>Invasive haemodynamics</td>
</tr>
<tr>
<td>LIDO</td>
<td>203/103</td>
<td>0.1-0.2, 24</td>
<td>Dobutamine</td>
<td>CHF/(III)-IV</td>
<td>Invasive haemodynamics</td>
</tr>
<tr>
<td>RUSSLAN</td>
<td>504/402</td>
<td>0.1-0.4, 6</td>
<td>Placebo</td>
<td>Post AMI/IV</td>
<td>Safety</td>
</tr>
<tr>
<td>REVIVE I</td>
<td>100/51</td>
<td>0.1-0.2, 24</td>
<td>Placebo</td>
<td>CHF/IV</td>
<td>Clinical composite</td>
</tr>
<tr>
<td>REVIVE II</td>
<td>600/299</td>
<td>0.1-0.2, 24</td>
<td>Placebo</td>
<td>CHF/IV</td>
<td>Clinical composite</td>
</tr>
<tr>
<td>SURVIVE</td>
<td>1327/664</td>
<td>0.1-0.2, 24</td>
<td>Dobutamine</td>
<td>CHF/IV</td>
<td>Mortality</td>
</tr>
</tbody>
</table>

* In all studies, a loading dose (3-36 μg/kg) preceded the continuous infusion.
LS = levosimendan, AMI = acute myocardial infarction, CHF = congestive heart failure

Dose-finding study: The therapeutic dose range of levosimendan administered over a 24-hour period was studied in a placebo-controlled, double-blind, parallel-group, randomised study including 151 patients with stable (mainly NYHA class III) heart failure of ischaemic origin. Patients were treated with a 24-hour intravenous infusion of levosimendan at doses ranging from 0.05-0.6 μg/kg/min.3

Dose escalation study: Forced up-titration, maintenance and withdrawal of levosimendan was studied in a placebo-controlled, double-blind, parallel-group, randomised, study in 146 patients hospitalised for decompensated heart failure (NYHA class III or IV) due to coronary artery disease or dilated cardiomyopathy. Patients were treated with an intravenous infusion of levosimendan at doses ranging from 0.1 to 0.4 μg/kg/min. The study was divided into three phases. During the first 6 hours, escalated doses of levosimendan (n=98) were compared with placebo (n=48). From 6 to 24 hours, the patients in the levosimendan group continued to receive the study medication as an open-label infusion. At 24 hours, the remaining patients were randomised to continue on levosimendan (levosimendan continuation group) or placebo (levosimendan withdrawal group), administered double-blind up to 48 hours.2,9
**LIDO study:** Levosimendan was compared with dobutamine in a double-blind, parallel-group, randomised study in 203 patients with low-output heart failure, with either an ischaemic or non-ischaemic aetiology of heart failure, who required right heart catheterisation and treatment with an intravenous inotropic drug. Patients randomised to levosimendan were treated with a 24-hour intravenous infusion of levosimendan at doses from 0.1-0.2 μg/kg/min.1

**RUSSLAN study:** The safety of levosimendan in patients with left ventricular failure complicating an acute myocardial infarction was studied in a placebo-controlled, double-blind, parallel-group, randomised study in 504 patients within 5 days of acute myocardial infarction.13 Patients randomised to levosimendan were treated with a 6-hour i.v. infusion of levosimendan at doses ranging from 0.1-0.4 μg/kg/min. Invasive haemodynamics were not measured in this study.

**The REVIVE studies:** The REVIVE I and REVIVE II studies evaluated the efficacy of levosimendan on symptoms of heart failure with a new composite endpoint. These were randomised, double-blind, placebo-controlled, parallel-group, trials in patients with ADHF. REVIVE I (n =100) was a pilot study designed to evaluate the suitability of the endpoint;154 REVIVE II (n=600) was the phase III study.6,155 Patients randomised to levosimendan were treated with a 24-hour intravenous infusion of levosimendan at doses from 0.1-0.2 μg/kg/min. Both studies were conducted mainly in the U.S. The study design for REVIVE II is shown in Figure 7.

**The SURVIVE study:** The SURVIVE study was a double-blind, parallel-group, randomised study in 1327 patients with severe systolic heart failure comparing the effects of levosimendan with dobutamine on mortality. Patients randomised to levosimendan were treated with a 24-hour intravenous infusion of levosimendan at doses from 0.1-0.2 μg/kg/min.7 The study design is shown in Figure 8.
Dyspnoea at rest after IV diuretics, hospitalised for worsening heart failure
Ejection Fraction ≤35%

Primary assessments

1 h 6 h 24 h Day 5

Stopped infusion

*patients on concurrent IV inotropes/vasodilators received 6 µg/kg

Figure 7. REVIVE II trial design.

Acute heart failure requiring inotropic support
LVEF ≤30%

Stopped infusion

5 µg/kg/min can titrate to maximum of 40 µg/kg/min

24 h

Levosimendan

Day 180

• Must maintain for at least for the first 24 hours at a minimum of 5 µg/kg/min
• Titrate as needed from 5–40 µg/kg/min
• Taper off infusion slowly

5 µg/kg/min

≥ 24 h

Dobutamine

Day 180

Figure 8. SURVIVE trial design.
HAEMODYNAMICS

Levosimendan produces significant, dose-dependent increases in cardiac output (Figure 9), stroke volume and heart rate, and decreases in pulmonary capillary wedge pressure (Figure 9), mean blood pressure, mean pulmonary artery pressure, mean right atrial pressure and total peripheral resistance.3

The effect of levosimendan on haemodynamic variables (cardiac output, stroke volume, heart rate and pulmonary capillary wedge pressure) was clearly evident already at the end of a 5-minute bolus infusion.153 There is no sign of development of tolerance even with a prolonged infusion up to 48 hours (Figure 10 and Figure 11).9

![Graph showing change in cardiac output (CO) and pulmonary capillary wedge pressure (PCWP) 24 hours post-baseline after a 24-hour infusion of levosimendan, placebo or dobutamine in patients with stable heart failure.](image)

Figure 9. Change in cardiac output (CO) and pulmonary capillary wedge pressure (PCWP) 24 hours post-baseline after a 24-hour infusion of levosimendan, placebo or dobutamine in patients with stable heart failure.9
Figure 10. Mean pulmonary capillary wedge pressure (PCWP) in the dose escalation trial.9

- a) Levosimendan vs. placebo at 6 hours
- b) Levosimendan at 6 hours vs. levosimendan at 24 hours
- c) Levosimendan continuation vs. withdrawal at 24 hours
- d) Levosimendan continuation vs. withdrawal at 48 hours

Figure 11. Mean stroke volume in the dose escalation trial.9

- a) Levosimendan vs. placebo at 6 hours
- b) Levosimendan at 6 hours vs. levosimendan at 24 hours
- c) Levosimendan continuation vs. withdrawal at 24 hours
- d) Levosimendan continuation vs. withdrawal at 48 hours
Due to the formation of an active metabolite, the haemodynamic effects are maintained several days after stopping levosimendan infusion (Figure 12).  

Compared with dobutamine, levosimendan produces a slightly greater increase in cardiac output and a profoundly greater decrease in pulmonary capillary wedge pressure. In contrast to dobutamine, the haemodynamic effects are not attenuated with concomitant beta-blocker use (Figure 13).

**Figure 12. Differences in the AUC for changes in Doppler echocardiography derived pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) in levosimendan for 24 hours (N = 11) vs. placebo (N=11).**

**Figure 13. Effect of previous beta-blocker use on cardiac output and pulmonary capillary wedge pressure (PCWP) after a 24-hour infusion of levosimendan or dobutamine at 24 hours post-baseline (LIDO).**
It has also been shown that at 48 hours after the start of infusion, a 24-hour infusion achieves superior haemodynamic effects over a 48-hour dobutamine infusion in patients with severe ADHF on beta-blockers (Figure 14).156

Figure 14. Mean change from baseline in cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) following a 24-hour levosimendan or 48-hour dobutamine infusion in patients with ongoing beta-blocker treatment.156
SYMPTOMS

In the dose escalation and withdrawal study, dyspnoea improved in significantly more patients treated with levosimendan compared with placebo at 6 hours after starting the treatment (Figure 15).²

In the LIDO study, symptoms improved equally well in the levosimendan and dobutamine treated patients at 24 hours after start of infusion. Dyspnoea improved in 68% and 59% (p = 0.865) of the patients with baseline symptoms in the levosimendan and dobutamine groups, respectively, while fatigue improved in 63% and 47% (p = 0.155), respectively.¹

In the REVIVE II study, symptoms over the 5-day assessment period improved significantly more with levosimendan than with placebo.

![Figure 15. Patients reporting improved symptoms of heart failure 6 hours after starting levosimendan or placebo infusion.²](image_url)

![Figure 16. Improvement of dyspnoea over time in REVIVE II.¹](image_url)
It should be noted that levosimendan (or placebo) was administered on top of the standard of care and that in the placebo group, the majority of the patients also improved.

**COMPOSITE ENDPOINT**

In the REVIVE II study, the primary endpoint was a composite consisting of patients’ subjective symptom assessments (at 6 hours, 24 hours, and 5 days) and signs of worsening symptoms (including death) during the 5 days after starting a 24-hour trial drug infusion.

Improvement was observed more frequently (19% vs. 15%) and worsening less frequently (19% vs. 27%) in levosimendan treated patients compared with placebo (p = 0.015) (Figure 17).

The improvement in the composite endpoint was accompanied by a lower need for rescue medication in the levosimendan group (Figure 18 and Table 4).

![Figure 17. The primary endpoint result in REVIVE.](image1)

![Figure 18. Use of rescue medication in REVIVE.](image2)
Table 4. Drugs used as rescue medication in REVIVE. 156

<table>
<thead>
<tr>
<th>Rescue medication</th>
<th>Levosimendan (n=45)</th>
<th>Placebo* (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>23</td>
<td>44</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Milrinone</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

* Patients received standard of care

**NEUROHORMONES**

Plasma concentrations of natriuretic peptides are useful biomarkers in the diagnosis of heart failure and in the management of patients with chronic heart failure. 158 Discharge BNP values have been shown to be strong predictors of subsequent outcomes in patients admitted for ADHF. 159, 160

Several studies indicate that levosimendan produces a rapid and sustained decrease in natriuretic peptides. Lilleberg et al. found that a 24-hour levosimendan infusion induced a 40% decrease in plasma N-terminal atrial natriuretic peptide (NT-proANP) and N-terminal pro-BNP (NT-proBNP) levels and the treatment effect was estimated to last up to 16 and 12 days, respectively (Figure 19). 8

![Figure 19. Median change in N-terminal prohormone atrial natriuretic peptide (NT-proANP) levels over 14 days (N=11 in both groups) in patients with heart failure receiving levosimendan or placebo for 24 hours.](image)

In the SURVIVE study, a similar decrease in BNP was seen (Figure 20). 7 The duration of the effect could not be determined as the last time-point for measuring BNP was 5 days. In the REVIVE II study the effect was also evident until day 5 (Figure 21 and Table 5). 155
Table 5. BNP concentrations (pg/ml) at 24 hours and 5 days after the start of infusion in REVIVE II.155

