

RESEARCH MONOGRAPH . COMPOUND PROFILE

Levosimendan

A pyridazinone-dinitrile inodilator developed at Orion Corporation as a calcium-sensitizing positive inotrope for acutely decompensated heart failure, distinguished from conventional inotropes by its ability to enhance myocardial contractility without increasing intracellular calcium concentration or myocardial oxygen consumption, and by its long-lived active metabolite OR-1896 that sustains hemodynamic effects for days beyond infusion cessation.

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ABSTRACT

Levosimendan, the (R)-enantiomer of simendan, is a pyridazinone-derivative calcium sensitizer and positive inotropic agent developed by Orion Corporation (Finland) and approved in approximately 60 countries for the short-term treatment of acutely decompensated severe chronic heart failure in situations where conventional therapy is not considered adequate. The compound exerts its principal pharmacological effects through three complementary mechanisms: calcium-dependent binding to the N-terminal domain of cardiac troponin C, which stabilizes the calcium-troponin C interaction and enhances myofilament sensitivity to calcium without increasing intracellular calcium concentration; selective inhibition of phosphodiesterase III (PDE3) in cardiac and vascular smooth muscle, which elevates cyclic adenosine monophosphate and contributes to positive inotropy and vasodilation; and opening of ATP-sensitive potassium channels (both sarcolemmal and mitochondrial) in vascular smooth muscle and cardiomyocytes, producing peripheral and coronary vasodilation and conferring cardioprotective effects against ischemia-reperfusion injury. The composite pharmacology produces the characteristic inodilator profile: simultaneous enhancement of cardiac contractility, reduction of cardiac preload and afterload, and improvement in coronary perfusion, all achieved without a proportional increase in myocardial oxygen demand.

The pharmacokinetic profile of levosimendan is distinguished by the formation of an active metabolite, OR-1896, through intestinal reduction of the parent compound to the amino-derivative OR-

1855 followed by hepatic N-acetylation. OR-1896 exhibits calcium-sensitizing and PDE3-inhibitory activity comparable to the parent compound and possesses an elimination half-life of approximately 75 to 80 hours in heart failure patients, compared to approximately 1 hour for the parent. This metabolite formation pathway introduces N-acetyltransferase 2 (NAT2) acetylator phenotype as a determinant of OR-1896 exposure, with slow acetylators demonstrating lower OR-1896 concentrations and potentially diminished sustained hemodynamic effects. The prolonged activity of OR-1896 sustains hemodynamic improvement for 7 to 9 days following cessation of a standard 24-hour intravenous infusion, a property unique among clinically available inotropic agents.

The clinical evidence base comprises six principal Phase II and Phase III randomized controlled trials (LIDO, RUSSLAN, CASINO, REVIVE-I, REVIVE-II, SURVIVE) enrolling more than 3,000 patients with acute decompensated heart failure, supplemented by extensive registry data, meta-analyses, and ongoing investigation in cardiac surgery, cardiogenic shock, septic cardiomyopathy, pulmonary hypertension, right ventricular failure, and advanced heart failure with intermittent ambulatory infusion protocols. The LIDO trial demonstrated hemodynamic superiority and a 31-day survival advantage over dobutamine. The SURVIVE trial, the largest randomized comparison (1,327 patients), demonstrated superior reduction in B-type natriuretic peptide but did not achieve the primary endpoint of reduced 180-day all-cause mortality compared to dobutamine, though subgroup analyses favored levosimendan in patients on chronic beta-blocker therapy and those with prior heart failure history. Levosimendan is marketed as Simdax (Orion Corporation) and is not approved by the United States Food and Drug Administration; the original new

drug application was withdrawn in 1999 following a request for additional trials. This monograph reviews the chemistry and stereochemistry, the triple-mechanism molecular pharmacology, the unique metabolite-driven pharmacokinetic profile, the comprehensive clinical evidence base, sourcing considerations, reconstitution and handling, drug interactions, adverse events, and a comparative assessment against five alternative inotropic agents on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Levosimendan.

Marketed name: Simdax (Orion Corporation, Finland). The product is marketed under this name in all approved jurisdictions.

Development codes: OR-1259 (Orion Corporation internal designation). The compound is the pharmacologically active (R)-enantiomer of the racemic compound simendan (OR-1259 refers specifically to the resolved levorotatory form).

Chemical Abstracts Service registry number: 141505-33-1 (free base). The compound is supplied and formulated as the free base.

International Union of Pure and Applied Chemistry name: 2-[[4-[(4R)-4-methyl-6-oxo-4,5-dihydro-1H-pyridazin-3-yl]phenyl]hydrazinylidene]propanedinitrile. The name reflects the three principal structural motifs: the pyridazinone heterocycle bearing the single chiral center, the para-substituted phenyl linker, and the hydrazono-malononitrile pharmacophore.

Other identifiers: PubChem CID 3033825; DrugBank DB00922; UNII: 349552KRHK; ChEMBL CHEMBL1075; ATC code C01CX08.

1.2 Structural class and chemistry

Levosimendan is a pyridazinone derivative bearing a hydrazono-malononitrile substituent. The structural class places it within a small family of calcium-sensitizing pyridazinones that emerged from the Orion medicinal chemistry program in the late 1980s and early 1990s. The compound is not structurally related to the catecholamine inotropes (dobutamine, dopamine), the bipyridine phosphodiesterase inhibitors (milrinone, amrinone), or the cardiac glycosides (digoxin).

Molecular formula: C₁₄H₁₂N₆O.

Molecular weight: 280.28 g/mol.

