For the use of Cardiologist Only 8038720-805

TOROFORCE

(Levosimendan Injection)

COMPOSITION

Each vial contains :

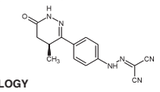
Levosimendan 2.5mg / ml

(Lyophilized)

DESCRIPTION

Levosimendan is a moderately lipophilic compound. It is Freely soluble in N,N'-Dimethyl formamide, Slightly soluble in Tetrahydrofuran and methanol, Practically insoluble in water.

Levosimendan is chemically named as [[4-[(4R-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)-phenyl]hydrazono]-propanedinitrile. It is a pale yellow to yellow powder with a molecular weight of 280.3, an empirical formula of $C_{14}H_{12}N_6O$ and the following structure



CLINICAL PHARMACOLOGY

Pharmacodynamics

Levosimendan is an inotrope agent with a unique mode of action. 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.

Pharmacokinetics

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 (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

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-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 levosimendan infusion) are attributed to these metabolites.

In vitro studies have shown that levosimendan, OR-1855 and OR-1896 do not inhibit CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 at concentrations achieved by the recommended dosing. In addition levosimendan does not inhibit CYP1A1 and neither OR-1855 nor OR-1896 inhibit CYP2C9. The results of drug interaction studies in humans with warfarin, felodipine and itraconazole confirmed that levosimendan does not inhibit 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: Levosimendan should not be administered to children as there is very limited experience using Levosimendan in children and adolescents under 18 years of age. 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 metabolites have not been investigated in children.

Renal impairment: The pharmacokinetics of Levosimendan has 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 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.

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 Pharmacokinetic Analyses: 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.

INDICATIONS

Levosimendan 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.

CONTRAINDICATIONS

Hypersensitivity to Levosimendan or to any of the excipients.

Severe hypotension and tachycardia. Significant mechanical obstructions affecting ventricular filling or outflow or both. Severe renal impairment (creatinine clearance < 30 mL/min) and severe hepatic impairment. History of Torsades de Pointes.

WARNINGS AND PRECAUTIONS

A haemodynamic effect of Levosimendan, which may be more pronounced in the beginning of therapy, 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.

As excessive decrease in cardiac filling pressure may limit the response to Levosi-mendan, severe hypovolaemia should be corrected prior to Levosimendan 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.

Levosimendan 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.

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. 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.

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.

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 using Levosimendan in children and adolescents under 18 years of age.

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

Effects on ability to drive and use machines

Not applicable.

Pregnancy and Lactation

Pregnancy (Category B3)

There is no experience of using Levosimendan in pregnant women. Animal studies have shown toxic effects on reproduction. 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, therefore, women receiving Levosimendan should not breastfeed.

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.

DOSAGE AND ADMINISTRATION

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. Levosimendan Injection 12.5mg is to be diluted prior to administration.

Levosimendan Injection 12.5mg 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 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. 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. 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 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.

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

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 <30mL/min).

Hepatic impairment

Levosimendan must be used with caution in patients with mild to moderate hepatic impairment. Levosimendan should not be used in patients with severe hepatic impairment.

Children

Levosimendan should not be administered to children and adolescents less than 18 years of age.

Infusion Preparation and Schedule

Reconstitute to 5ml with 4.1ml of sterile water for injection I.P. or 5 % dextrose injection I.P. To prepare 0.025mg/ml infusion, mix 5ml of reconstituted solution 2.5mg/ml with 500ml 5% dextrose injection

Table 1 provides detailed **infusion rates** for both the loading and maintenance infusion doses for a 0.025 mg/mL preparation of Levosimendan 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(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
110	158	317	13	26	53
120	173	346	14	29	58

To prepare the 0.05mg/mL infusion, mix 25mg of Levosimendan for Injection with 500mL of 5% glucose solution.

Table 2 provides detailed **infusion rates** for both the loading and maintenance infusion doses of a **0.05 mg/mL** preparation of Levosimendan 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(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

Compatibilities

Incompatibilities with Levosimendan 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. In patients with mild to moderate renal or mild to moderate hepatic impairment monitoring is recommended for at least 5 days.

ADVERSE 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 (≥ 1/10), common (≥ 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	Headache
	Common	Dizziness
Cardiac disorders	Very Common	Ventricular Tachycardia
	Common	Myocardial Ischemia
		Cardiac failure
		Atrial fibrillation
		Tachycardia
		Ventricular extrasystoles
		Extrasystoles
Vascular disorders	Very Common	Hypotension
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 Levosimendan.

DRUG INTERACTIONS

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.

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 Levosimendan infusion.

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. 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 Levosimendan. No pharmacokinetic or pharmacodynamic interactions were observed between Levosimendan and alcohol.

OVERDOSAGE

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 adrenaline 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 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 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.

EXPIRY DATE

Do not use later than expiry date

STORAGE

Store at 2°C-8°C. Do not freeze. Keep out of reach of children.

PRESENTATION

Levosimendan Injection 12.5mg (Lyophilized) is available in 20 ml vials.

Each ml contains 2.5 mg of levosimendan.

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist.: Mehsana, INDIA.
At : G-17/1, MIDC, Tarapur Industrial area,
Boisar, Dist.: Thane, Maharashtra.