<table>
<thead>
<tr>
<th>Group</th>
<th>Time after start of infusion</th>
<th>N</th>
<th>Median (IQR) BNP At baseline</th>
<th>Median (IQR) BNP At visit</th>
<th>% change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levosimendan</td>
<td>24 hours</td>
<td>256</td>
<td>651 (291, 1260)</td>
<td>294 (110, 572)</td>
<td>-54.7 (-69.6, -30.6)a</td>
</tr>
<tr>
<td></td>
<td>5 days</td>
<td>212</td>
<td>701 (304, 980)</td>
<td>312 (118, 609)</td>
<td>-52.6 (-71.3, -22.8)a</td>
</tr>
<tr>
<td>Placebo</td>
<td>24 hours</td>
<td>252</td>
<td>639 (347, 1370)</td>
<td>560 (252, 1180)</td>
<td>-18.6 (-42.2, 9.9)b</td>
</tr>
<tr>
<td></td>
<td>5 days</td>
<td>210</td>
<td>649 (347, 1340)</td>
<td>489 (237, 977)</td>
<td>-24.2 (-49.7, 11.2)b</td>
</tr>
</tbody>
</table>

*aP<0.001 (Kruskall-Wallis). b Not significant. IQR = interquartile range.
MORTALITY

In the LIDO study, mortality was followed as a secondary endpoint for 31 days. During that time, 8% of patients assigned to levosimendan died, compared with 17% assigned to dobutamine (hazard ratio 0.43, \( p=0.049 \)). The follow-up was retrospectively extended to 180 days, at which point the respective figures were 26% for levosimendan and 38% for dobutamine (hazard ratio 0.57, \( p=0.029 \)) (Figure 22).1

In the RUSSLAN study, mortality was prospectively followed for 14 days after starting the treatment. The mortality rate was 12% in levosimendan- and 20% in placebo-treated patients (\( p=0.031 \)). There was a trend for maintaining this positive effect up to 180 days in a retrospective analysis (23 vs. 31%, respectively, \( p=0.053 \)) (Figure 23).13

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Figure 22. All-cause mortality up to 180 days after starting a 24-hour infusion of levosimendan or dobutamine in patients hospitalised for ADHF (LIDO).1

Figure 23. All-cause mortality up to 180 days after a 6-hour infusion of levosimendan or placebo in patients with heart failure complicating an acute myocardial infarction (RUSSLAN).13
In the REVIVE II study, survival was numerically, but not statistically significantly, lower in the levosimendan group, with 45 (15%) deaths in the levosimendan group and 35 (12%) in the placebo group during the 90-day study period (hazard ratio 1.33, p=0.21).

In the SURVIVE study, there was no significant difference in survival between levosimendan and dobutamine. The all-cause mortality at 180 days was 26% in the levosimendan group and 28% in the dobutamine group (hazard ratio 0.91; 95% CI, 0.74-1.13; p=0.40), a net benefit of 12 fewer deaths with levosimendan.7

The pooled mortality data of the sponsored studies is presented in Figure 24. Both in the placebo- and dobutamine-controlled studies, the hazard ratio is favouring levosimendan, but the result is statistically non-significant.

| Study Events Total Events Total RR 95% CI |
|-----------------------------------------|------------------|-----------------|-----------------|-----------------|
| DOBUTAMINE CONTROLLED                   |                  |                 |                 |                 |
| Dose-finding 1 95 1 20                  |                 | 0.21 (0.01; 3.23) |
| LIDO 8 103 17 100                       |                 | 0.46 (0.21; 1.01) |
| SURVIVE 79 664 91 663                   |                 | 0.87 (0.65; 1.15) |

| Study Events Total Events Total RR 95% CI |
|-----------------------------------------|------------------|-----------------|-----------------|-----------------|
| PLACEBO CONTROLLED                       |                  |                 |                 |                 |
| Dose-finding 1 95 0 36                   |                 | 1.15 (0.05; 27.51) |
| Dose-escalation and withdrawal RUSSLAN 59 402 21 102 |     | 0.71 (0.46; 1.12) |
| REVIVE I 1 51 4 49                       |                 | 0.24 (0.03; 2.07) |
| REVIVE II 20 299 12 301                  |                 | 1.68 (0.84; 3.37) |
| Pooled analysis* 172 1807 149 1319       |                 | 0.82 (0.67; 1.01) |

* Pooled statistics calculated using the Cochran-Mante-Haenszel test, controlling for study.

Figure 24. Pooled 31-day mortality analysis from the main levosimendan studies.

Independent investigators have published their own analyses which have included – in addition to the studies above – outcome data from randomised investigator-initiated studies. The recent meta-analysis by Landoni et al. is the most comprehensive meta-analysis and statistically the most robust.16 It includes 45 clinical trials with intravenous levosimendan with a total of 5480 patients (of which 2915 received levosimendan). The studies had to be randomised and controlled, and studies
which lacked mortality data were excluded. Twenty-three studies used levosimendan in a cardiological setting, while 17 studies used it in cardiac surgery patients. The results from the studies in a cardiology setting are described below.

The 23 studies in the cardiology setting included 4100 patients (of which 2207 received levosimendan). Levosimendan significantly reduced mortality in this population compared with the control arm (20.0% vs. 25.6%, respectively; risk ratio 0.67 with 95% CI 0.51-0.86).

The demonstrated survival benefit of levosimendan is in contrast to previous results with conventional inotropes, where rather a detrimental effect has been observed.\cite{66,161} Levosimendan is thus the first inotropic agent which seems to improve survival in patients with acute heart failure.

A registry study, ALARM-HF, reviewed in-hospital treatments in eight countries.\cite{162} Unadjusted analysis showed a significantly higher in-hospital mortality rate in patients receiving intravenous inotropes (25.9%) compared to those who did not (5.2%) (p<0.0001). Propensity-based matching (n=954 pairs) confirmed that intravenous catecholamine use was associated with a 1.5-fold increase for dopamine or dobutamine use and a >2.5-fold increase for norepinephrine or epinephrine use. A propensity-based analysis was performed to compare in-hospital mortality of patients treated only with intravenous levosimendan versus those treated only with catecholamine within 24 h of therapy initiation. Propensity score matching produced 104 matched pairs and showed that the use of levosimendan resulted in a significant reduction in the risk of in-hospital mortality (hazard ratio 0.25, 95% CI: 0.07-0.85) (Figure 25).

![Figure 25. Effect of the main intravenous (i.v.) drugs administered during first 48 h in acute heart failure (AHF) patients on in-hospital mortality in the ALARM-HF study, presented by Dr E Knobel at ESICM 2009.\cite{161,163}](image-url)
Subgroup analyses from REVIVE II and SURVIVE data

Baseline blood pressure in REVIVE II
The REVIVE II data showed that levosimendan significantly decreased blood pressure compared to placebo. Accordingly, the current SPC-labelling suggests levosimendan to be used with caution in patients with low baseline systolic or diastolic blood pressure or those at risk for a hypotensive episode.

Post-hoc analyses identified systolic blood pressure <100 mmHg or diastolic blood pressure <60 mmHg at baseline as a factor increasing mortality risk. In patients with low blood pressure at baseline, mortality was 27% for levosimendan vs. 16% for placebo. Conversely, in patients with higher blood pressure at baseline (systolic ≥100 mmHg and diastolic ≥60 mmHg), mortality was 8% for levosimendan and 9% with placebo (hazard ratio 0.92, p=0.81). Of importance is the finding that the primary endpoint was still positive in the subgroup with higher baseline blood pressure (Table 6).

Table 6. Primary and secondary outcomes in REVIVE II divided by baseline blood pressure.

<table>
<thead>
<tr>
<th>Study outcome</th>
<th>All REVIVE II patients</th>
<th>Patients according to current labelling (BP &gt;100/60 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levosimendan (N=299)</td>
<td>Placebo (N=301)</td>
</tr>
<tr>
<td>Primary (N, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>58 (19.4%)</td>
<td>44 (14.6%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>183 (61.2%)</td>
<td>175 (58.1%)</td>
</tr>
<tr>
<td>Worsened</td>
<td>58 (19.4%)</td>
<td>82 (27.2%)</td>
</tr>
<tr>
<td>Secondary (N, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death during index admission</td>
<td>15 (5.0%)</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Death during follow-up</td>
<td>29 (9.7%)</td>
<td>29 (9.6%)</td>
</tr>
<tr>
<td>Total deaths</td>
<td>44 (14.7%)</td>
<td>35 (11.6%)</td>
</tr>
</tbody>
</table>

Mortality subgroup analyses in SURVIVE
The primary endpoint of the study was 180-day mortality and no significant difference between levosimendan and placebo was observed. However, there was a non-significant net benefit in favour of levosimendan seen early at the course of the study (Figure 26).
A majority (88%) of the patients had a history of ADHF. In those patients, levosimendan outperformed dobutamine. In the subgroup of patients with a history of heart failure, mortality was significantly (p=0.046) lower with levosimendan, with a net benefit of 19 fewer deaths up to 31 days.\textsuperscript{10}

In the subgroup of patients with concomitant beta-blocker, mortality was significantly lower with levosimendan (Figure 27).\textsuperscript{10}

Figure 26. Hazard ratios for all-cause mortality rates up to 31 days after levosimendan and dobutamine therapy (SURVIVE).

<table>
<thead>
<tr>
<th>Day</th>
<th>Use of (\beta)-blocker</th>
<th>Favours</th>
<th>Deaths, N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Levosimendan</td>
<td>Dobutamine</td>
<td>Levosimendan</td>
</tr>
<tr>
<td>0–5</td>
<td>Yes</td>
<td>5 (1.5)</td>
<td>17 (5.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24 (7.3)</td>
<td>23 (7.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0–14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>15 (4.5)</td>
<td>25 (7.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>44 (13.4)</td>
<td>44 (13.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0–31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>24 (7.1)</td>
<td>31 (9.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>55 (16.8)</td>
<td>60 (18.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 27. Hazard ratios for all-cause mortality rates up to 31 days after levosimendan and dobutamine therapy (SURVIVE) stratified for beta-blocker use at the start of the study.
HOSPITALISATION

One way to consider the effect of a medication on both mortality and morbidity is to assess the number of days a patient is both alive and out of hospital during the follow-up period. In the LIDO study, patients in the levosimendan group spent significantly more days alive and out of hospital than dobutamine-treated patients in a retrospective 180-day follow-up analysis (median 157 vs. 133 days for levosimendan and dobutamine, respectively; p=0.027).\textsuperscript{1} In the RUSSLAN study, the combined risk of death and worsening heart failure was significantly lower in patients treated with levosimendan than in patients treated with placebo, both during the infusion period (2 vs. 6%, respectively; p=0.033) and at 24 hours (4 vs. 9%, respectively; p=0.044).\textsuperscript{11}

In the REVIVE II study, the mean duration of the initial hospitalisation was almost 2 days shorter in the levosimendan group (7.0 days) than in the placebo group (8.9 days). Significantly more patients treated with levosimendan were released within 5 days and fewer had extended hospitalisations (p=0.008).\textsuperscript{6, 155} In line with these results, in the earlier mentioned meta-analysis by Landoni et al., the mean length of stay in hospital was 1.59 (95% CI 0.85-2.33) days shorter in levosimendan treated patients in the cardiology setting (p<0.0001).\textsuperscript{16}

In a recent single centre study\textsuperscript{164} on a population of acute heart failure patients (147 treated with levosimendan and 147 with standard of care), the mean length of hospitalisation was 12.1 and 13.6 days in the levosimendan and control groups, respectively (p<0.05). Re-hospitalisation rates were lower in the levosimendan group at 12 months (7.6 vs. 14.3%; p<0.05), and mortality rate at 1 month was 2.1% vs. 6.9%.