Physical properties: Orange to yellow crystalline powder. Sparingly soluble in water at neutral pH; soluble in dimethyl sulfoxide and in acidic aqueous solutions. The compound is formulated for intravenous administration as a 2.5 mg/mL concentrate in ethanol-containing vehicle (Simdax), diluted in 5% dextrose or normal saline prior to infusion.

Stereochemistry: Levosimendan contains a single chiral center at the 4-position of the pyridazinone ring and is supplied as the pure (R)-enantiomer. The (S)-enantiomer (dextrosimendan) exhibits approximately 10-fold lower potency at troponin C in functional assays and has not been developed clinically. The levorotatory designation refers to the direction of optical rotation of the (R)-configuration. Enantiomeric purity of pharmaceutical-grade material is greater than 99.5 percent by chiral high-performance liquid chromatography.

1.3 Synthesis

The published synthesis of levosimendan proceeds through a convergent strategy involving three principal components: preparation of the 4(R)-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl fragment by asymmetric synthesis or chiral resolution; preparation of the 4-hydrazinophenyl intermediate; and condensation of the assembled hydrazinophenyl-pyridazinone with a malononitrile equivalent to install the terminal dinitrile pharmacophore. The stereoselective introduction of the (R)-methyl substituent at the pyridazinone 4-position is the key step, achieved either by enantioselective catalytic methods or by classical resolution of the racemate using chiral acids. The final product is purified by recrystallization and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, chiral high-performance liquid chromatography, and X-ray powder diffraction. Industrial synthesis at Orion achieves enantiomeric purity greater than 99.5 percent and chemical purity greater than 99.0 percent [1, 2].

2. Abstract

Levosimendan is a calcium-sensitizing inodilator that enhances myocardial contractility by stabilizing the calcium-bound conformation of cardiac troponin C, inhibits phosphodiesterase III (PDE3) to elevate intracellular cyclic adenosine monophosphate, and opens ATP-sensitive potassium channels to produce peripheral and coronary vasodilation with cardioprotective properties. These three mechanisms operate simultaneously at clinically achieved plasma concentrations and together produce the inodilator effect: positive inotropy with reduced preload and afterload and without a proportional increase in myocardial oxygen consumption [3, 4].

The compound was discovered at Orion Corporation in Finland in the early 1990s, first approved in Sweden in 2000, and is now registered in approximately 60 countries for the short-term intravenous treatment of acutely decompensated heart failure. It is marketed as Simdax. The compound has not been approved by the United States Food and Drug Administration; the original new drug application was submitted in 1998 and withdrawn in 1999 after the FDA requested additional trials [5].

The pharmacokinetic profile is characterized by a short parent compound half-life of approximately 1 hour and the formation of an active metabolite, OR-1896, with an elimination half-life of 75 to 80 hours. OR-1896 is formed through intestinal reduction of levosimendan to OR-1855 followed by hepatic N-acetylation and sustains the hemodynamic effects of a single 24-hour infusion for 7 to 9 days. The N-acetyltransferase 2 (NAT2) acetylator phenotype determines OR-1896 exposure, with slow acetylators producing lower metabolite concentrations [6, 7].

Six principal randomized controlled trials constitute the clinical evidence base: LIDO (n=203, levosimendan versus dobutamine, hemodynamic and mortality superiority at 31 and 180 days) [8]; RUSSLAN (n=504, levosimendan versus placebo in acute myocardial infarction with heart failure, safety and efficacy) [9]; CASINO (n=227, levosimendan versus dobutamine versus placebo, mortality benefit) [10]; REVIVE-I (n=100) and REVIVE-II (n=600, levosimendan versus placebo, symptom improvement and reduced hospitalization duration but increased adverse events) [11]; and SURVIVE (n=1,327, levosimendan versus dobutamine, no significant differ-

ence in 180-day mortality, superior BNP reduction, subgroup benefit in beta-blocker-treated patients) [12]. Subsequent investigation has extended the evidence to cardiac surgery, cardiogenic shock, septic cardiomyopathy, right ventricular failure, pulmonary hypertension, and intermittent ambulatory infusion in advanced chronic heart failure [13, 14].

The principal adverse events are hypotension (5 to 8 percent), headache (approximately 5 percent), tachycardia, atrial fibrillation, nausea, and hypokalemia. The hypotensive effect is an extension of the vasodilatory pharmacology and is the principal dose-limiting adverse event. Levosimendan does not increase myocardial oxygen consumption or produce the proarrhythmic intracellular calcium loading observed with catecholamine inotropes and PDE3 inhibitors at high doses, conferring a theoretical and observed safety advantage in ischemic heart failure populations [15, 16].

3. Discovery and Development History

3.1 Origin

Levosimendan was discovered in the early 1990s at the Orion Corporation Research Center in Espoo, Finland, as part of a medicinal chemistry program directed at identifying calcium-sensitizing compounds that could enhance myocardial contractility without increasing intracellular calcium concentration. The program was motivated by the recognition that conventional positive inotropes (catecholamines and phosphodiesterase inhibitors) increased myocardial oxygen consumption and promoted arrhythmogenesis through elevation of intracellular calcium, properties associated with increased mortality in chronic heart failure trials (the PROMISE trial with milrinone, the Xamoterol in Severe Heart Failure Study, and other programs that established the inotrope paradox of improved hemodynamics but worsened survival) [17].

The parent compound simendan (the racemate) was identified from a series of pyridazinone derivatives screened for calcium-sensitizing activity in skinned cardiac fiber preparations. Resolution of the racemate demonstrated that the (R)-enantiomer (levosimendan) was approximately 10-fold more potent than the (S)-enantiomer at stabilizing the troponin C-calcium complex, and levosimendan was selected for clinical development [1].

