Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levosimendan 2.5 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 2.5 mg levosimendan.
Each vial with 5 ml of solution contains 12.5 mg levosimendan.

Excipient with known effect
This medicinal product contains 785 mg/ml ethanol (alcohol).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Clear yellow or orange solution, practically free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Levosimendan 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).

Levosimendan is indicated in adults.

4.2 Posology and method of administration

Levosimendan 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.

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 micrograms/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 micrograms/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 micrograms/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 micrograms/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 levosimendan 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 levosimendan 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.

Special populations

Elderly
No dose adjustment is required for elderly patients.

Renal impairment
Levosimendan must be used with caution in patients with mild to moderate renal impairment. Levosimendan 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
Levosimendan must be used with caution in patients with mild to moderate hepatic impairment although no dose adjustment appears necessary for these patients. Levosimendan should not be used in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

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

Method of administration

For intravenous use.
Levosimendan 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.

The following table (Table 1) provides detailed infusion rates for both the loading and maintenance infusion doses of a 0.05 mg/ml preparation of Levosimendan infusion.

Table 1 Infusion rates for 0.05 mg/ml preparation of Levosimendan infusion

Patient's weight (kg)	Loading dose is given as an infusion over 10 minutes with the infusion rate (ml/h) below		Continuous infusion rate (ml/h)		
	Loading dose 6 microgram/kg	Loading dose 12 microgram/kg	0.05 microgram/kg/minute	0.1 microgram/kg/minute	0.2 microgram/kg/minute
40	29	58	2	5	10
50	36	72	3	6	12
60	43	86	4	7	14
70	50	101	4	8	17
80	58	115	5	10	19
90	65	130	5	11	22
100	72	144	6	12	24
110	79	158	7	13	26
120	86	173	7	14	29

The following table (Table 2) provides detailed infusion rates for both the loading and maintenance infusion doses for a 0.025 mg/ml preparation of Levosimendan infusion.

Table 2 Infusion rates for 0.025 mg/ml preparation of Levosimendan infusion

Patient's weight (kg)	Loading dose is given as an infusion over 10 minutes with the infusion rate (ml/h) below		Continuous infusion rate (ml/h)		
	Loading dose 6 microgram/kg	Loading dose 12 microgram /kg	0.05 microgram/kg/ minute	0.1 microgram/kg/ minute	0.2 microgram/kg/ minute
40	58	115	5	10	19
50	72	144	6	12	24
60	86	173	7	14	29
70	101	202	8	17	34
80	115	230	10	19	38
90	130	259	11	22	43
100	144	288	12	24	48
110	158	317	13	26	53
120	173	346	14	29	58

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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).
- Severe hepatic impairment.
- History of *Torsades de Pointes*.

4.4 Special warnings and 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 may be needed.

Levosimendan 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).

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

Levosimendan 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 levosimendan 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.

Levosimendan 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 levosimendan in the following disorders: restrictive cardiomyopathy, hypertrophic cardiomyopathy, severe mitral valve insufficiency, myocardial rupture, cardiac tamponade, and right ventricular infarction.

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

Limited experience is available on the use of levosimendan in severe heart failure in patients awaiting heart transplantation.

Excipients
A dose of 20.86 mg (8.3 ml) of this medicine administered to an adult weighing 70 kg would result in exposure to 93 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 15.5 mg/100 ml.
Because this medicine is usually given slowly over 24 hours, the effects of alcohol may be reduced.

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).

Co-administration of isosorbide mononitrate and levosimendan in healthy volunteers resulted in significant potentiation of the orthostatic hypotensive response.

No pharmacokinetic interactions have been observed in a population analysis of patients receiving digoxin and levosimendan infusion. Levosimendan infusion can be used in patients receiving beta-blocking agents without loss of efficacy.