![Figure 28. Mean duration of initial hospitalisation divided by time spent in ICU and in general ward in REVIVE II.](image-url)
SAFETY

Adverse events

Levosimendan infusion has generally been rather well tolerated in this very ill patient population. Based on the data from the two largest studies conducted so far, the REVIVE II and SURVIVE studies, hypotension was more frequently seen with levosimendan compared with placebo, but not when compared with dobutamine (Table 7 and Table 8).

Levosimendan was also associated with a higher incidence of atrial fibrillation both compared with placebo and with dobutamine. However, conflicting results have been presented with regard to ventricular arrhythmias. In REVIVE II a higher incidence of ventricular tachycardia was observed with levosimendan compared with placebo. In SURVIVE, ventricular tachycardia was observed with similar frequency in the levosimendan and dobutamine groups. In both studies, cardiac failure as an adverse event was less frequent in levosimendan arm, although the result was statistically significant only in SURVIVE (Table 7 and Table 8).

Table 7. Incidence (%) of selected adverse events in REVIVE II. Data on file

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Levosimendan (N=292)</th>
<th>Placebo* (N=294)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>50.2</td>
<td>36.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>24.6</td>
<td>17.3</td>
<td>0.031</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>22.9</td>
<td>27.2</td>
<td>0.225</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8.5</td>
<td>2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular extrasystoles</td>
<td>7.5</td>
<td>2.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0.3</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Torsade de Pointes</td>
<td>0.3</td>
<td>0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Patients received standard of care. NS = not significant

Table 8. Incidence (%) of selected adverse events in SURVIVE.7

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Levosimendan (N=660)</th>
<th>Placebo (N=660)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>15.5</td>
<td>13.9</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>7.9</td>
<td>7.3</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>12.3</td>
<td>17.0</td>
<td>0.019</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9.1</td>
<td>6.1</td>
<td>0.048</td>
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<tr>
<td>Ventricular extrasystoles</td>
<td>6.1</td>
<td>3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1.5</td>
<td>0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Torsade de Pointes</td>
<td>0.6</td>
<td>0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant
Safety laboratory values

The changes in safety laboratory variables have been modest in levosimendan studies. Clinically insignificant decreases in haemoglobin, erythrocyte and red blood cell counts have been observed. Also decrease in potassium levels have been seen with levosimendan more often than with comparators.

Other clinical trials

CARDIAC SURGERY

Introduction

Acute cardiovascular dysfunction occurs perioperatively in more than 20% of patients undergoing cardiac surgery; yet current acute heart failure classification is not applicable to this period. Indicators of major perioperative risk include unstable coronary syndromes, decompensated heart failure, significant arrhythmias and valvular disease. Clinical risk factors include history of heart disease, compensated heart failure, cerebrovascular disease, presence of diabetes mellitus, renal insufficiency and high-risk surgery.

Preserving heart function during cardiac surgery, with aggressive measures as needed, is a major goal. The aim of monitoring is to detect and assess the mechanisms underlying perioperative cardiovascular dysfunction early. Volume status should be assessed by dynamic measurement of haemodynamic parameters including Doppler echocardiography and pulmonary artery catheter (especially in right heart dysfunction) and crystalloids and colloids should be administered to achieve euvolemma. In vasoplegia-induced hypotension, norepinephrine is the drug of choice in maintaining adequate perfusion pressure. Inotropic agents are used to treat myocardial dysfunction. The traditional choices are, either alone or in combination, low-to-moderate doses of dobutamine and epinephrine and milrinone. In heart dysfunction with suspected coronary hypoperfusion, an intra-aortic balloon pump (IABP) is recommended. A ventricular assist device should be considered before end-organ dysfunction becomes evident. Extracorporeal membrane oxygenation is a rationale solution as a bridge to recovery and/or decision making.

Optimal perioperative use of inotropes and vasopressors in cardio-surgery remains controversial, and further large multinational studies are needed. Further, the use of an IABP is associated with substantial morbidity, including artery injury, aortic perforation, femoral artery thrombosis, peripheral embolisation, femoral vein cannulation, limb ischaemia, and visceral ischaemia. Cheng et al. compared the newer left ventricular assist devices (LVADs) to the IABP in a meta-analysis in cardiogenic shock patients. Although the use of LVAD resulted
in a better haemodynamic profile compared with IABP, the LVAD use was associated with higher morbidity (increased leg ischaemia, device related bleeding), without improvement in 30-day survival.

The drawbacks related to current treatment options warrant new alternatives on the treatment armamentarium. Levosimendan, due to its cardioprotective effects, is a promising new agent in this field. The current comparative data on levosimendan with the traditional inotropic agents, suggest that the drug has potential to become a drug of choice among the agents with inotropic properties.

**Levosimendan in cardiac surgery**

Orion has conducted four studies with levosimendan in cardiac surgery. In addition, numerous investigator-initiated studies have been conducted. These studies have demonstrated that levosimendan protects the myocardium and improves tissue perfusion, while minimising the tissue damage during the cardiac surgery and reperfusion periods.

Current data suggest that levosimendan is superior to traditional inotropes (dobutamine, PDE-inhibitors) as it achieves:
- Sustained haemodynamic improvement.
- Diminished myocardial injury.
- Better outcome and less hospital days.

Vasopressors should be used concomitantly with levosimendan (as with other inodilators), but there is a greater need for vasopressors with PDE inhibitors.

The data further suggest that initiation of levosimendan should preferably be early (preoperatively) than later (postoperatively), although both options have shown positive effects.

**Orion-sponsored studies**

In one of the early studies, levosimendan was administered as an 18 µg/kg loading dose followed by 0.2 µg/kg/min for 6 hours, or 36 µg/kg followed by 0.3 µg/kg/min after cardiopulmonary bypass (CPB) in 18 patients with normal preoperative cardiac function in a placebo-controlled study. Both doses increased cardiac output and stroke volume significantly and reduced peripheral vascular resistance. Levosimendan did not affect arterial oxygenation and was well tolerated and without arrhythmogenic effects. The lower dose of levosimendan was as effective as the higher dose, but was associated with less hypotension and tachycardia.

Another placebo-controlled study with two bolus doses of levosimendan (8 and 24 µg/kg) in 23 patients after CPB showed that levosimendan transiently increased cardiac output and reduced systemic and pulmonary vascular resistances, without adversely affecting myocardial metabolism.
An open-label study using only a bolus dose of 24 µg/kg in patients after CPB showed levosimendan transiently increased cardiac output and stroke volume, and reduced systemic vascular resistance. Levosimendan did not impair isovolumic relaxation. An increase in coronary graft flow was observed.\textsuperscript{169}

Levosimendan was compared with placebo in a randomised double-blind study of 60 patients with 3-vessel coronary disease and LVEF <50%.\textsuperscript{146} Levosimendan with a bolus of 12 µg/kg was started immediately after induction of anaesthesia, followed by an infusion of 0.2 µg/kg/min for 24 hours. Primary weaning, the primary endpoint, was successful in 22 patients (73%) in the levosimendan group and 10 patients (33%) in the placebo group (p=0.002). The odds ratio for failure in primary weaning was 0.182 (95% CI, 0.060 to 0.552) (Figure 29). Four patients in the placebo group failed the second weaning and underwent IABP compared with none in the levosimendan group (p=0.112).

Levosimendan treatment was associated with lower levels of lactate, indicating a better tissue perfusion (Figure 30) and lower levels of troponin T, indicating less myocardial damage (Figure 31). Fewer inotropic agents, but more vasoconstrictors, were needed in the levosimendan-treated patients.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{weaning.png}
\caption{Weaning from cardiopulmonary bypass (CPB) in cardiac surgery patients treated with levosimendan (12 µg/kg bolus followed by a 0.2 µg/kg/min infusion for 24 hours) or placebo. Epinephrine was added at the second weaning attempt.\textsuperscript{146}}
\end{figure}
Figure 30. Cardiac index and serum lactate levels (mean ±SEM) in cardiac surgery patients treated with levosimendan (12 μg/kg bolus followed by 0.2 μg/kg/min infusion for 24 hours) or placebo.146

Figure 31. Troponin T levels up to 48 hours in cardiac surgery patients treated with levosimendan (12 μg/kg bolus followed by 0.2 μg/kg/min infusion for 24 hours) or placebo.146
Investigator-initiated studies

The most important investigator-initiated studies and the recent meta-analyses are described below.

Levosimendan was compared to milrinone in a randomised, blinded study in patients undergoing elective cardiac surgery with CPB. In this study, 30 patients with preoperative LVEF <30% were randomised to milrinone (mean 0.5 µg/kg/min for 83 hours, n=15) or to levosimendan (mean 0.1 µg/kg/min for 19 hours, n=15). Study drugs were started immediately after the release of the aortic crossclamp and all patients received additional dobutamine 5 µg/kg/min. Levosimendan showed similar haemodynamic effects to milrinone on stroke volume during the first hours after starting the surgery, immediately after the end of CPB, and significantly more pronounced effect at 12, 24 and 48 hours after arrival at the ICU (Figure 32).

Significantly higher dobutamine and norepinephrine use and significantly longer time on IABP and tracheal intubation time in the milrinone group were reported. Mortality was numerically higher in milrinone treated patients. This study demonstrated the effectiveness of levosimendan administered at a low infusion dose (0.1 µg/kg/min) without bolus.

Levin et al. performed an open-label, randomised study in cardiac surgery patients developing postoperative low cardiac output syndrome (LCOS). Levosimendan (10 µg/kg for 1 hour followed by 0.1 µg/kg/min for 24 hours), or dobutamine (5-12.5 µg/kg/min) were started to treat LCOS. Diagnosis of LCOS was made within 6 hours after opera-
tion with the following criteria: pulmonary capillary wedge pressure ≥16 mmHg, cardiac index <2.2 l/min/m², and mixed venous saturation <60%. In total, 1004 consecutive heart surgeries were evaluated. In 137 patients (13.6%) LCOS was detected and 69 patients were randomised to levosimendan and 68 to dobutamine. Levosimendan showed superior effect on cardiac index (Figure 33) and mixed venous saturation (Figure 34), less need for an additional inotropic drug (8.7 vs. 36.8%; p <0.05), need for a vasopressor (11.6 vs. 30.9%; p<0.05), or need for balloon counterpulsation (2.9 vs. 14.7%; p<0.05). More importantly, the outcome effects were in favour of levosimendan; statistically significantly fewer perioperative myocardial infarctions, acute renal failures, ventricular arrhythmias, prolonged ventilator assistance and sepsis were observed in the levosimendan group. Also mortality (8.7 vs. 25%) and length of ICU stay (66 vs. 158 h) were significantly (p<0.05) lower in levosimendan treated patients.

![Cardiac index (min/m²)](Figure 33. Mean cardiac index in cardiac surgery patients developing low cardiac output syndrome after operation.171)
Tritapepe et al. performed a randomised, double-blind, placebo-controlled study in 106 patients undergoing elective multivessel coronary artery bypass grafting (CABG). Levosimendan, administered as a bolus only (24 μg/kg over 10 minutes), or placebo was given before the initiation of CPB. Significantly higher postoperative values of mean arterial pressure, cardiac index and cardiac power index and lower systemic vascular resistance index were observed in the levosimendan group. Troponin I increases were significantly lower with levosimendan. The need for inotropic agents was greater; the time on ventilator and length of ICU stay were longer in the placebo group.