3.2 Preclinical and early clinical development

Preclinical characterization in canine, porcine, and rodent heart failure models demonstrated that levosimendan increased cardiac output, reduced pulmonary capillary wedge pressure, and decreased systemic vascular resistance without increasing myocardial oxygen consumption at doses producing comparable inotropic effect to dobutamine and milrinone. The absence of increased oxygen consumption was attributed to the calcium-sensitization mechanism: enhancing myofilament responsiveness to existing calcium transients rather than increasing calcium cycling through the sarcoplasmic reticulum [3, 18].

Phase I studies in healthy volunteers characterized the pharmacokinetic profile, including the identification of the active metabolite OR-1896 and its prolonged elimination half-life. Phase II dose-ranging studies in acute heart failure patients established the intravenous infusion dose range of 0.05 to 0.2 micrograms per kilogram per minute, with or without a 6 to 24 microgram per kilogram loading dose administered over 10 minutes [6].

3.3 Registration and market authorization

Orion Corporation submitted a new drug application to the United States Food and Drug Administration in 1998. The FDA requested additional clinical trials, and Orion withdrew the application in November 1999. The compound was first approved in Sweden in 2000 and subsequently received market authorization in Finland, other European Union member states, and multiple jurisdictions in South America, Asia, and the Middle East. As of the most recent revision, levosimendan is approved in approximately 60 countries but remains unapproved in the United States and Canada [5].

3.4 Abbott and subsequent partnerships

In 2004, Orion entered a licensing agreement with Abbott Laboratories (now AbbVie) for the development and marketing of the intravenous formulation of levosimendan (Simdax) in specified territories. Abbott assumed responsibility for further clinical development, including the SURVIVE and REVIVE trials, and received extended marketing rights. The collaboration was subsequently modified as the clinical development trajectory evolved [19].

3.5 Oral formulation development

Orion has pursued development of an oral formulation of levosimendan for indications including amyotrophic lateral sclerosis (ALS, based on the diaphragmatic contractility-enhancing properties of the compound) and pulmonary hypertension associated with heart failure with preserved ejection fraction. Data on oral levosimendan in ALS were presented at the 30th International Symposium on ALS/MND in 2019. The LEVEL trial, a Phase 3 randomized double-blind placebo-controlled study of oral levosimendan in pulmonary hypertension due to heart failure with preserved ejection fraction, is ongoing as of the most recent revision [20, 21].

4. Mechanism of Action

Levosimendan is a multi-mechanism agent. Its principal molecular activities, characterized in isolated protein systems, skinned cardiac fibers, intact cardiomyocytes, isolated heart preparations, and in vivo hemodynamic models, are calcium sensitization of the cardiac myofilament, inhibition of phosphodiesterase III, and opening of ATP-sensitive potassium channels. These activities operate at functionally relevant concentrations achieved by the registered intravenous infusion and contribute differentially to the observed positive inotropic, vasodilatory, and cardioprotective effects.

4.1 Calcium sensitization of cardiac troponin C

The defining pharmacological property of levosimendan is its calcium-dependent binding to the N-terminal regulatory domain of cardiac troponin C (cTnC). Troponin C is the calcium-sensing subunit of the troponin complex (troponin C, troponin I, troponin T) that regulates the interaction between actin and myosin in the cardiac sarcomere. When intracellular calcium rises during systole, calcium binds to troponin C, triggering a conformational change that releases the troponin I inhibitory peptide from actin and permits cross-bridge formation [3, 4].

Levosimendan binds to the calcium-saturated conformation of cTnC and stabilizes the open (calcium-bound) conformation, prolonging the duration of the calcium-troponin C interaction within each cardiac cycle. The binding is calcium-dependent: levosimendan has negligible affinity for calcium-free (apo) troponin C and therefore does not impair diastolic relaxation. During diastole, when intracellular calcium falls, the troponin C-calcium complex dissociates normally, levosimendan releases, and myofilament relaxation proceeds without impairment. This calcium-dependent on-off binding is the molecular basis for the enhancement of systolic contractility without diastolic dysfunction [3, 22].

The dissociation constant (K_d) of levosimendan for calcium-saturated cTnC has been reported in the range of 0.2 to 1 micromolar, depending on assay conditions, with functional calcium sensitization observed at nanomolar to low-micromolar concentrations in skinned fiber and intact cardiomyocyte preparations [22, 23].

4.2 Phosphodiesterase III inhibition

Levosimendan is a selective inhibitor of phosphodiesterase III (PDE3), the cyclic nucleotide phosphodiesterase isoform predominantly expressed in cardiac muscle and vascular smooth muscle. Inhibition of PDE3 prevents the hydrolysis of cyclic adenosine monophosphate (cAMP), elevating intracellular cAMP concentration in cardiomyocytes and vascular smooth muscle cells [24, 25].

In cardiomyocytes, elevated cAMP activates protein kinase A (PKA), which phosphorylates L-type calcium channels (increasing calcium influx), phospholamban (relieving inhibition of the sarcoplasmic reticulum calcium ATPase and enhancing diastolic calcium reuptake), and troponin I (reducing myofilament calcium sensitivity). The net effect of PDE3 inhibition in the heart is positive inotropy and positive lusitropy (enhanced relaxation). In vascular smooth muscle, elevated cAMP produces vasodilation through PKA-mediated phosphorylation of myosin light chain kinase and potassium channel activation [25].