Levosimendan has shown to be an inhibitor of CYP2C8 *in vitro*, and it can therefore not be excluded that levosimendan can increase the exposure of concomitantly administered drugs that are primarily metabolised by CYP2C8. Therefore, co-administration of levosimendan with sensitive CYP2C8 substrates such as loperamide, pioglitazone, repaglinide and enzalutamide should be avoided when possible.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no experience of using levosimendan in pregnant women. Animal studies have shown reproductive toxicity (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.

Breast-feeding
Information from post marketing use in breast feeding women indicates that the active metabolites of levosimendan OR-1896 and OR-1855 are excreted in breast milk and were detected in milk for at least 14 days after the start of the 24-h levosimendan infusion. Women receiving levosimendan should not breast-feed in order to avoid potential cardiovascular adverse effects in the infant.

Fertility
Animal studies have shown toxic effects on reproduction (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

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 (Table 3) 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 to < 1/10).

Table 3 Summary of adverse reactions
SURVIVE Clinical Study, REVIVE Programme, and LIDO/RUSSLAN/300105/3001024 Clinical Studies combined

Body System	**Frequency**	**Preferred Term**
Metabolism and nutrition disorders	Common	Hypokalaemia
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness
Cardiac disorders	Very common	Ventricular tachycardia
	Common	Atrial fibrillation Tachycardia Ventricular extrasystoles Cardiac failure Myocardial ischaemia Extrasystoles
Vascular disorders	Very common	Hypotension
Gastrointestinal disorders	Common	Nausea Constipation Diarrhoea Vomiting
Investigations	Common	Haemoglobin decreased

Post-marketing adverse reactions
In post-marketing experience, ventricular fibrillation has been reported in patients being administered levosimendan.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose of levosimendan may induce hypotension and tachycardia. In clinical trials with levosimendan, hypotension has been successfully treated with vasopressors (e.g. dopamine in patients with congestive heart failure and noradrenaline in patients following cardiac surgery). Excessive decreases in cardiac filling pressures may limit the response to levosimendan and can be treated with parenteral fluids. High doses (at or above 0.4 micrograms/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 levosimendan, continuous ECG monitoring, repeated determinations of serum electrolytes and invasive haemodynamic monitoring should be undertaken. Levosimendan 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: Cardiac therapy, other cardiac stimulants, 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 (percutaneous transluminal coronary angioplasty) 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 systolic blood pressure, diastolic blood pressure, pulmonary capillary wedge pressure, right atrial pressure, and peripheral vascular resistance.

Levosimendan 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 levosimendan 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 in acute heart failure
Levosimendan has been evaluated in clinical trials involving over 2800 heart failure patients. The efficacy and safety of levosimendan 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 levosimendan, a beneficial response as measured by the clinical composite endpoint over placebo plus standard of care was observed in the levosimendan-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 micrograms/kg followed by a protocol-specified stepped titration of levosimendan to 0.05-0.2 micrograms/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 ≥ 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 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 levosimendan 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/m^2, pulmonary capillary wedge pressure (PCWP) > 15 mmHg) and in need of inotropic support received levosimendan (loading dose 24 micrograms/kg over 10 minutes followed by a continuous infusion of 0.1-0.2 micrograms/kg/min) or dobutamine (5-10 micrograms/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 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 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 LIDO and RUSSLAN trials.

Clinical trials in cardiac surgery
Two of the largest placebo-controlled studies are presented below.