Lahtinen et al. reported a randomised, double-blind, placebo-controlled study in 200 patients assigned to undergo heart valve or combined heart valve and CABG surgery. Levosimendan was given as a 24-hour infusion started at the induction of anaesthesia with a 24 μg/kg bolus over 30 min and thereafter at a dose of 0.2 μg/kg/min. The primary outcome measure was heart failure, defined as cardiac index <2.0 l/min/m² or failure to wean from CPB necessitating inotrope administration for at least 2 hours postoperatively after CPB. Heart failure was less frequent in the levosimendan compared to the placebo group: 15% in the levosimendan and 58% in the placebo group, p<0.001. In line, a rescue inotrope, epinephrine, was needed less frequently in the levosimendan group (risk ratio 0.11; 95% CI 0.01-0.89), and IABP was utilised in one patient (1%) in the levosimendan and in nine patients (9%) in the placebo group (risk ratio 0.11; 95% CI 0.01-0.87). The cardiac enzymes

Figure 34. Mean mixed venous saturation in cardiac surgery patients developing low cardiac output syndrome after operation. Levosimendan (N=69) Placebo (N=68)

*between group difference statistically significant (expressed as mean [SD] and calculated using the Student t test).
(creatinine kinase MB isoenzyme mass) indicating myocardial damage were lower in the levosimendan group on the first postoperative day, \( p=0.011 \). The levosimendan group had more hypotension and needed norepinephrine more often; 83 vs. 52 patients, \( p<0.001 \). No difference in in-hospital and 6-month mortality was seen (12% of the patients died in both groups).

In a meta-analysis by Zangrillo et al. in 139 cardiac surgery patients from 5 randomised controlled studies, levosimendan was associated with lower troponin level increases following surgery compared to control treatments, indicating a cardioprotective effect.

In another meta-analysis by Landoni et al. in 440 patients undergoing cardiac surgery, levosimendan showed statistically significantly lower mortality than control patients (5 vs. 13%, \( p=0.003 \)). Also postoperative myocardial infarction (1 vs. 6%), atrial fibrillation (23 vs. 31%) and acute renal failure (7 vs. 24%) occurred with statistically significantly lower frequency in the levosimendan treated patients than in controls.

Maharaj and Metaxa have later performed a similar meta-analysis with higher number of patients with similar results. The meta-analysis included 729 patients from 17 studies. Levosimendan was associated with a mortality reduction after coronary revascularisation, (19/386 in the levosimendan group vs. 39/343 in the control arm) odds ratio 0.40 (95% CI 0.21-0.76, \( p=0.005 \)). Levosimendan also had a favourable effect on cardiac index (mean difference 1.63, 95% CI 1.43-1.83, \( p<0.00001 \)), length of ICU stay (mean difference -26 hours 95% CI 46-6, \( p=0.01 \)), reductions in the rate of atrial fibrillation (odds ratio 0.54,
95% CI 0.36–0.82, p=0.004, and troponin I levels (mean difference -1.59, 95% CI 1.78–1.40, p<0.00001).

The most recent and comprehensive meta-analysis by Landoni et al. on mortality with intravenous levosimendan identified 17 studies in cardiac surgery patients. These studies included 1233 patients (of which 635 received levosimendan). Levosimendan reduced mortality compared with the control arm significantly in cardiac surgery patients (5.8% in the levosimendan group versus 12.9% in the control arm; risk ratio 0.52 with 95% CI 0.35–0.76) (Figure 36).

It is noteworthy that levosimendan seems to improve survival both in patients with acute heart failure (see page 34) as well as in patients undergoing cardiac surgery. 

![Forest plot for the risk of mortality comparing levosimendan vs. control in cardiac surgery setting.](image-url)
ADVANCED CHRONIC HEART FAILURE

Introduction
Most patients with heart failure due to reduced LVEF respond favourably to pharmacological and non-pharmacological treatments and enjoy a good quality of life and enhanced survival. However, some patients do not improve or experience rapid recurrence of symptoms despite optimal medical therapy. Such patients characteristically have symptoms at rest or on minimal exertion (NYHA III-IV), including profound fatigue; cannot perform most activities of daily living; frequently have evidence of cardiac cachexia; and typically require repeated and/or prolonged hospitalisations for intensive management. These patients represent the most advanced stage of heart failure and should be considered for specialised treatment strategies, such as mechanical circulatory support, continuous intravenous positive inotropic therapy, referral for cardiac transplantation or hospice care. Before a patient is considered to have refractory heart failure, physicians should confirm the accuracy of the diagnosis, identify any contributing conditions, and ensure that all conventional medical strategies have been optimally employed.

Patients with refractory heart failure are hospitalised frequently for clinical deterioration, and during such admissions, they commonly receive infusions of both positive inotropic agents (dobutamine, dopamine, or milrinone) and vasodilator drugs in an effort to improve cardiac performance, facilitate diuresis and promote clinical stability. Despite favourable haemodynamic and symptomatic improvement in small clinical studies, concerns on the safety of intermittent or continuous inotropic therapy have been raised. Both dobutamine and milrinone increase the myocardial oxygen demand and intracellular calcium concentration, thus increasing the susceptibility for arrhythmic events and possibly excessive mortality. The theoretical advantages of levosimendan over these agents include:
• No increase in intracellular calcium concentration or myocardial oxygen demand.
• Prolonged effect via the formation of an active metabolite.
• Beneficial haemodynamic (pulmonary capillary wedge pressure and cardiac output), neurohormonal (natriuretic peptides) and symptomatic effects.
• No attenuation of the effects in beta-blocked patients.
• Beneficial effect in renal function and peripheral organ perfusion.
• Meta-analysis in decompensated heart failure has shown superior mortality effect in comparison with placebo and dobutamine.

Levosimendan in advanced chronic heart failure
A number of small-scale investigator-initiated studies in which levosimendan has been administered repeatedly to patients with advanced chronic heart failure have been reported and are shortly described.
below. The results can be summarised as follows:

• Improvements in haemodynamics, neurohormones and outcome.
• Overall data more favourable than for any other drug with inotropic properties.
• Optimum dosing scheme not established.

Nanas et al. exposed 36 consecutive patients with NYHA IV heart failure, resistant to a 24-hour continuous infusion of dobutamine, 1) to continuous infusion of dobutamine 10 µg/kg/min for at least 48 hours, followed by weekly (or more often if needed) intermittent infusions of 8 hours (n=18) or 2) after the initial 24-hour infusion of dobutamine, to a 24-hour infusion of levosimendan (0.2 µg/kg/min) followed by further biweekly 24-hour infusions at the same dose. The addition of intermittent levosimendan infusions was accompanied with a prolonged survival (45-day survival rates 6 vs. 61%; p=0.0002).

Mavrogeni et al. performed an open prospective study in 50 patients with advanced heart failure (NYHA III or IV). Half of the patients received 24-hour infusions of levosimendan (0.1 - 0.2 µg/kg/min with a 6 µg/kg loading dose) on monthly basis for 6 months in addition to standard of care and half of the patients were treated with standard of care. At the end of the study, the proportion of patients reporting improvement in symptoms of heart failure was larger in the levosimendan group than in the control group (65 vs. 20%; p<0.01). After 6 months, the levosimendan group had a significant increase in mean LVEF (28 ± 7%; p = 0.003 vs. controls 21 ± 4%). There were no significant differences in the results of 24-hour Holter-recordings between the groups (Table 9).

Two patients in the levosimendan group died during the 6-month follow-up period, compared with 8 patients in the control group (p<0.05).

Parle et al. reported their experience in 44 consecutive heart failure patients with systolic impairment, who received repeated infusions of levosimendan. The number of infusions per patient varied between 2 and 26, and the total number of levosimendan administrations was 156. The bolus dose was omitted in 65% of the administrations and the maximum maintenance infusion was 0.2 µg/kg/min in 60% of the patients. The interpretation of efficacy and safety is hampered by the absence of a control group. However, a significant drop in BNP levels and NYHA class was observed and overall the infusions were well-tolerated.

Parissis et al. performed an open, randomised, placebo-controlled trial in 25 patients with decompensated chronic heart failure. Five infusions of levosimendan, each for 24 hours (bolus 6 µg/kg/10 min, then 0.1 µg/kg/min) every 3 weeks (n=17) or placebo (n=8) were given. Levosimendan treatment was accompanied by significant reductions in cardiac end-systolic and end-diastolic dimensions and volume indices.
LVEF was significantly enhanced and left ventricular end-systolic wall stress was reduced. Significant reductions in NT-proBNP (p<0.01), high-sensitivity C-reactive protein (p<0.01) and plasma IL-6 (p=0.05) were observed in the levosimendan group. The number of patients with a positive troponin T (≥0.01 ng/ml) did not differ between the two groups at baseline, but was significantly higher in the placebo-treated group during the final evaluation (p<0.05). In the placebo group, no statistically significant improvements in any of the variables were seen.

The effects of long-term, intermittent treatment of levosimendan, dobutamine, and the combination of levosimendan with dobutamine on outcome have recently been studied in 63 patients with decompen-sated end-stage heart failure. Three groups, each of 21 patients were assigned to dobutamine 10 µg/kg/min, to levosimendan 0.3 µg/kg/min, or to dobutamine 10 µg/kg/min and concomitant levosimendan 0.2 µg/kg/min. The durations of the infusions were 6 hours, and the drugs were given weekly for 6 months. All patients were given oral amiodarone (400 mg/day). The 6-month survival was 80% in the levosimendan-only group, 48% in the dobutamine-only group and 43% in the combined group. Cardiac index was significantly increased and pulmonary capillary wedge pressure significantly decreased only in the levosimendan group.

An Orion-sponsored study in 28 patients with pulmonary hypertension of various aetiologies (including secondary to left-sided heart failure) was conducted. The patients were randomised 2:1 to levosimendan

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan</th>
<th>Controls</th>
<th>P-value*</th>
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</thead>
<tbody>
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<td>Inclusion</td>
<td>6 months</td>
</tr>
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<td>LVEF (%)</td>
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<td>10±7</td>
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</table>

*a P-value for repeated measures analysis of variance (inclusion vs. 6 months) between levosimendan and controls

FS = shortening fraction of left ventricle, EDV = end-diastolic volume of left ventricle, ESV = end-systolic volume of left ventricle, MR = mitral regurgitation, RVSP = right ventricular systolic pressure, HR = heart rate, SVB = supraventricular beats, PVB = premature ventricular beats, NSVT = nonsustained ventricular tachycardia

(p<0.01 vs. baseline). LVEF was significantly enhanced and left ventricular end-systolic wall stress was reduced. Significant reductions in NT-proBNP (p<0.01), high-sensitivity C-reactive protein (p<0.01) and plasma IL-6 (p=0.05) were observed in the levosimendan group. The number of patients with a positive troponin T (≥0.01 ng/ml) did not differ between the two groups at baseline, but was significantly higher in the placebo-treated group during the final evaluation (p<0.05). In the placebo group, no statistically significant improvements in any of the variables were seen.

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An Orion-sponsored study in 28 patients with pulmonary hypertension of various aetiologies (including secondary to left-sided heart failure) was conducted. The patients were randomised 2:1 to levosimendan
and placebo and they received in total five infusions of the study drug. The initial 24-hour levosimendan infusion (12 µg/kg bolus followed by the maintenance infusion of 0.1-0.2 µg/kg/min) produced a significant decrease in pulmonary vascular resistance (Figure 37). Thereafter, levosimendan was administered every 2 weeks as a 6-hour infusion with the infusion rate of 0.2 µg/kg/min. These repeated administrations were found to be safe and similar efficacy on pulmonary vascular resistance was still seen with the last infusion (Figure 37).