The relative contributions of calcium sensitization and PDE3 inhibition to the overall inotropic effect of levosimendan have been debated. Orstavik et al. (2014) reported that in failing human ventricular myocardium, PDE3 inhibition was sufficient to account for the positive inotropic effect, with calcium sensitization contributing only a minor role at clinically relevant concentrations [26]. Other investigators have argued that the calcium-sensitizing mechanism predominates at lower concentrations and that the PDE3 contribution becomes more significant at higher concentrations, producing a concentration-dependent shift in mechanism [4, 27]. The consensus position, as articulated in the Pollesello et al. (2016) expert panel, is that both mechanisms contribute to the clinical effect and that their relative contributions vary with drug concentration, tissue type, and disease state [28].

4.3 ATP-sensitive potassium channel opening

Levosimendan opens ATP-sensitive potassium channels (KATP channels) in vascular smooth muscle and in cardiac mitochondria. Two functionally distinct KATP channel populations are relevant [29, 30].

Sarcolemmal KATP channels (sarc-KATP) in vascular smooth muscle: opening of these channels produces membrane hyperpolarization and smooth muscle relaxation, contributing to peripheral and coronary vasodilation. This mechanism is the

principal driver of the afterload reduction and coronary flow enhancement observed with levosimendan, and operates independently of the PDE3-mediated vasodilatory mechanism [29].

Mitochondrial KATP channels (mito-KATP) in cardiomyocytes: opening of mito-KATP channels is a recognized mechanism of ischemic preconditioning and cardioprotection. Levosimendan activates mito-KATP channels and confers protection against ischemia-reperfusion injury in isolated heart preparations and in vivo ischemia models. The cardioprotective effect has been attributed to preservation of mitochondrial membrane potential, reduction of mitochondrial calcium overload, and attenuation of oxidative stress during reperfusion [30, 31].

4.4 Composite pharmacology

The composite pharmacology of levosimendan at the standard intravenous infusion rate of 0.1 micrograms per kilogram per minute produces plasma concentrations in the range of 30 to 100 nanograms per milliliter (approximately 100 to 350 nanomolar). At these concentrations, all three mechanisms are engaged: calcium sensitization enhances systolic contractility; PDE3 inhibition contributes to inotropy and lusitropy and to vascular smooth muscle relaxation; and KATP channel opening produces additional vasodilation and cardioprotection [4, 28].

The hemodynamic consequence is the inodilator profile: increased cardiac output (typically 25 to 40 percent increase), decreased pulmonary capillary wedge pressure (typically 25 to 35 percent decrease), decreased systemic vascular resistance (typically 15 to 25 percent decrease), and decreased mean pulmonary artery pressure, all without a proportional increase in heart rate or myocardial oxygen consumption. The absence of increased oxygen consumption distinguishes levosimendan from dobutamine (which increases oxygen consumption through beta-1-adrenergic calcium loading) and from milrinone at higher doses [8, 12].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and bioavailability

The primary clinical formulation of levosimendan is intravenous (Simdax, 2.5 mg/mL concentrate). Oral levosimendan has been characterized in Phase I and Phase II studies with bioavailability of approximately 85 percent, indicating minimal first-pass metabolism of the parent compound. Oral formulation development is ongoing for specific indications (pulmonary hypertension, ALS) [6, 20].

5.2 Distribution

Levosimendan is extensively bound to plasma proteins, predominantly albumin, with protein binding of approximately 97 to 98 percent. The volume of distribution at steady state is approximately 0.2 liters per kilogram, consistent with predominantly intravascular and well-perfused tissue distribution. The compound crosses cell membranes readily and accesses the intracellular troponin C binding site in cardiomyocytes [6, 7].

5.3 Metabolism and the active metabolite OR-1896

Levosimendan undergoes a unique metabolic pathway that produces the pharmacologically active metabolite OR-1896. The pathway proceeds in two sequential steps [6, 7, 32]:

Step 1: Intestinal reduction. Levosimendan excreted into the small intestine via biliary secretion is reduced by intestinal bacteria at the hydrazono-malononitrile group to produce the amino derivative OR-1855.

Step 2: Hepatic N-acetylation. OR-1855 undergoes N-acetylation catalyzed by N-acetyltransferase 2 (NAT2) to produce the N-acetylated metabolite OR-1896.

OR-1896 retains calcium-sensitizing and PDE3-inhibitory activity comparable to the parent compound and has an elimination half-life of approximately 75 to 80 hours in heart failure patients (compared to approximately 1 hour for the parent

compound). The prolonged half-life of OR-1896 is responsible for the sustained hemodynamic effects observed for 7 to 9 days after cessation of a standard 24-hour intravenous levosimendan infusion [7, 32].

Peak plasma concentrations of OR-1896 are reached approximately 48 to 72 hours after completion of a 24-hour infusion. The NAT2 acetylator phenotype determines OR-1896 formation rate: rapid acetylators produce higher OR-1896 concentrations, while slow acetylators (approximately 50 percent of Caucasian and 10 to 15 percent of East Asian populations) produce lower concentrations. The clinical significance of this polymorphism is that slow acetylators may experience less sustained hemodynamic improvement following infusion cessation [32, 33].

5.4 Elimination

Levosimendan undergoes extensive metabolism; less than 5 percent of the administered dose is excreted unchanged in urine. Total clearance of the parent compound is approximately 200 to 360 mL/min, consistent with hepatic and extrahepatic metabolism. The parent compound terminal half-life is approximately 1 hour. OR-1896 is eliminated renally and hepatically with the 75- to 80-hour half-life noted above [6, 7].

Renal impairment modestly affects OR-1896 elimination; dose adjustment is generally not required in mild to moderate renal impairment but the compound is listed as contraindicated in severe renal impairment in some prescribing labels. Hepatic impairment can prolong both parent compound and metabolite elimination [6].

