1. NAME OF THE MEDICINAL PRODUCT
Simdax 2.5 mg/ml concentrate for solution for infusion.

2. 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.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.
The concentrate is a clear yellow or orange solution for dilution prior to administra-
tion.

4. 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/minute (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/minute (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/minute.
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 0.05 microgram/kg</th>
<th>Loading dose 0.1 microgram/kg</th>
<th>Continuous infusion rate (ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>29</td>
<td>58</td>
<td>2</td>
</tr>
<tr>
<td>50</td>
<td>36</td>
<td>72</td>
<td>3</td>
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<tr>
<td>60</td>
<td>43</td>
<td>86</td>
<td>4</td>
</tr>
<tr>
<td>70</td>
<td>50</td>
<td>101</td>
<td>4</td>
</tr>
<tr>
<td>80</td>
<td>58</td>
<td>115</td>
<td>5</td>
</tr>
<tr>
<td>90</td>
<td>65</td>
<td>130</td>
<td>5</td>
</tr>
<tr>
<td>100</td>
<td>72</td>
<td>144</td>
<td>6</td>
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<tr>
<td>110</td>
<td>79</td>
<td>158</td>
<td>7</td>
</tr>
<tr>
<td>120</td>
<td>86</td>
<td>173</td>
<td>7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Patient’s weight (kg)</th>
<th>Loading dose 0.025 microgram/kg</th>
<th>Loading dose 0.05 microgram/kg</th>
<th>Continuous infusion rate (ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>58</td>
<td>115</td>
<td>3</td>
</tr>
<tr>
<td>50</td>
<td>72</td>
<td>144</td>
<td>6</td>
</tr>
<tr>
<td>60</td>
<td>86</td>
<td>173</td>
<td>8</td>
</tr>
<tr>
<td>70</td>
<td>101</td>
<td>202</td>
<td>10</td>
</tr>
<tr>
<td>80</td>
<td>115</td>
<td>230</td>
<td>10</td>
</tr>
<tr>
<td>90</td>
<td>130</td>
<td>259</td>
<td>11</td>
</tr>
<tr>
<td>100</td>
<td>144</td>
<td>288</td>
<td>11</td>
</tr>
<tr>
<td>110</td>
<td>158</td>
<td>317</td>
<td>13</td>
</tr>
<tr>
<td>120</td>
<td>173</td>
<td>346</td>
<td>14</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 (see sections 5.1).

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

4.6 Monitoring of treatment
Physicians should monitor treatment response to the patient’s condition and response (see sections 4.4, 4.5, 5.1 and 5.2).
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).

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 ofisosorbide 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.

### Table 3

<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>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>Common</td>
<td>Ventricular Extrasystoles</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Cardiac Failure</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Myocardial Ischaemia</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>Common</td>
<td>Constipation</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Vomiting</td>
</tr>
</tbody>
</table>

### Investigations
- Common
- Haemoglobin Decreased

Post-marketing adverse reactions:
In post-marketing experience, ventricular fibrillation has been reported in patients receiving 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.

5. 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, levosimendan 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 levosimendan 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 levosimendan 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, levosimendan increased cardiac output, stroke volume, ejection fraction, and heart rate and reduced systemic 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 endotoxin-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 care was observed in the Simdax-treated patients.

REVIVE II
A double-blind, placebo-controlled pivotal study in 600 patients who were administered 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 levosimendan 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 fraction 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 > 100 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 sustained 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 levosimendan 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. Approximately 90% of patients entered the trial due to dyspnoea at rest.

The results of SURVIVE 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 mortality 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 dilatative 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 simultaneous decrease of PCWP by ≥ 25% at 24 hours. This was reached in 28% of levosimendan 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 the dobutamine treatment. Improvement in dyspnoea scores was seen in 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 LIDO and RUSSLAN trials.

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 N-acetylated cysteinylglycine and cysteine conjugates. Approximately 5% of the dose is metabolised in the intestine by reduction to aminophenylpyridazinone (OR-1855), which after re-absorption is metabolised by N-acetyltransferase 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 iraconazole 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 (≤0.5 % of the dose) are excreted as unchanged levosimendan in the urine. The circulating metabolite OR-1855 and OR-1896 are formed and eliminated slowly. Peak plasma concen-
In animal studies, levosimendan was not teratogenic, but it caused a gene hazard for humans in short term use. Conventional studies on general toxicity and genotoxicity revealed no special volume of distribution and total clearance are dependent on weight. Population analysis has shown no effects of age, ethnic origin or gender on the developmental toxicity (decreased pups per litter and increased the number of early resorptions and post-implantation losses) in the female rat. The effects 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 clearance are low (approximately 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 to 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 suprascipital 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.

6. 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
- Glyceryl trinitrate 0.1 mg/ml

7. MARKETING AUTHORISATION HOLDER
To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)
To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
2000-09-22 / 2010-09-22

10. DATE OF REVISION OF THE TEXT
11 June, 2010