![Figure 37. Mean ±SEM change in pulmonary vascular resistance during 24-hour and 6-hour infusions of levosimendan to patients with pulmonary hypertension at day 0 and week 8, respectively.][1]

The largest study with repetitive dosing with levosimendan is an ongoing study by Altenberger et al. They have published the study design of their randomised, double-blind, placebo-controlled study in advanced chronic heart failure, the LevoRep study. Levosimendan is administered as 6-hour infusions with infusion rate 0.2 µg/kg/min every 2 weeks for 8 weeks (4 infusions per patient). In total, 120 patients will be recruited and the composite primary endpoint consists of 6-minute walk test and quality of life using Kansas QoL instrument.
RIGHT VENTRICULAR FAILURE

Introduction
Right ventricular failure is most commonly related to left ventricular heart failure. Biventricular failure has worse outcome than pure left ventricular failure. In isolated right ventricular failure there is low output syndrome in the absence of pulmonary congestion, with increased jugular venous pressure, with or without hepatic congestion, and a low left ventricular filling pressure. Right ventricular failure can be caused by myocardial ischaemia, volume overload and/or pressure overload. Theoretical advantages of levosimendan in right ventricular failure are:

• Improved right (and left) ventricular contractility via calcium sensitisation.
• Decreased right (and left) ventricular afterload via opening of KATP channels.
• Anti-ischaemic effects via mitochondrial potassium channels.
• No increase in myocardial oxygen consumption.
• No impairment of right (or left) ventricular diastolic function.
• Prolonged effect via formation of the active metabolite.

Levosimendan in right ventricular failure
A few investigator initiated studies have been performed in patients with right ventricular failure. In these studies, levosimendan has been shown to:

• Reduce the increased right ventricular afterload.
• Improve right ventricular contractility.
• Improve diastolic function of the right ventricle.

Parissis et al. showed in a placebo-controlled study in 54 patients with advanced right ventricular heart failure (NYHA III-IV, LVEF < 35%) that levosimendan (0.1-0.2 μg/kg/min for 24 hours) improved Doppler echocardiographic markers of systolic and diastolic right ventricular function.

Poelzl et al. administered open-label levosimendan (6-12 μg/kg + 0.075-0.2 μg/kg/min for 24 hours to 18 patients with acute heart failure (LVEF ≤30%, cardiac index ≤2.5 l/min/m², right atrial pressure ≥10 mmHg, pulmonary capillary wedge pressure ≥15 mmHg). Levosimendan improved right ventricular contractility but did not affect right ventricular afterload.

Russ et al. evaluated right ventricular function in 25 consecutive acute myocardial infarction patients with cardiogenic shock not responding sufficiently to conventional treatment. A 24-hour levosimendan infusion (12 μg/kg bolus + 0.1-0.2 μg/kg/min) decreased pulmonary vascular resistance and improved cardiac power index (including both right and left ventricles), indicating decreased right ventricular afterload and improved right ventricular contractility.
Morelli et al. studied 35 mechanically ventilated patients with acute respiratory distress syndrome (ARDS) related to septic shock. Patients were treated with a 24-hour infusion of levosimendan (0.2 μg/kg/min, n=18) or placebo (n=17). Levosimendan decreased the elevated pulmonary pressures (PVR and MPAP) and improved cardiac index and right ventricular ejection fraction and mixed venous oxygen saturation.

CARDIOGENIC SHOCK

Introduction
Cardiogenic shock is a rare but often fatal complication of acute coronary syndrome, typically of STEMI (ST-elevation myocardial infarction). The underlying pathophysiology is profound depression of myocardial contractility and the state can be defined as decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume.

Haemodynamic criteria for cardiogenic shock are:

• Sustained hypotension (systolic blood pressure <90 mmHg >30 minutes).
• End-organ hypoperfusion (cool extremities or a urine output of <30 ml/h).
• Reduced cardiac index (<2.2 l/min/m2).
• Elevated pulmonary capillary wedge pressure (>15 mmHg).

The standard of care consists of primary percutaneous coronary intervention for STEMI, fluid therapy, vasopressors, inotropes and IABP counterpulsation. Levosimendan may improve the contractility of the failing heart and preserve ischaemic myocardium in this setting.

Levosimendan in cardiogenic shock
The data with levosimendan in cardiogenic shock are still scarce with few investigator initiated studies. Adding levosimendan to standard therapy in cardiogenic shock appears to be safe and improves haemodynamics. The current studies are too small to draw any conclusions about effects on survival.

In a nonrandomised study in 22 patients, the haemodynamic effects of levosimendan (bolus 12 μg/kg i.v., followed by continuous infusion 0.1 μg/kg/min for 24 h) compared favourably with those seen after IABP placement in patients with cardiogenic shock. At 24 hours, the treatments induced similar haemodynamic effects, but those with levosimendan were seen earlier; after 3 hours of treatment, cardiac index and systemic vascular resistance had significantly improved in patients treated with levosimendan but not in the IABP group.

Fuhrmann et al. performed a prospective, randomised open-label study comparing levosimendan and enoximone, a PDE III inhibitor, in refractory cardiogenic shock complicating acute myocardial infarction. The
standard of care consisted of immediate revascularisation by percutaneous coronary intervention; IABP, fluid resuscitation and conventional inotropes. Thirty-two patients were randomised to receive either levosimendan (loading dose 12 µg/kg followed by 0.1 µg/kg/min infusion for 23 hours or enoximone (loading dose 0.5 µg/kg followed by 2-10 µg/kg/min infusion). Although no significant differences in invasive haemodynamic parameters were noted, survival rate at 30 days was significantly higher in the levosimendan treated group (69 vs. 37%, p=0.023). There was a lower cumulative dose of catecholamines in the levosimendan treated patients at 72 hours. Systemic inflammation as assessed by fever and leukocytosis was more common in the enoximone group, which may be due to the anti-inflammatory effects of levosimendan.

In 22 patients with cardiogenic shock levosimendan (bolus 24 µg/kg i.v., followed by continuous infusion 0.1 µg/kg/min for 24 hours or dobutamine (5 µg/kg/min for 24 hours) were compared. Levosimendan improved invasive haemodynamics (cardiac index, cardiac power index and pulmonary wedge pressure) and Doppler echocardiographic measures of systolic (LVEF) and diastolic function (isovolumic relaxation time, E/A-ratio) significantly more than dobutamine, but 3 of the patients in the levosimendan vs. 1 in the dobutamine group died during 1-year follow-up (ns). Omerovic et al. could not see any difference in the outcome of levosimendan treated and non-levosimendan treated patients for cardiogenic shock. It should be noted that this study was a non-randomised single-centre experience on 46 patients treated with levosimendan in 2004-2005 followed by 48 patients without levosimendan in 2005-2006.

**SEPTIC SHOCK**

**Introduction**
Sepsis and septic shock are among the leading causes of death in intensive care units (ICUs) with mortality up to 70%. Sepsis causes myocardial depression of both ventricles by impaired response of beta-receptors to endogenous and exogenous catecholamines and via diminished sensitivity of contractile myofilaments to calcium. Levosimendan is thus theoretically a lucrative agent to support failing heart in septic shock.

**Levosimendan in septic shock**
So far, only few investigator initiated studies with levosimendan in septic shock have been conducted. The results in these trials suggest that levosimendan might have some beneficial effects in this highly vulnerable patient population.
Morelli et al. randomly exposed 28 septic patients with persisting LF dysfunction after 48 hours of conventional treatment to receive a 24-hour infusion of either levosimendan (0.2 µg/kg/min, n=15) or dobutamine (5 µg/kg/min, n=13). In addition to improved haemodynamics, levosimendan increased gastric mucosal flow, creatinine clearance and urinary output and decreased lactate levels, without negatively affecting mean arterial pressure (Table 10).

### Table 10. Haemodynamic and laboratory parameters in septic patients with left ventricular dysfunction who received either levosimendan or dobutamine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>24 h</td>
</tr>
<tr>
<td>CI (l min⁻¹ m⁻²)</td>
<td>4.1 ± 0.2</td>
<td>4.5 ± 0.2*</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>26.2 ± 2.4</td>
<td>23.1 ± 2.4***</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>16.8 ± 1.2*</td>
<td>12.0 ± 0.6***</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76.2 ± 2.8</td>
<td>75.0 ± 3.3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37.1 ± 3.0</td>
<td>45.4 ± 8.4*</td>
</tr>
<tr>
<td>GMP (%)</td>
<td>-</td>
<td>55.3 ± 20.1***</td>
</tr>
<tr>
<td>Arterial lactate (mmol l⁻¹)</td>
<td>4.9 ± 1.2</td>
<td>3.7 ± 0.7***</td>
</tr>
<tr>
<td>Creatinine clearance (ml min⁻¹)</td>
<td>43.9 ± 12.8</td>
<td>72.1 ± 16.2***</td>
</tr>
</tbody>
</table>

*P<0.05 baseline vs. 24 h, **P<0.05 levosimendan vs. dobutamine at baseline, ***P<0.05 levosimendan vs. dobutamine after 24 h

CI = cardiac index, MPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, MAP = mean arterial pressure, LVEF = left ventricular ejection fraction, GMP = gastric mucosal perfusion

In another study by Morelli et al., 35 mechanically ventilated patients with acute respiratory distress syndrome (ARDS) related to septic shock were treated with a 24-hour infusion of levosimendan (0.2 µg/kg/min, n=18) or placebo (n=17). Levosimendan decreased the elevated pulmonary pressures (PVR and MPAP) and improved cardiac index and right ventricular ejection fraction and mixed venous oxygen saturation.

In a mechanistic study, Morelli et al. showed that levosimendan improved sublingual microcirculation in septic shock patients. The result may explain the beneficial effect of levosimendan on e.g. renal function and gastric mucosal flow as impairment in microvessel function is typically associated with end-organ dysfunction.
POSSIBLE OTHER THERAPEUTIC USES

Case reports, uncontrolled small series or small-scale comparative studies with levosimendan have been published e.g. in non-cardiac surgery, peripartum and Takozubo cardiomyopathy, paediatric patients and in patients difficult to wean from ventilator.\textsuperscript{196-208}

The results have been favourable for levosimendan, but the interpretation is hampered by e.g. the lack of a comparator, the small patient samples and therefore larger comparative studies are needed to verify the potential benefits.

Pharmacoeconomic data

Heart failure is a major public health problem because of its high prevalence and impact on mortality, morbidity, quality of life and cost of care. Prolonged duration of hospital stay and high re-hospitalisation rate lead to the fact that the management of acute heart failure is one of the most costly diagnosis-related groups in hospital systems. Finding cost-effective therapeutic options that shorten the length of stay in hospital reduce re-hospitalisation and in-hospital mortality is therefore highly desirable.

The effects of levosimendan on hospital resource use and costs, and the cost-effectiveness of levosimendan vs. standard therapies were demonstrated based on several clinical trials using well-established pharmacoeconomic modelling techniques. Findings from these analyses are summarised below.

ECONOMIC ANALYSES

The economic analyses of the LIDO, SURVIVE and REVIVE II trials are based on two major data components:

- Actual use of study medications and actual length of hospital stay during the study period, i.e. the primary “index” or initial hospital stay, when trial treatment was first administered and a 180-day follow-up period
- Actual survival by study group up to the end of follow-up of 180 days.