5.5 Routes and dosing

The standard clinical route is intravenous infusion. The registered dosing protocol consists of an optional loading dose of 6 to 12 micrograms per kilogram administered over 10 minutes, followed by a continuous infusion of 0.05 to 0.2 micrograms per kilogram per minute for up to 24 hours. The loading dose produces rapid hemodynamic improvement but is associated with a higher incidence of hypotension and is omitted in many clinical protocols, particularly in patients with low baseline blood pressure [15, 34].

Steady-state plasma concentrations of the parent compound are achieved within approximately 4 hours of continuous infusion at a fixed rate. Dose titration within the infusion range is guided by hemodynamic response and tolerability [6].

5.6 Special populations

Pediatric pharmacokinetics have been characterized in multiple studies. Levosimendan has been used off-label in pediatric cardiac surgery and pediatric heart failure at weight-adjusted doses (typically 0.1 to 0.2 micrograms per kilogram per minute infusion). Dedicated pediatric pharmacokinetic studies have demonstrated similar volume of distribution and clearance parameters to adults on a weight-adjusted basis [35].

Geriatric pharmacokinetics do not require dose adjustment beyond that dictated by renal and hepatic function. Pregnancy data are limited; the compound has not been systematically studied in pregnant patients and is not recommended during pregnancy or lactation [6].

6. Preclinical Pharmacology

6.1 In vitro cardiac preparations

In skinned cardiac fiber preparations from human failing and non-failing myocardium, levosimendan shifts the force-pCa relationship to the left (toward lower calcium concentrations), indicating enhanced calcium sensitivity of the contractile apparatus. The shift is concentration-dependent in the range of 0.1 to 10 micromolar and is reversed by removal of the drug, consistent with reversible troponin C binding [3, 22].

In intact isolated cardiomyocytes, levosimendan increases the amplitude of cell shortening without increasing the amplitude of the intracellular calcium transient (measured by Fura-2 or Indo-1 fluorescence), confirming that the inotropic mechanism operates at the myofilament level rather than through enhanced calcium cycling [3].

6.2 In vivo hemodynamic models

In canine and porcine heart failure models induced by rapid ventricular pacing or coronary microembolization, levosimendan produces dose-dependent increases in cardiac output, decreases in pulmonary capillary wedge pressure, and decreases in systemic vascular resistance. Myocardial oxygen consumption is not increased at doses producing equivalent inotropic effect to dobutamine, a finding replicated across species and heart failure models [18, 36].

6.3 Ischemia-reperfusion protection

In isolated perfused rat and rabbit hearts subjected to global ischemia and reperfusion, levosimendan pretreatment reduces infarct size, improves post-ischemic functional recovery, and preserves mitochondrial membrane potential. The cardioprotective effect is attenuated by the mito-KATP channel blocker 5-hydroxydecanoate, supporting the mito-KATP mechanism [30, 31].

6.4 Vascular effects

In isolated vascular smooth muscle preparations (aortic rings, pulmonary artery rings, mesenteric arteries), levosimendan produces concentration-dependent relaxation that is partially attenuated by KATP channel blockers (glibenclamide) and partially attenuated by PDE3 inhibition, consistent with dual vasorelaxant mechanisms. The pulmonary vasodilatory effect is relevant to the clinical application in pulmonary hypertension and right ventricular failure [29, 37].

6.5 Anti-inflammatory and organ-protective effects

Preclinical studies have demonstrated that levosimendan possesses anti-inflammatory properties, including reduction of proinflammatory cytokine release (tumor necrosis factor alpha, interleukin-6, interleukin-1 beta) in lipopolysaccharide-stimulated monocytes and in sepsis models. These effects are attributed to the cAMP-elevating (PDE3-inhibitory) mechanism and may contribute to the multiorgan protective effects observed in critical illness settings [38].

7. Clinical Evidence Base

7.1 LIDO trial

The Levosimendan Infusion versus Dobutamine (LIDO) trial was a multicenter, randomized, double-blind study comparing levosimendan (24-microgram/kg loading dose followed by 0.1 microgram/kg/min infusion for 24 hours) with dobutamine (5 micrograms/kg/min infusion for 24 hours) in 203 patients with severe low-output heart failure (left ventricular ejection fraction less than 35 percent and cardiac index less than 2.5 L/min/m²) [8]. The primary endpoint was hemodynamic improvement, defined as an increase in cardiac output of at least 30 percent and a decrease in pulmonary capillary wedge pressure of at least 25 percent at 24 hours. Levosimendan was superior to dobutamine on the primary endpoint (28 percent versus 15 percent responder rate, $p=0.022$). Secondary mortality analysis demonstrated 31-day mortality of 8 percent with levosimendan versus 17 percent with dobutamine ($p=0.049$), and 180-day mortality of 26 percent versus 38 percent ($p=0.029$) [8].

7.2 RUSSLAN trial

The Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure due to an Acute Myocardial Infarct (RUSSLAN) was a multicenter, randomized, double-blind, placebo-controlled study in 504 patients with acute myocardial infarction complicated by left ventricular failure [9]. Four doses of levosimendan (0.1 to 0.4 microgram/kg/min for 6 hours) were compared with placebo. The primary endpoint was the incidence of hypotension or ischemia. Levosimendan was well tolerated at all doses, and the combined risk of death and worsening heart failure was significantly lower in levosimendan-treated patients during infusion (2 percent versus 6 percent) and at 24 hours (4 percent versus 9 percent). A 14-day mortality benefit was observed (11.7 percent versus 19.6 percent, $p=0.031$) [9].

