

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SIMDAX 2.5mg/mL injection concentrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

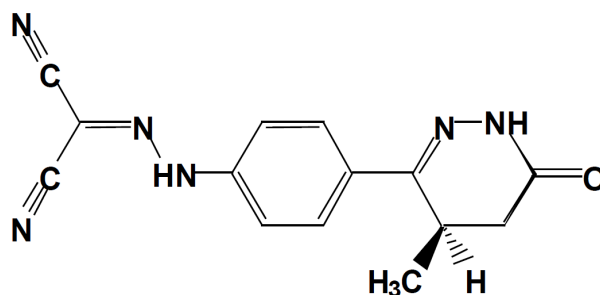
Each 1 mL contains 2.5 mg of levosimendan.

Levosimendan is an inotrope agent with a unique mode of action. It is a calcium sensitizer, which increase cardiac contractility by enhancing the sensitivity of the myocardium to calcium. As a result, levosimendan produces positive inotropic effects that are independent of beta-receptors or cyclic AMP.

It also has a vasodilator effect, by opening ATP- sensitive potassium channels in vascular smooth muscles, which results in smooth muscle relaxation.

The combination of inotropic and vasodilator actions results in an increased force of contraction with decreased preload and afterload in the myocardium.

Levosimendan is chemically named as (-)-(R)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)-phenyl]hydrazono]-propanedinitrile. It is a yellow to brownish-yellow powder with a molecular weight of 280.3, an empirical formula of C₁₄H₁₂N₆O and the following structure:



Levosimendan is a moderately lipophilic compound. Its solubility in distilled water is 0.04mg/mL, in ethanol 7.8 mg/mL, and at a pH of 8 in phosphate buffer (67 mM) 0.9mg/ML.

Excipient with known effect: contains 78.5% w/v alcohol (see *section 4.4 Special warnings and precautions for use*).

For a full list of excipients, see *section 6.1 List of excipients*.

3. PHARMACEUTICAL FORM

The concentrate is a clear, yellow or orange solution for dilution prior to administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Simdax is indicated for the short-term treatment of acutely decompensated 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, Pharmacodynamics*).

4.2 Dose and method of administration

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.

Simdax 2.5mg/mL injection concentrate is to be diluted prior to administration.

Simdax 2.5mg/mL injection concentrate is intended for single use only. As for all parenteral medicinal products, inspect the diluted solution visually for particulate matter and discoloration prior to administration.

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 expiration date if storage instructions have been followed.

The infusion is for intravenous use only and can be administered by the peripheral or central route.

Dosing Schedule

The dose and duration of treatment should be individualised according to the patient's clinical condition and response.

The treatment may be initiated with a loading dose of 6-12 µg/kg infused over 10 minutes followed by a continuous infusion of 0.1 µg/kg/min (see *section 5.1, Pharmacodynamics*). The lower loading dose of 6 µg/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 µg/kg/min or discontinued (see *section 4.4, Special warnings and precautions for use*). If the initial dose is tolerated and an increased haemodynamic effect is required, the rate of the infusion can be increased to 0.2 µg/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 5.1, Pharmacodynamics; section 4.4, Special warnings and precautions for use; section 4.5, Interaction with other medicines and other forms of interaction*).

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 µg/kg) was administered with baseline concomitant vasoactive agents.

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 <30mL/min) (see *section 5.2, Pharmacokinetics; section 4.3, Contraindications; section 4.4, Special warnings and precautions for use*).

Hepatic impairment

Simdax must be used with caution in patients with mild to moderate hepatic impairment. Simdax should not be used in patients with severe hepatic impairment (see section 5.2, *Pharmacokinetics*; section 4.3, *Contraindications*; section 4.4, *Special warnings and precautions for use*).

Children

Simdax should not be administered to children and adolescents under 18 years of age (see section 5.2, *Pharmacokinetics*; section 4.4, *Special warnings and precautions for use*).

Infusion Preparation and Schedule

To prepare the 0.05mg/mL infusion, mix 10mL of Simdax 2.5mg/mL injection concentrate with 500mL of 5% glucose (dextrose) solution.

Table 1 provides detailed infusion rates for both the loading and maintenance infusion doses of a 0.05 mg/mL preparation of Simdax infusion:

Table 1:

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 µg/kg	Loading dose 12 µg/kg	0.05 µg/kg/min	0.1 µg/kg/min	0.2 µg/kg/min
40	29	58	2	5	10
50	36	72	3	6	12
60	43	86	4	7	14
70	50	101	4	8	17
80	58	115	5	10	19
90	65	130	5	11	22
100	72	144	6	12	24
110	79	158	7	13	26
120	86	173	7	14	29

To prepare the 0.025mg/mL infusion, mix 5mL of Simdax 2.5mg/mL injection concentrate with 500mL of 5% glucose (dextrose) solution.