The second data component consists of overall survival by study group, as projected for patients alive at 180 days, based on long-term survival of similar population in the CONSENSUS and COPERNICUS trials.\textsuperscript{209, 210}
CLINICAL ENDPOINTS AND HOSPITAL RESOURCE USE

The LIDO trial was a smaller scale study including a total of 203 patients. After discharge from initial hospital period, patient mortality data and hospital days were collected retrospectively up to 180 days. In the LIDO trial, the patients stayed alive for longer, with no increase in hospital days (Figure 38). Effectively, levosimendan offered more days alive and out of hospital.

In the LIDO trial in patients with severe low-output heart failure, 11% more levosimendan patients were alive at the 6 months follow-up and therefore were also at risk of hospitalisation for longer. Despite this, there was no increase in inpatient days on levosimendan.

Based on a long-term projection of overall survival the additional cost of levosimendan per life year saved (3205 €/LYS) is relatively low when compared with other well-established cardiology interventions.

According to the prescribing information, levosimendan should be used with caution in patients with low baseline systolic or diastolic blood pressure (SPC). The economic analyses of both the SURVIVE and REVIVE II trials bring this aspect in focus.6,30 Duration of hospital stay and the associated costs have been analysed both regarding “All patients treated” and the “Per label subset” (i.e. excluding patients with a baseline systolic blood pressure <100 mmHg or diastolic blood pressure <60 mmHg).

In the SURVIVE trial, there was a slight numerical survival benefit favouring levosimendan in the overall study population. However, in the REVIVE II trial there were a few more deaths in the levosimendan group within 180 days. Neither of the above results was statistically significant. Post-hoc analyses of the clinical data indicated that the slight

Figure 38. Days alive and out of hospital after initial discharge in the LIDO trial - mean (range).29
increase in mortality was specific to patients with low baseline blood pressure. In a subset of patients excluding those with low blood pressure, survival was found to be in favour of levosimendan (ns).

**Differences in hospital length of stay during study follow-up**

Differences in index (initial) admission stay are relevant directly to the hospital initiating inotropic therapy. Depending on the study and population assessed, the mean initial hospital stay was reduced by 7-46 hours with levosimendan compared to standard of care.

In practice, this represents from one to almost six 8-hour working shifts of nursing staff. In the REVIVE II trial, the ICU stay in the levosimendan group was 8 hours, i.e. one working shift shorter (Figure 39).

![Figure 39. Duration (hours) of the initial hospital stay in SURVIVE and REVIVE II (all patients).](image)

The mean duration of total hospital stay during the 180-day follow-up was 12-22 hours shorter with levosimendan (1-3 shifts).

**Differences in cost of care during study follow-up**

To calculate the costs of the ICU/coronary care unit and overall hospital stays per group from each study the following were used:
- Country-specific cost estimates per type of hospital day (LIDO).
- Average of unit costs from UK, France and Germany (SURVIVE).
- US-specific unit costs (REVIVE II).

The cost of 600 - 700 €/vial of levosimendan used as basis for the three analyses closely corresponds with the current, actual cost of levosimendan in most European countries.

When considering all study patients, the costs of total hospital care in the levosimendan group were just slightly higher in LIDO and SURVIVE studies. In the REVIVE II trial the costs were significantly lower for the levosimendan group compared with standard of care (Table 11).
Table 11. Costs of total hospital care (all patients).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total follow-up period (all patients treated)</th>
<th>Levosimendan</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIDO, €</td>
<td>12853</td>
<td>12728</td>
<td></td>
</tr>
<tr>
<td>SURVIVE, €</td>
<td>5396</td>
<td>5275</td>
<td></td>
</tr>
<tr>
<td>REVIVE II, $</td>
<td>23073</td>
<td>26068</td>
<td></td>
</tr>
</tbody>
</table>

Data based on de Lissovoy et al. and Figure 39.

**COST-EFFECTIVENESS ANALYSIS BASED ON AN OVERALL SURVIVAL MODEL**

In the LIDO trial, the actual survival benefit of levosimendan at 6 months was 0.0265 life years gained (LYG). The overall projected LYG was approximately 0.35 translating into nearly 4.5 months. Thus, the additional cost of levosimendan was 3205 €/LYG, which is well within generally acceptable limits.

Two recent meta-analyses suggested reduction in length of stay in the hospital for patients treated with levosimendan. Maharaj and Metaxa analysed 8 studies where levosimendan was used after coronary revascularisation and showed a significant reduction of length of stay of 26 hours vs. comparator. Landoni et al. showed that length of stay was reduced in the levosimendan group (weighted mean difference = -1.31 days, p=0.007) when all the 17 studies reporting this outcome were included. The reduction in length of stay was confirmed in the cardiology setting (weighted mean difference = -1.59 days, p<0.0001) with 8 studies included.

An Italian research group analysed a study population of acute heart failure patients derived from a single centre Italian observational registry (147 treated with levosimendan and 147 with standard of care). Mean length of hospitalisation was 12.1 and 13.6 days in the levosimendan and control groups, respectively (p<0.05). Re-hospitalisation rates were lower in the levosimendan group at 12 months (7.6% vs. 14.3%; p<0.05), and mortality rate at 1 month was 2.1% vs. 6.9% in the levosimendan and control group, respectively (p<0.05). The per-capita cost of treatment with levosimendan was 79 € higher than that with standard of care during the first hospitalization, but 280 € lower when the re-hospitalisation rate was also considered.

Levosimendan is widely used for ADHF for its beneficial haemodynamic effects. In conclusion, the pharmacoeconomic studies on levosimendan indicate that this treatment is cost-effective and thus a recommendable alternative to standard of care in patients with decompensated heart failure.
Conclusions and guidance for clinical use

The clinical programme with approximately 3500 patients supports the overall conclusion that levosimendan is effective and well tolerated. The trials have been conducted in a variety of hospital settings pertinent to clinical practice, making levosimendan one of the most studied therapies for the treatment of severe ADHF. In addition, more than 500,000 patients have been treated worldwide since its first launch in 2000.

The infusion of levosimendan has very consistently been shown to enhance left ventricular performance and to decrease left ventricular filling pressure and plasma BNP concentrations without an increase in myocardial oxygen consumption. Neither age nor gender has influenced the responses to levosimendan.

Following a 24-hour infusion of levosimendan, the slowly formed and eliminated active metabolite(s) reaches pharmacologically active plasma levels, resulting in a prolonged haemodynamic effect. After a 24-hour infusion, the effects persist for at least 7 days. There have been no signs of tolerance development (which is a problem with beta-agonists) to levosimendan, even with prolonged administration.

The haemodynamic and neurohumoral improvement is associated with symptomatic benefit that is sustained and superior to placebo. Unlike with dobutamine, the effects of levosimendan are not attenuated with concomitant beta-blocker use.

In two earlier phase III studies, a significant mortality benefit with levosimendan was observed in comparison with both placebo (RUSSLAN) and dobutamine (LIDO). These favourable results were not, however, confirmed in two large-scale studies where levosimendan was compared with placebo (REVIVE II) and dobutamine (SURVIVE). Subgroup analyses from the SURVIVE study indicate that levosimendan outperforms dobutamine in beta-blocked patients and in patients with acute decompensation of an existing chronic failure. Recent independent meta-analyses on the effect of levosimendan on mortality suggest a survival benefit of levosimendan both compared to placebo and dobutamine. A trend towards a more favourable outcome effect was noted with lower levosimendan doses (≤0.1 μg/kg/min).16

Levosimendan infusion has generally been rather well tolerated in this very ill patient population. Based on the data from the two largest studies conducted so far, the REVIVE II and SURVIVE studies, hypotension was more frequently seen when compared to placebo, but not when compared to dobutamine. Levosimendan was also associated with higher incidence of atrial fibrillation both compared to placebo and dobutamine.
Table 12 summarises the haemodynamic and other clinical features of levosimendan.

**Table 12. Clinical effects of levosimendan.**

<table>
<thead>
<tr>
<th>Haemodynamic and neurohormonal effects</th>
<th>Other clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary capillary wedge pressure ↓↓↓</td>
<td>Relief of symptoms of heart failure</td>
</tr>
<tr>
<td>Cardiac output (index)</td>
<td>Effects maintained also with beta-blockers</td>
</tr>
<tr>
<td>Stroke volume ↑</td>
<td>Sustained effects due to an active metabolite</td>
</tr>
<tr>
<td>Systemic vascular resistance ↑↑↑</td>
<td>No development of tolerance</td>
</tr>
<tr>
<td>Pulmonary vascular resistance ↓↓</td>
<td>No increase in myocardial oxygen consumption</td>
</tr>
<tr>
<td>Natriuretic peptide levels ↓↓↓</td>
<td>Anti-ischemic effect</td>
</tr>
<tr>
<td></td>
<td>No impairment of diastolic function</td>
</tr>
</tbody>
</table>

↓ = decrease, ↑ = increase

The pharmacologic and pharmacodynamic properties differentiate levosimendan from other inotropes. It should be borne in mind that, in addition to contractility increasing effects, levosimendan has profound vasodilatory effects. Accordingly, the current ESC guideline recommends the use of levosimendan, not only for the ADHF patients who are treated with traditional inotropes (e.g. dobutamine), but also for those who are normally treated with vasodilators. The guideline also notes that levosimendan is an alternative for patients on beta-blocker therapy. Clinical studies have indicated that levosimendan should be given cautiously to patients with low blood pressure, especially in case of hypovolaemia. In these patients lower infusion rates without the loading dose should be considered. In line with this, the ESC guideline recommends not to use a loading dose in patients with systolic blood pressure <100 mmHg.

Based on the current knowledge, the following dosing guidance for SIMDAX® in ADHF can be given:
- Loading dose (6-12 mg/kg over 10 min) only if immediate effect needed and systolic blood pressure >100 mmHg.
- Maintenance infusion rate 0.05-0.2 mg/kg/min with individualised dosing regimen.
- Infusion duration up to 24 hours.
- Hypovolaemia to be avoided before and during the treatment (fluid resuscitation as needed; intravenous diuretics with caution).

In case of unintended overdose, pronounced haemodynamic effects would be expected; mainly hypotension and increased heart rate/arrhythmias. Hypotension should be treated with fluid resuscitation (crystalloids/colloids) and vasoconstrictors, as needed. Arrhythmias may require e.g. intravenous beta-blockade or amiodarone (if blood pressure allows). Due to the formation of the active metabolite, the follow-up may need to be prolonged, if the amount of the total dose is substantial.
The current clinical data with levosimendan have focused on ADHF and less attention has been paid on other potential uses of the compound.

Several pilot-sized studies by the sponsor and by independent investigators have, however, been performed in patients undergoing cardiac surgery. The data suggests that levosimendan may be superior to traditional inotropes (dobutamine, milrinone) as it has sustained haemodynamic effects, causes less myocardial injury, is associated with improved outcome and the length of ICU stay is shorter. If levosimendan is used in these patients, the physician should pay attention to vasodilatory effects of the drug and be prepared to intervene with intravenous fluids (crystalloids/colloids) and vasoconstrictors (e.g. norepinephrine) as needed.

Another field of on-going research is repetitive dosing of levosimendan in advanced chronic heart failure.
List of references

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Summary of Product Characteristics

Name of the Medicinal Product
Simdax 2.5 mg/ml concentrate for solution for infusion.

Qualitative and Quantitative Composition
Each ml of concentrate contains 2.5 mg of levosimendan.
One 5 ml vial contains 12.5 mg of levosimendan.
One 10 ml vial contains 25 mg of levosimendan.
For a full list of excipients, see section 6.1.

Pharmaceutical Form
Concentrate for solution for infusion.
The concentrate is a clear yellow or orange solution for dilution prior to administration.