7.3 CASINO trial

The Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure (CASINO) study was a three-arm randomized trial comparing levosimendan, dobutamine, and placebo in 227 patients with advanced heart failure. The study was terminated early by the data safety monitoring board due to an excess mortality signal in the dobutamine arm. Levosimendan demonstrated a mortality benefit at 1, 6, and 12 months compared to both dobutamine and placebo [10].

7.4 REVIVE trials

REVIVE-I (n=100) was a proof-of-concept trial that established the feasibility of a composite clinical endpoint for levosimendan in acute heart failure. REVIVE-II (n=600) was a multicenter, randomized, double-blind, placebo-controlled study in patients with acutely decompensated heart failure receiving standard therapy [11]. Levosimendan (6 to 12 microgram/kg loading dose followed by 0.1 to 0.2 microgram/kg/min for 24 hours) improved the primary composite endpoint (patient self-assessment at 6, 24, and 120 hours) compared to placebo. Levosimendan reduced the average length of initial hospitalization by 1.9 days (7.0 versus 8.9 days). However, levosimendan-treated patients experienced more adverse events, including hypotension, ventricular tachycardia, and atrial fibrillation, and a non-significant trend toward higher 90-day mortality (15.1 percent versus 11.6 percent) that influenced regulatory interpretation [11].

7.5 SURVIVE trial

The Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial was the largest randomized comparison of levosimendan versus dobutamine, enrolling 1,327 patients with acute decompensated heart failure requiring inotropic support [12]. The primary endpoint was 180-day all-cause mortality. Levosimendan did not significantly reduce 180-day mortality compared to dobutamine (26.1 percent versus 28.0 percent, hazard ratio 0.91, 95 percent confidence interval 0.74 to 1.13, p=0.40). Levosimendan produced significantly greater reduction in B-type natriuretic peptide (BNP) at 24 hours and at 5 days. Subgroup analyses demonstrated that levosimendan was superior to dobutamine in patients with a history of chronic heart failure and in those receiving chronic beta-blocker therapy. The SURVIVE trial was the principal basis for the FDA's position that the existing evidence did not support a survival benefit claim [12].

7.6 Cardiac surgery

The LEVO-CTS trial (n=849) and the CHEETAH trial (n=506) evaluated levosimendan in cardiac surgery patients at risk for low cardiac output syndrome [39, 40]. Neither trial demonstrated a significant benefit of levosimendan on the primary endpoints (a composite of death, renal replacement therapy, perioperative myocardial infarction, and mechanical cardiac support in LEVO-CTS; 30-day mortality in CHEETAH). These negative results tempered enthusiasm for routine perioperative use but do not preclude benefit in selected high-risk subgroups [39, 40].

7.7 Cardiogenic shock and sepsis

Observational and small randomized studies have evaluated levosimendan in cardiogenic shock, with evidence supporting hemodynamic improvement and potential survival benefit compared to dobutamine in selected populations. In sepsis-associated myocardial dysfunction, the LeoPARDS trial (n=515) found no benefit of levosimendan added to standard care versus standard care alone, with a higher rate of supraventricular tachyarrhythmia in the levosimendan group [41]. Expert consensus following the LeoPARDS trial does not support routine use of levosimendan in septic shock [14].

7.8 Intermittent ambulatory infusion

Intermittent ambulatory levosimendan infusion (repeated 24-hour infusions at 2- to 4-week intervals) has been investigated in advanced chronic heart failure as a bridge to transplant or as palliative therapy. Multiple small randomized trials and registry studies have demonstrated improvements in functional capacity, quality of life, reduction in heart failure rehospitalization, and in some studies, survival benefit. The LevoRep trial (n=120) demonstrated improvement in the 6-minute walk distance and reduction in NT-proBNP but did not meet the composite primary endpoint [42]. Ongoing investigation continues to refine patient selection and dosing protocols for intermittent use [13].

8. Sourcing and Quality Verification

Pharmaceutical-grade levosimendan is available exclusively as the intravenous formulation Simdax (Orion Corporation), supplied as a 2.5 mg/mL concentrate in 5 mL amber glass vials (12.5 mg per vial). The formulation contains the parent compound in a vehicle of ethanol, poloxamer 188, and citric acid. The product is available in jurisdictions where the compound is registered (approximately 60 countries, excluding the United States and Canada).

Research-grade levosimendan is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich catalog number L5545, MedChemExpress, Selleckchem, Cayman Chemical, Tocris, BOC Sciences, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the free base. Pricing is moderate for a specialty pharmaceutical compound, typically in the range of \$100 to \$400 per 100 milligrams of research-grade material.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (281.29 for the protonated free base $[M+H]^+$, consistent with $C_{14}H_{12}N_6O$)
- Chiral HPLC or polarimetry confirmation of enantiomeric purity (greater than 99 percent enantiomeric excess of the (R)-form)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. Given the importance of stereochemical purity to pharmacological activity (the (S)-enantiomer is approximately 10-fold less potent), chiral purity confirmation is particularly important for mechanistic research.

9. Reconstitution and Handling

The pharmaceutical formulation (Simdax 2.5 mg/mL concentrate) is diluted prior to intravenous infusion. Standard preparation involves diluting the 12.5 mg vial content (5 mL) in 250 mL of 5 percent dextrose (yielding a final concentration of 0.05 mg/mL) or in 500 mL (yielding 0.025 mg/mL). The diluted solution should be inspected visually for particulate matter and discoloration; the solution appears yellow to orange.

The diluted infusion solution is stable for 24 hours at room temperature (15 to 25 degrees Celsius) and should be used within this period. The concentrate vials should be stored at room temperature (15 to 25 degrees Celsius) and protected from light. Freezing should be avoided. The concentrate should not be mixed with other drugs in the same infusion line without compatibility data [15].