LEVO-CTS
In a double-blind, placebo-controlled study in 882 patients undergoing cardiac surgery, levosimendan (0.2 µg/kg/min for 60 min, followed by 0.1 µg/kg/min for 23 h) was started at the induction of anaesthesia to patients with preoperative left ventricular ejection fraction less than or equal to 35 %. The study failed to meet the composite primary endpoints. The four-component primary end point (death through day 30, renal-replacement therapy through day 30, perioperative myocardial infarction through day 5, or use of a mechanical cardiac assist device through day 5) occurred in 24.5 % in the levosimendan group and in 24.5 % in the placebo group (adjusted OR, 1.00; 99 % CI, 0.66 to 1.54). The two-component primary end point (death through day 30 or use of a mechanical cardiac assist device through day 5) occurred in 13.1 % in the levosimendan group and in 11.4 % in the placebo group (adjusted odds ratio, 1.18; 96 % CI, 0.76 to 1.82). At 90 days, death had occurred in 4.7 % of the patients in the levosimendan group and 7.1 % of those in the placebo group (unadjusted hazard ratio, 0.64; 95 % CI, 0.37 to 1.13). Hypotension was seen in 36 % in the levosimendan group and in 33 % in the placebo group. Atrial fibrillation was seen in 38 % in the levosimendan group and in 33 % in the placebo group.

LICORN

An investigator-initiated, multi-center, randomised, placebo-controlled, double-blind clinical trial including 336 adult patients with LVEF ≤ 40 % scheduled to undergo coronary artery bypass grafting (with or without valve surgery). Levosimendan infusion 0.1 µg/kg/min, without a loading dose, was given for 24 hours after anaesthesia induction. The primary outcome was a composite of catecholamine infusion persisting beyond 48 hours, the need for circulatory mechanical assist devices in the postoperative period, or the need for renal replacement therapy. The primary end point occurred in 52 % of levosimendan patients and 61 % of placebo patients (absolute risk difference,−7 %; 95 % CI, −17 % to 3 %). The estimated 10 % risk reduction was mainly related to the need for catecholamine infusion at 48 h. Mortality at 180 days was 8 % in the levosimendan group and 10 % in the placebo group. Hypotension was seen in 57 % in the levosimendan group and in 48 % in the placebo group. Atrial fibrillation was seen in 50 % in the levosimendan group and in 40 % in the placebo group.

5.2 Pharmacokinetic properties

General
The pharmacokinetics of levosimendan are linear in the therapeutic dose range 0.05-0.2 micrograms/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.

Biotransformation
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 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-acetyltransferase-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 levosimendan infusion) are attributed to these metabolites.

In vitro studies have shown that levosimendan, OR-1855 and OR-1896 do not inhibit CYP1A2, CYP2A6, CYP2B6, 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 CYP2C8 or CYP2C9. Levosimendan has shown to be an inhibitor of CYP2C8 *in vitro* (see section 4.5).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
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 and adolescents
Levosimendan should not be administered to children and adolescents (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 risk 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K 12
Citric acid
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

18 months.

Shelf life after dilution
Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8 °C and 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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

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 after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml solution in colourless glass vial closed with bromobutyl rubber stopper, with plastic flip-off cap and aluminium seal. Vials are packed in outer cartons.

Pack sizes: 1 or 4 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

The medicinal product should be visually inspected prior to use. Only clear solutions free from particles should be used.

Once opened, the medicinal product should be used immediately. Any remaining contents should be discarded.

Levosimendan 2.5 mg/ml concentrate for solution for infusion should not be diluted into a higher concentration than 0.05 mg/ml as instructed below, otherwise opalescence and precipitation may occur.

To prepare the 0.025 mg/ml infusion, mix 5 ml of Levosimendan 2.5 mg/ml concentrate for solution for infusion with 500 ml of 5 % glucose or 0.9 % sodium chloride solution for infusion.
To prepare the 0.05 mg/ml infusion, mix 10 ml of Levosimendan 2.5 mg/ml concentrate for solution for infusion with 500 ml of 5 % glucose or 0.9 % sodium chloride solution for infusion.

As for all parenteral medicinal products, inspect the diluted solution visually for particulate matter and discolouration prior to administration.

The following medicinal products can be given simultaneously with levosimendan in connected intravenous lines:

- Furosemide 10 mg/ml
- Digoxin 0.25 mg/ml
- Glyceryl trinitrate 0.1 mg/ml.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AS Kalceks
Krustpils Iela 71e
Riga
1057
Latvia

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10 DATE OF REVISION OF THE TEXT

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