Table 2 provides detailed infusion rates for both the loading and maintenance infusion doses for a 0.025 mg/mL preparation of Simdax infusion:

Table 2:

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 µg/kg	Loading dose 12 µg/kg	0.05 µg/kg/min	0.1 µg/kg/min	0.2 µg/kg/min
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

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 µg/kg	Loading dose 12 µg/kg	0.05 µg/kg/min	0.1 µg/kg/min	0.2 µg/kg/min
110	158	317	13	26	53
120	173	346	14	29	58

Compatibilities

Incompatibilities with Simdax and the following medications have not been observed in connected intravenous lines:

- Frusemide 10mg/mL
- Digoxin 0.25mg/mL
- Glyceryl trinitrate 0.1mg/mL

Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluents except those stated in *Dosage and Administration – Infusion Preparation and Schedule; Dosage and Administration – Compatibilities*.

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. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°-8°C for not more than 24 hours. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Storage and in-use time after dilution should never exceed 24 hours.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

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, Special warnings and precautions for use*). In patients with mild to moderate renal or mild to moderate hepatic impairment monitoring is recommended for at least 5 days.

4.3 Contraindications

- Hypersensitivity to Simdax or to any of the excipients.
- Severe hypotension and tachycardia (see *section 5.1, Pharmacodynamics; section 4.4, Special warnings and precautions for use*).
- 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

A haemodynamic effect of Simdax, which may be more pronounced in the beginning of therapy, may be a decrease in systolic and diastolic blood pressure, therefore, Simdax 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 *section 5.1, Pharmacodynamics*; *section 4.2, Dose and method of administration – Dosing Schedule*; *section 4.5, Interaction with other medicines and other forms of interaction*).

As excessive decrease in cardiac filling pressure may limit the response to Simdax, severe hypovolaemia should be corrected prior to Simdax infusion by administration of parenteral fluids. If excessive changes in blood pressure or heart rate are observed, the rate of infusion should be reduced or the infusion discontinued.

Haemodynamically favourable effects on cardiac output and pulmonary capillary wedge pressure persist for at least 24 hours after discontinuation of (a 24-hour) infusion. The exact duration of all haemodynamic effects has not been determined, however, the effects on blood pressure generally last for 3-4 days and the effects on heart rate for 7-9 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. Interactions with the elimination of the active metabolites could lead to more pronounced and prolonged haemodynamic effects. Non-invasive monitoring for at least 3 days after the end of infusion or until the patient is clinically stable is recommended. In patients with mild to moderate renal or mild to moderate hepatic impairment monitoring is recommended for at least 5 days (see *section 5.2, Pharmacokinetics*).

Simdax should be used cautiously in patients with mild to moderate renal or mild to moderate hepatic impairment. Only limited data are available in patients with impaired renal function. Impaired hepatic or renal function may lead to increased concentrations of the metabolite, which may result in more pronounced and prolonged haemodynamic effects.

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. Consistent with current medical practice, Simdax should be used with caution when used with other intravenous vasoactive medicinal products due to a potentially increased risk of hypotension.

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, Overdose*).

The use of Simdax 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 using Simdax in children and adolescents under 18 years of age (see *section 5.2, Pharmacokinetics*).

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

This medicine contains 3925 mg of alcohol (anhydrous ethanol) in each 5 ml vial, which is equivalent to appr 98 vol %. The amount in one 5 ml vial of this medicine is equivalent to 99,2 ml beer or 41,3 ml wine. Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 decreased the number of corpora lutea, implantations and 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.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies utilizing human liver microsomes have shown that levosimendan is unlikely to cause significant drug-drug interactions with agents metabolised by cytochrome P450 (CYP) enzymes due to its apparent low affinity to various CYP-isoforms (see *section 5.2, Pharmacokinetics*).

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.

A possible interaction between the active metabolites OR-1855 and OR-1896 and other drugs with hemodynamic effects could lead to more pronounced and prolonged haemodynamic effects. The duration of this effect could be longer than the 7-9 days normally seen after a Simdax infusion.

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. Concomitant captopril treatment did not affect the pharmacokinetics or hemodynamics of Simdax.

The amount of alcohol in this medicinal product may alter the effects of other medicines. Because this medicine is usually given slowly over 24 hours, the effects of alcohol may be reduced.

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.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy

There is no experience of using Simdax in pregnant women. Animal studies have shown toxic effects on reproduction (see section 4.4, *Special warnings and precautions for use: Carcinogenesis, Mutagenesis and Impairment of Fertility*). Therefore, Simdax 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 Simdax is excreted in human milk, therefore, women receiving Simdax should not breastfeed.