Research-grade levosimendan (free base powder) is reconstituted in dimethyl sulfoxide (DMSO) for in vitro applications. The compound is soluble in DMSO at concentrations up to 50 mg/mL (approximately 178 mM). Stock solutions in DMSO are stable at minus 20 degrees Celsius for at least 6 months when stored in aliquots to avoid repeated freeze-thaw cycles. For aqueous in vitro assays, the DMSO stock is diluted into the assay buffer at the working concentration, with final DMSO concentration maintained below 0.1 percent (v/v) to avoid solvent effects on cellular assays [43].

For in vivo research applications in rodents, levosimendan can be dissolved in a small volume of DMSO and then diluted in a vehicle of polyethylene glycol 400 and saline for intraperitoneal or intravenous administration. Alternatively, it can be dissolved in acidified saline (pH 3.5 to 4.0 with citric acid) at concentrations up to 0.5 mg/mL for intravenous infusion in animal models [18].

10. Stack Interactions and Combinations

Levosimendan has been characterized for pharmacokinetic and pharmacodynamic interactions with multiple drug classes relevant to heart failure management. Investigators and clinicians administering levosimendan in combination with other agents should consider the following:

Beta-blockers: Levosimendan retains its inotropic efficacy in patients receiving chronic beta-blocker therapy, a clinically important distinction from dobutamine, whose beta-1-adrenergic mechanism is directly antagonized by beta-blockers. The SURVIVE subgroup analysis demonstrated that levosimendan was superior to dobutamine specifically in beta-blocker-treated patients [12]. No pharmacokinetic interaction has been identified.

Diuretics: Concurrent loop diuretics (furosemide, bumetanide) are standard in acute heart failure management and produce no characterized pharmacokinetic interaction with levosimendan. However, diuretic-induced hypovolemia may potentiate levosimendan-induced hypotension. Electrolyte monitoring (particularly potassium and magnesium) is recommended, as levosimendan can produce hypokalemia through KATP channel-mediated effects [15, 44].

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: No pharmacokinetic interaction. The additive vasodilatory effect may potentiate hypotension and should be monitored.

Digoxin: No clinically important pharmacokinetic interaction has been demonstrated between levosimendan and digoxin in formal interaction studies. The combination is pharmacologically rational (complementary inotropic mechanisms) but has not been systematically studied for additive benefit [6].

Warfarin: No clinically important pharmacokinetic interaction. Levosimendan does not affect the pharmacokinetics or anticoagulant activity of warfarin [6].

Other inotropes (dobutamine, milrinone): Concurrent use produces additive hemodynamic effects. The combination of levosimendan with dobutamine or milrinone has been used in clinical practice for refractory low cardiac output states, but

systematic evidence for additive survival benefit is limited.

Vasopressors (norepinephrine, vasopressin): Concurrent vasopressor support is frequently required to counteract levosimendan-induced hypotension in critically ill patients. The combination is standard in cardiogenic shock management [14].

Isosorbide mononitrate and other nitrates: No pharmacokinetic interaction. Additive hypotension is predictable and should be managed with dose adjustment.

Itraconazole and other CYP3A4 inhibitors: No clinically important pharmacokinetic interaction has been demonstrated, as levosimendan is not primarily metabolized by CYP3A4.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events reported in clinical trials at standard infusion doses are:

- Hypotension (5 to 8 percent, dose-dependent; the principal dose-limiting effect, reflecting vasodilation through KATP channel opening and PDE3 inhibition)
- Headache (approximately 5 percent)
- Tachycardia and palpitations (3 to 5 percent, reflecting baroreflex-mediated sympathetic activation in response to vasodilation)
- Nausea (1 to 5 percent)
- Dizziness (1 to 5 percent)
- Hypokalemia (dose-dependent, reflecting KATP channel activation; clinically significant hypokalemia requires monitoring and correction)
- Insomnia (1 to 3 percent)

These adverse-event rates are generally similar to or lower than those observed with dobutamine in the SURVIVE trial, with the exception of hypotension, which is more common with levosimendan [12, 15].

11.2 Cardiac arrhythmias

Atrial fibrillation was reported at higher rates in levosimendan-treated patients in the REVIVE-II and LeoPARDS trials (approximately 5 to 9 percent versus 1 to 4 percent with placebo or standard care). Ventricular tachycardia was reported in approximately 3 to 8 percent of levosimendan-treated patients, similar to or lower than rates observed with dobutamine. Levosimendan does not produce the intracellular calcium loading that drives catecholamine-induced arrhythmogenesis, and the proarrhythmic signal is generally considered lower than with dobutamine or milrinone at equivalent inotropic effect [11, 12, 16].

11.3 Prolonged effects and the active metabolite

The long half-life of OR-1896 means that adverse effects, particularly hypotension and hypokalemia, can persist or emerge days after infusion cessation. Patients should be monitored for hemodynamic instability for at least 4 to 5 days after a standard 24-hour infusion. This prolonged pharmacodynamic tail is both a clinical advantage (sustained hemodynamic improvement without continuous infusion) and a safety consideration (inability to rapidly reverse the drug effect) [7, 32].

11.4 Mortality signal in REVIVE-II

The non-significant trend toward higher 90-day mortality in levosimendan-treated patients in REVIVE-II (15.1 percent versus 11.6 percent) was a principal concern in the regulatory evaluation of the compound. The mortality signal was not replicated in the larger SURVIVE trial and has been attributed by some investigators to the higher loading dose used in REVIVE-II and to the inclusion of sicker patients with lower baseline blood pressures who were more vulnerable to levosimendan-induced hypotension [11, 16].