Clinical Particulars

4.1 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 (see section 5.1.).

4.2 Posology and method of 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.

Method of administration
Simdax is to be diluted prior to administration (see section 6.6).
The infusion is for intravenous use only and can be administered by the peripheral or central route.

Posology
The dose and duration of treatment should be individualised according to the patient’s clinical condition and response.
The treatment should be initiated with a loading dose of 6-12 microgram/kg infused over 10 minutes followed by a continuous infusion of 0.1 microgram/kg/min (see section 5.1). The lower loading dose of 6 microgram/kg is recommended for patients on concomitant intravenous vasodilators or inotropes or both at the start of the infusion.
Higher loading doses within this range will produce a stronger haemodynamic response but may be associated with a transient increased incidence of adverse reactions. The response of the patient should be assessed with the loading dose or within 30 to 60 minutes of dose adjustment and as clinically indicated if the response is deemed excessive (hypotension, tachycardia), the rate of the infusion may be decreased to 0.05 microgram/kg/min or discontinued (see section 4.4). If the initial dose is tolerated and an increased haemodynamic effect is required, the rate of the infusion can be increased to 0.2 microgram/kg/min.
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 (see section 4.4).
Experience of repeated administration of Simdax is limited. Experience with concomitant use of vasoactive agents, including inotropic agents (except digoxin) is limited. In the REVIVE programme, a lower loading dose (6 micrograms/kg) was administered with baseline concomitant vasoactive agents (see sections 4.4, 4.5 and 5.1).
**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 (see section 4.4). 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) (see sections 4.3, 4.4 and 5.2).

**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 (see section 4.3, 4.4 and 5.2).

**Children**

Simdax should not be administered to children and adolescents under 18 years of age (see sections 4.4 and 5.2).

The following table provides detailed infusion rates for both the loading and maintenance infusion doses of a 0.05 mg/ml preparation of Simdax infusion:

<table>
<thead>
<tr>
<th>Patient’s weight (kg)</th>
<th>Loading dose 6 microgram/kg</th>
<th>Loading dose 12 microgram/kg</th>
<th>0.05 microgram/kg/minute</th>
<th>0.1 microgram/kg/minute</th>
<th>0.2 microgram/kg/minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>29</td>
<td>58</td>
<td>2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>35</td>
<td>72</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>60</td>
<td>43</td>
<td>86</td>
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<td>7</td>
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<tr>
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<tr>
<td>80</td>
<td>58</td>
<td>115</td>
<td>5</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>90</td>
<td>65</td>
<td>130</td>
<td>5</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>100</td>
<td>72</td>
<td>144</td>
<td>6</td>
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<td>24</td>
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<tr>
<td>110</td>
<td>79</td>
<td>158</td>
<td>7</td>
<td>13</td>
<td>26</td>
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<tr>
<td>120</td>
<td>86</td>
<td>173</td>
<td>7</td>
<td>14</td>
<td>29</td>
</tr>
</tbody>
</table>

The following table provides detailed infusion rates for both the loading and maintenance infusion doses for a 0.025 mg/ml preparation of Simdax infusion:

<table>
<thead>
<tr>
<th>Patient’s weight (kg)</th>
<th>Loading dose 6 microgram/kg</th>
<th>Loading dose 12 microgram/kg</th>
<th>0.05 microgram/kg/minute</th>
<th>0.1 microgram/kg/minute</th>
<th>0.2 microgram/kg/minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>58</td>
<td>115</td>
<td>5</td>
<td>10</td>
<td>19</td>
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<tr>
<td>50</td>
<td>72</td>
<td>144</td>
<td>6</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>60</td>
<td>86</td>
<td>173</td>
<td>7</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>70</td>
<td>101</td>
<td>202</td>
<td>8</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>80</td>
<td>115</td>
<td>230</td>
<td>10</td>
<td>19</td>
<td>38</td>
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<tr>
<td>90</td>
<td>130</td>
<td>259</td>
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<td>22</td>
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<tr>
<td>100</td>
<td>144</td>
<td>288</td>
<td>12</td>
<td>24</td>
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<td>110</td>
<td>158</td>
<td>317</td>
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<td>26</td>
<td>53</td>
</tr>
<tr>
<td>120</td>
<td>173</td>
<td>346</td>
<td>14</td>
<td>28</td>
<td>56</td>
</tr>
</tbody>
</table>

**4.3 Contraindications**

Hypersensitivity to levosimendan or to any of the excipients.

Severe hypotension and tachycardia (see sections 4.4 and 5.1). 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.

**4.5 Special warnings and special precautions for use**

An initial haemodynamic effect of levosimendan may be a decrease in systolic and dia-
stolic 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 (see sections 4.2, 4.5 and 5.1).

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 should be used cautiously in patients with mild to moderate renal impairment. Limited data on the elimination of the active metabolites are available in patients with impaired renal function. Impaired renal function may lead to increased concentrations of the active metabolites, which may result in a more pronounced and prolonged haemodynamic effect (see section 5.2).

Simdax should be used cautiously in patients with mild to moderate hepatic impairment. Impaired hepatic function may lead to prolonged exposure to the active metabolites, which may result in a more pronounced and prolonged haemodynamic effect (see section 5.2).

Simdax infusion may cause a decrease in serum potassium concentration. Thus, low serum potassium concentrations should be corrected prior to the administration of Simdax and serum potassium should be monitored during treatment. As with other medicinal products for heart failure, infusions of Simdax may be accompanied by decreases in haemoglobin and haematocrit and caution should be exercised in patients with ischaemic cardiovascular disease and concurrent anaemia.

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

Experience with repeated administration of Simdax is limited. Experience with concomitant use of vasoactive agents, including inotropic agents (except digoxin), is limited. Benefit and risk should be assessed for the individual patient.

Simdax should be used cautiously and under close ECG monitoring in patients with ongoing coronary ischaemia, long QTc interval regardless of aetiology, or when given concomitantly with medicinal products that prolong the QTc interval (see section 4.9).

The use of levosimendan in cardiogenic shock has not been studied. No information is available on the use of Simdax in the following disorders: restrictive cardiomyopathy, hypertrophic cardiomyopathy, severe mitral valve insufficiency, myocardial rupture, cardiac tamponade, and right ventricular infarction.

Simdax should not be administered to children as there is very limited experience of use in children and adolescent under 18 years of age (see section 5.2).

Limited experience is available on the use of Simdax in patients with heart failure after surgery, and in severe heart failure in patients awaiting heart transplantation.

4.5 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 (see section 4.4).

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.
4.6 Pregnancy and lactation

**Pregnancy**

There is no experience of using levosimendan in pregnant women. Animal studies have shown toxic effects on reproduction (see section 5.3). Therefore, levosimendan should be used in pregnant women only if the benefits for the mother outweigh the possible risks to the foetus.

**Lactation**

It is not known whether levosimendan is excreted in human milk. Studies in rats have shown excretion of levosimendan in breast milk, therefore women receiving levosimendan should not breastfeed.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

In placebo-controlled clinical trials for ADHF (REVIVE programme), 53% of patients experienced adverse reactions, the most frequent of which were ventricular tachycardia, hypotension, and headache.

In a dobutamine-controlled clinical trial for ADHF (SURVIVE), 18% of patients experienced adverse reactions, the most frequent of which were ventricular tachycardia, atrial fibrillation, hypotension, ventricular extrasystoles, tachycardia, and headache.

The following table describes the adverse reactions observed in 1% or greater of patients during REVIVE I, REVIVE II, SURVIVE, LIDO, RUSSLAN, 300105, and 3001024 clinical trials. If the incidence of any particular event in an individual trial was greater than that seen across the other trials, then the higher incidence is reported in the table. The events considered at least possibly related to levosimendan are displayed by system organ class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10).

<table>
<thead>
<tr>
<th>Body System</th>
<th>Frequency</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Hypokalaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very Common</td>
<td>Headache</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very Common</td>
<td>Ventricular Tachycardia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Ventricular Extrasystoles</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Myocardial Ischaemia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Extrasystoles</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very Common</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td>Investigations</td>
<td>Common</td>
<td>Haemoglobin Decreased</td>
</tr>
</tbody>
</table>
Post-marketing adverse reactions:
In post-marketing experience, ventricular fibrillation has been reported in patients being administered Simdax.

4.9 Overdose
Overdose of Simdax may induce hypotension and tachycardia. In clinical trials with Simdax, hypotension has been successfully treated with vasopressors (e.g. dopamine in patients with congestive heart failure and adrenaline in patients following cardiac surgery). Excessive decreases in cardiac filling pressures may limit the response to Simdax and can be treated with parenteral fluids. 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. In the event of an overdose of Simdax, continuous ECG monitoring, repeated determinations of serum electrolytes and invasive haemodynamic monitoring should be undertaken. 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.

Pharmacological Properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other cardiac stimulants (calcium sensitisers), ATC code: C01CX08
Pharmacodynamic effects
Levosimendan enhances the calcium sensitivity of contractile proteins by binding to cardiac troponin C in a calcium-dependent manner. Levosimendan increases the contraction force but does not impair ventricular relaxation. In addition, levsimendan opens ATP-sensitive potassium channels in vascular smooth muscle, thus inducing vasodilatation of systemic and coronary arterial resistance vessels and systemic venous capacitance vessels. Levosimendan is a selective phosphodiesterase III inhibitor in vitro. The relevance of this at therapeutic concentrations is unclear. In patients with heart failure, the positive inotropic and vasodilatory actions of levsimendan result in an increased contractile force, and a reduction in both preload and afterload, without adversely affecting diastolic function. Levosimendan activates stunned myocardium in patients after PTCA or thrombolysis.

Haemodynamic studies in healthy volunteers and in patients with stable and unstable heart failure have shown a dose-dependent effect of levsimendan given intravenously as loading dose (3 micrograms/kg to 24 micrograms/kg) and continuous infusion (0.05 to 0.2 micrograms/kg per minute). Compared with placebo, levsimendan increased cardiac output, stroke volume, ejection fraction, and heart rate and reduced systolic blood pressure, diastolic blood pressure, pulmonary capillary wedge pressure, right atrial pressure, and peripheral vascular resistance.

Simdax infusion increases coronary blood flow in patients recovering from coronary surgery and improves myocardial perfusion in patients with heart failure. These benefits are achieved without a significant increase in myocardial oxygen consumption. Treatment with Simdax infusion significantly decreases circulating levels of endothelin-1 in patients with congestive heart failure. It does not increase plasma catecholamine levels at recommended infusion rates.