4.7 Effects on ability to drive and use machines

No data available.

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 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 ($\geq 1/10$), common ($\geq 1/100, < 1/10$).

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 Common	Headache Dizziness
Cardiac disorders	Very Common Common	Ventricular Tachycardia Myocardial Ischemia Cardiac failure Atrial fibrillation Tachycardia Ventricular extrasystoles Extrasystoles
Vascular disorders	Very Common	Hypotension

Body System	Frequency	Preferred Term
Gastrointestinal disorders	Common	Diarrhoea Vomiting Nausea Constipation
Investigations	Common	Haemoglobin decreased

Post-marketing adverse reactions:

In post-marketing experience, ventricular fibrillation has been reported in patients being administered Simdax.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

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 noradrenaline 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 µg/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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 vessels and systemic venous vessels. Levosimendan has demonstrated selective phosphodiesterase III inhibitor properties in vitro. The relevance of this at therapeutic concentrations is unclear. In patients with heart failure, the positive calcium-dependent inotropic and vasodilatory actions of levosimendan result in an increased contractile force and a reduction in both preload and after load, without adversely affecting diastolic function. Levosimendan activates stunned myocardium in patients after percutaneous transluminal coronary angioplasty (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 µg/kg to 24 µg/kg) and continuous infusion (0.05 to 0.2 µg/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.

5.2 Pharmacokinetic properties

General

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

Distribution

The volume of distribution of levosimendan (V_{ss}) 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

A major part of the levosimendan dose is metabolised by conjugation to cyclic or N-acetylated cysteinylglycine and cysteine conjugates. Only about 5% of the levosimendan is metabolised in the intestine by reduction to aminophenylpyridazinone (OR-1855), which after reabsorption to the systemic circulation is metabolised in the plasma 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 hemodynamic 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 – Interactions with other medicines and other forms of interaction*). The results of drug interaction studies in humans with warfarin, felodipine and itraconazole confirmed that levosimendan does not inhibit CYP3A or CYP2C9, and metabolism of levosimendan is not affected by CYP3A inhibitors.

Elimination and excretion

Clearance is about 3.0 mL/min/kg and a 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 concentrations for OR-1855 and OR-1896 are 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 predominately in urine. Potential interactions can not be predicted.

Special Populations:

Children: Simdax should not be administered to children as there is very limited experience using Simdax in children and adolescents under 18 years of age. Limited data indicate that the pharmacokinetics of Simdax after a single dose in children (age 3 months to 6 years) are similar to those in adults. The pharmacokinetics of the active metabolites have not been investigated in children. (see *section 5.2, Pharmacokinetics; section 4.4, Special warnings and precautions for use*).

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

Compared to healthy subjects, the unbound fraction of Simdax 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.

Simdax is not dialyzable. While OR-1855 and OR-1896 are dialyzable, 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. (see *section 5.2, Pharmacokinetics; section 4.4, Special warnings and precautions for use; section 4.3, Contraindications*).

Hepatic impairment: No differences in the pharmacokinetics or protein binding of Simdax were found in subjects with mild or moderate cirrhosis versus healthy subjects. The pharmacokinetics of Simdax, 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. (see *section 5.2, Pharmacokinetics; section 4.4, Special warnings and precautions for use; section 4.3, Contraindications*).

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

5.3 Preclinical safety data

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 administered a 10 minute loading dose of 6-12 µg/kg followed by a protocol-specified stepped titration of levosimendan to 0.05-0.2 µg/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 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 μ g/kg over 10 minutes followed by a continuous infusion of 0.1-0.2 μ g/kg/min) or dobutamine (5-10 μ g/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 $\geq 30\%$ and a simultaneous decrease of PCWP by $\geq 25\%$ 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone, citric acid and anhydrous ethanol.

6.2 Incompatibilities

No data available.

6.3 Shelf life

24 months from the date of manufacture.

6.4 Special precautions for storage

Store at 2° - 8°C. Refrigerate. 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 expiration date if storage instructions have been followed.

6.5 Nature and contents of container

Levosimendan 2.5 mg/mL concentrate is available in 5 mL and 10 mL vials.

- 8 or 10 mL Type I glass vials containing 2.5mg levosimendan/mL.
- 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)

No data available.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Orion Pharma (NZ) Limited

c/o Max Health Ltd

PO Box 44452

Pt Chevalier Auckland 1246

Telephone: (09) 815 2664

9. DATE OF FIRST APPROVAL

29 March 2010

10. DATE OF REVISION OF THE TEXT

16 May 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Change sponsor details.