Clinical Trials
Simdax has been evaluated in clinical trials involving over 2800 heart failure patients. The efficacy and safety of Simdax for the treatment of ADHF were assessed in the following randomised, double-blind, multi-national clinical trials:

REVIVE Programme

REVIVE I
In a double-blind, placebo-controlled pilot study in 100 patients with ADHF who received a 24 hour infusion of Simdax, a beneficial response as measured by the clinical composite endpoint over placebo plus standard of care was observed in the Simdax-treated patients.
REVIVE II
A double-blind, placebo-controlled pivotal study in 600 patients who were adminis-
tered a 10 minute loading dose of 6-12 microgram/kg followed by a protocol-specified
stepped titration of levosimendan to 0.05-0.2 microgram/kg/minute for up to 24 hours
that provided a benefit in clinical status in patients with ADHF who remained dyspnoeic
after intravenous diuretic therapy.
The REVIVE clinical programme was designed to compare the effectiveness of levo-
simendan plus standard-of-care to placebo plus standard-of-care in the treatment of
ADHF.
Inclusion criteria included patients hospitalised with ADHF, left ventricular ejection frac-
tion less than or equal to 35% within the previous 12 months, and dyspnoea at rest. All
baseline therapies were allowed, with the exception of intravenous milrinone. Exclusion
criteria included severe obstruction of ventricular outflow tracts, cardiogenic shock, a
systolic blood pressure of ≤ 90 mmHg or a heart rate ≥ 120 beats per minute (persistent
for at least five minutes), or a requirement for mechanical ventilation.
The results of the primary endpoint demonstrated that a greater proportion of patients
were categorised as improved with a smaller proportion of patients categorised as
worsened (p-value 0.015) as measured by a clinical composite endpoint reflecting sus-
tained benefits to clinical status over three time points: six hours, 24 hours and five days.
B-type natriuretic peptide was significantly reduced vs. placebo and standard of care at
24 hours and through five days (p-value=0.001).
The Simdax group had a slightly higher, although not statistically significant, death rate
compared with the control group at 90 days (15% vs. 12%). Post hoc analyses identified
systolic blood pressure < 100 mmHg or diastolic blood pressure < 60 mmHg at baseline
as factors increasing the mortality risk.

SURVIVE
A double-blind, double-dummy, parallel group, multicentre study comparing levosi-
mendan vs. dobutamine evaluated 180 day mortality in 1327 patients with ADHF who
required additional therapy after an inadequate response to intravenous diuretics or
vasodilators. The patient population was generally similar to the patients in the REVIVE II
study. However, patients without a previous history of heart failure were included (e.g.,
acute myocardial infarction), as were patients requiring mechanical ventilation. Approxi-
mately 90% of patients entered the trial due to dyspnoea at rest.
The results of SUVIVE did not demonstrate a statistically significant difference between
levosimendan and dobutamine in all-cause mortality at 180 days (Hazard Ratio = 0.91
(95% CI [0.74, 1.13] p-value 0.401)). However, there was a numerical advantage in mor-
tality at Day 5 (4% levosimendan vs. 6% dobutamine) for levosimendan. This advantage
persisted through the 31-day period (12% levosimendan vs. 14% dobutamine) and was
most prominent in those individuals who received baseline beta-blocker therapy. In both
treatment groups, patients with low baseline blood pressure experienced higher rates of
mortality than did those with higher baseline blood pressure.

LIDO
Levosimendan has been shown to lead to dose-dependent increases in cardiac output
and stroke volume as well as dose-dependent decrease in pulmonary capillary wedge
pressure, mean arterial pressure and total peripheral resistance.
In a double-blind multicentre trial, 203 patients with severe low output heart failure
(ejection fraction < 0.35, cardiac index <2.5 l/min/m², pulmonary capillary wedge
pressure (PCWP)>15 mmHg) and in need of inotropic support received levosimendan
(loading dose 24 microgram/kg over 10 minutes followed by a continuous infusion of
0.1-0.2 microgram/kg/min) or dobutamine (5-10 microgram/kg/min) for 24 hours. The
aetiology of heart failure was ischaemic in 47% of the patients; 45% had idiopathic
dilative cardiomyopathy. 76 % of the patients had dyspnoea at rest. Major exclusion
criteria included systolic blood pressure below 90 mmHg and heart rate above 120 beats
per minute. The primary endpoint was an increase in cardiac output by ≥ 30% and a si-
multaneous decrease of PCWP by ≥ 25% at 24 hours. This was reached in 28% of levo-
simendan treated patients compared with 15% after dobutamine treatment (p= 0.025).
Sixty-eight percent of symptomatic patients had an improvement in their dyspnoea
scores after levosimendan treatment, compared with 59% after dobutamine treatment.
Improvement in fatigue scores were 63% and 47% after levosimendan and dobutamine.

---

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Sixty-eight percent of symptomatic patients had an improvement in their dyspnoea
scores after levosimendan treatment, compared with 59% after dobutamine treatment.
Improvement in fatigue scores were 63% and 47% after levosimendan and dobutamine.
treatment, respectively. All-cause 31-day mortality was 7.8% for levosimendan and 17% for dobutamine treated patients.

RUSSLAN

In a further double-blind multicentre trial carried out primarily to evaluate safety, 504 patients with decompensated heart failure after acute myocardial infarction who were assessed to require inotropic support were treated with levosimendan or placebo for 6 hours. There were no significant differences in the incidence of hypotension and ischaemia between the treatment groups.

No adverse effect on survival up to 6 months was observed in a retrospective analysis of the LIDOC and RUSSLANtrials.

5.2 Pharmacokinetic properties

**General**
The pharmacokinetics of levosimendan are linear in the therapeutic dose range 0.05-0.2 microgram/kg/min.

**Distribution**
The volume of distribution of levosimendan (Vss) is approximately 0.2 l/kg. Levosimendan is 97-98% bound to plasma proteins, primarily to albumin. For OR-1855 and OR-1896, the mean protein binding values were 39% and 42%, respectively in patients.

**Metabolism**
Levosimendan is completely metabolised and negligible amounts of unchanged parent drug are excreted in urine and faeces. Levosimendan is primarily metabolised by conjugation to cyclic or N-acetylated cysteinylglycine and cysteine conjugates. Approximately 5 % of the dose is metabolised in the intestine by reduction to aminophenylpyridazine-none (OR-1855), which after re-absorption is metabolised by N-acetyltranseferase to the active metabolite OR-1896. The acetylation level is genetically determined. In rapid acetylators, the concentrations of the metabolite OR-1896 are slightly higher than in slow acetylators. However, this has no implication for the clinical haemodynamic effect at recommended doses.

In systemic circulation the only significant detectable metabolites following levosimendan administration are OR-1855 and OR-1896. These metabolites in vivo reach equilibrium as a result of acetylation and de-acetylation metabolic pathways, which are governed by N-acetyl transferase-2, a polymorphic enzyme. In slow acetylators, the OR-1855 metabolite predominates, while in rapid acetylators the OR-1896 metabolite predominates. The sum of exposures for the two metabolites is similar among slow and rapid acetylators, and there is no difference in the haemodynamic effects between the two groups. The prolonged haemodynamic effects (lasting up to 7-9 days after discontinuation of a 24 hour Simdax infusion) are attributed to these metabolites.

**In vitro** studies have shown that levosimendan, OR-1855 and OR-1896 do not inhibit CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at concentrations achieved by the recommended dosing. In addition levosimendan does not inhibit CYP1A1 and neither OR-1855 nor OR-1896 inhibit CYP2C9. The results of drug interaction studies in humans with warfarin, felodipine, and itraconazole confirmed that levosimendan does not inhibit CYP3A4 or CYP2C9, and metabolism of levosimendan is not affected by CYP3A inhibitors.

**Elimination and excretion**
Clearance is about 3.0 ml/min/kg and the half-life about 1 hour. 54 % of the dose is excreted in urine and 44 % in faeces. More than 95 % of the dose is excreted within one week. Negligible amounts (<0.05 % of the dose) are excreted as unchanged levosimendan in the urine. The circulating metabolites OR-1855 and OR-1896 are formed and eliminated slowly. Peak plasma concentration is reached about 2 days after termination of a levosimendan infusion. The half-lives of the metabolites are about 75-80 hours. Active metabolites of levosimendan, OR-1855 and OR-1896, undergo conjugation or renal filtration, and are excreted predominantly in urine.

**Special populations**

**Children:**
Levosimendan should not be administered to children (see section 4.4).

Limited data indicate that the pharmacokinetics of levosimendan after a single dose in
children (age 3 months to 6 years) are similar to those in adults. The pharmacokinetics of the active metabolite have not been investigated in children.

**Renal impairment:**

The pharmacokinetics of levosimendan have been studied in subjects with varying degrees of renal impairment who did not have heart failure. Exposure to levosimendan was similar in subjects with mild to moderate renal impairment and in subjects undergoing haemodialysis, while the exposure to levosimendan may be slightly lower in subjects with severe renal impairment.

Compared to healthy subjects, the unbound fraction of levosimendan appeared to be slightly increased, and AUCs of the metabolites (OR-1855 and OR-1896) were up to 170% higher in subjects with severe renal impairment and patients undergoing haemodialysis. The effects of mild and moderate renal impairment on the pharmacokinetics of OR-1855 and OR-1896 are expected to be less than those of severe renal impairment.

Levosimendan is not dialysable. While OR-1855 and OR-1896 are dialysable, the dialysis clearances are low (approximately 8-23 ml/min) and the net effect of a 4-hour dialysis session on the overall exposure to these metabolites is small.

**Hepatic impairment:**

No differences in the pharmacokinetics or protein binding of levosimendan were found in subjects with mild or moderate cirrhosis versus healthy subjects. The pharmacokinetics of levosimendan, OR-1855 and OR-1896 are similar between healthy subjects and subjects with moderate hepatic impairment (Child-Pugh Class B), with the exception that elimination half-lives of OR-1855 and OR-1896 are slightly prolonged in subjects with moderate hepatic impairment.

Population analysis has shown no effects of age, ethnic origin or gender on the pharmacokinetics of levosimendan. However, the same analysis revealed that volume of distribution and total clearance are dependent on weight.

### 5.3 Preclinical safety data

Conventional studies on general toxicity and genotoxicity revealed no special hazard for humans in short term use.

In animal studies, levosimendan was not teratogenic, but it caused a generalised reduction in the degree of ossification in rat and rabbit foetuses with anomalous development of the supraoccipital bone in the rabbit. When administered before and during early pregnancy, levosimendan reduced fertility (decreased the number of corpora lutea and implantations) and exhibited developmental toxicity (decreased pups per litter and increased the number of early resorptions and post-implantation losses) in the female rat. The effects were seen at clinical exposure levels.

In animal studies, levosimendan was excreted into maternal milk.

### Pharmaceutical Particulars

#### 6.1 List of excipients

- Povidone
- Citric Acid, anhydrous
- Ethanol, anhydrous

#### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluents except those stated in section 6.6.

#### 6.3 Shelf-life

3 years

**After dilution**

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Storage and in-use time after dilution should never exceed 24 hours.
6.4 Special precautions for storage
Store in a refrigerator (2°C-8°C) Do not freeze.
The colour of the concentrate may turn to orange during storage, but there is no loss of potency and the product may be used until the indicated expiry date if storage instructions have been followed.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and content of container
- 8 or 10 ml Type I glass vials
- Chlorobutyl or bromobutyl rubber closure with fluoropolymer coating

Pack sizes
- 1, 4, 10 vials of 5 ml
- 1, 4, 10 vials of 10 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Simdax 2.5 mg/ml concentrate for solution for infusion is intended for single use only.
As for all parenteral medicinal products, inspect the diluted solution visually for particulate matter and discolouration prior to administration.
To prepare the 0.025 mg/ml infusion, mix 5 ml of Simdax 2.5 mg/ml concentrate for solution for infusion with 500 ml of 5% glucose solution.
To prepare the 0.05 mg/ml infusion, mix 10 ml of Simdax 2.5 mg/ml concentrate for solution for infusion with 500 ml of 5% glucose solution.
The following medicinal products can be given simultaneously with Simdax in connected intravenous lines:
- Furosemide 10 mg/ml
- Digoxin 0.25 mg/ml
- Glycerol trinitrate 0.1 mg/ml

Marketing Authorisation Holder
To be completed nationally

Marketing Authorisation Number(s)
To be completed nationally

Date of First Authorisation/Renewal of the Authorisation
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