11.5 Contraindications

The principal contraindications listed in prescribing information are: significant mechanical obstruction affecting ventricular filling or outflow (severe aortic stenosis, hypertrophic obstructive cardiomyopathy); severe hypotension (systolic blood pressure less than 85 mmHg) and tachycardia (heart rate greater than 120 beats per minute); severe renal impairment (creatinine clearance less than 30 mL/min in some labels); severe hepatic impairment; history of torsade de pointes; and known hypersensitivity to levosimendan or excipients [15].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative inotropic or inodilator agents against levosimendan, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal positive inotropes and inodilators with substantive clinical evidence in acute heart failure.

12.1 Dobutamine

Mechanism: Synthetic catecholamine; beta-1-adrenergic receptor agonist with minor beta-2 and alpha-1 activity. Increases intracellular calcium through beta-1-mediated activation of adenylyl cyclase, cAMP elevation, PKA-mediated phosphorylation of L-type calcium channels, and enhanced calcium cycling. The mechanism fundamentally increases myocardial oxygen consumption [45].

Novelty: Low. Dobutamine has been in clinical use since the 1970s and is the reference standard inotrope against which all newer agents are compared.

Effect size: Substantial hemodynamic improvement. Cardiac output increases of 20 to 50 percent are achievable at standard doses (2.5 to 20 micrograms/kg/min). However, chronic or repeated use is associated with increased mortality in multiple randomized trials, establishing the "inotrope paradox" [17].

Promising potential: Declining. Guidelines recommend dobutamine as a second-line agent after levosimendan in jurisdictions where levosimendan is available. The compound remains the reference comparator in clinical trials but is increasingly viewed as a bridging agent rather than a definitive therapy.

Side-effect profile: Significant. Tachycardia, arrhythmia (both atrial and ventricular), myocardial ischemia, and increased myocardial oxygen consumption are dose-dependent effects. Tolerance (tachyphylaxis) develops with continuous infusion beyond 48 to 72 hours. The proarrhythmic and oxygen-wasting properties are the principal safety disadvantages relative to levosimendan [45].

Overall validation: High. The most extensively studied inotrope with decades of clinical experience and thousands of patients in randomized trials. The extensive evidence paradoxically supports both its acute hemodynamic efficacy and its chronic safety limitations.

Comparison to levosimendan: Levosimendan is superior to dobutamine in hemodynamic response rate (LIDO), BNP reduction (SURVIVE), and in patients on beta-blocker therapy. Levosimendan does not produce the oxygen-wasting or proarrhythmic calcium loading of dobutamine. The SURVIVE trial did not demonstrate a mortality advantage for levosimendan at 180 days. The practical advantage of dobutamine is availability, familiarity, and titratable short half-life; the practical advantage of levosimendan is the sustained effect through OR-1896 and the favorable oxygen consumption profile.

12.2 Milrinone

Mechanism: Selective phosphodiesterase III (PDE3) inhibitor. Elevates cAMP in cardiomyocytes and vascular smooth muscle, producing positive inotropy and vasodilation through the same PDE3-dependent pathway as levosimendan but without the additional calcium-sensitizing and KATP channel-opening mechanisms [46].

Novelty: Low. Milrinone has been in clinical use since the late 1980s.

Effect size: Comparable hemodynamic improvement to dobutamine. The OPTIME-CHF trial (n=949) demonstrated no benefit of milrinone over placebo in acute heart failure and a trend toward increased hypotension and atrial arrhythmias, particularly in ischemic cardiomyopathy patients [47].

Promising potential: Stable but not expanding. Milrinone remains a standard of care for perioperative low cardiac output syndrome and is preferred over dobutamine in some cardiac surgery protocols. The compound is not a focus of active new-indication development.

Side-effect profile: Moderate. Hypotension (more pronounced than dobutamine, comparable to levosimendan), atrial and ventricular arrhythmias, and thrombocytopenia. The PROMISE trial demonstrated increased mortality with oral milrinone in chronic heart failure, establishing the safety limitations of PDE3 inhibition as a chronic therapy [17].

Overall validation: High in perioperative settings; moderate in medical heart failure. The compound is well characterized and widely available.

Comparison to levosimendan: Milrinone shares the PDE3-inhibitory mechanism with levosimendan but lacks the calcium-sensitizing and KATP channel-opening components. Levosimendan is superior to milrinone in gastric mucosal oxygenation (Schwarte et al. 2005) and in meta-analytic comparisons of hemodynamic outcomes in cardiac surgery [48]. Levosimendan has the additional advantages of sustained effect through OR-1896, cardioprotection through mito-KATP activation, and absence of the proarrhythmic calcium-loading signal that limits higher-dose PDE3 inhibition.

12.3 Enoximone

Mechanism: Selective PDE3 inhibitor, structurally and mechanistically related to milrinone. Produces positive inotropy and vasodilation through cAMP elevation [49].

Novelty: Low. Enoximone has been available since the 1980s and is primarily used in European cardiac surgery centers.

Effect size: Comparable to milrinone. In a randomized comparison of levosimendan versus enoximone in cardiogenic shock secondary to acute myocardial infarction, levosimendan demonstrated comparable hemodynamic improvement with a trend toward lower mortality [49].

Promising potential: Low. The compound is not a focus of active new-indication development and has been largely superseded by milrinone in most jurisdictions.

Side-effect profile: Similar to milrinone. Hypotension, arrhythmia, and the chronic mortality signal associated with PDE3 inhibition.

Overall validation: Moderate. The clinical evidence base is smaller than for milrinone and dobutamine.

Comparison to levosimendan: Levosimendan is mechanistically more diverse and has a larger clinical evidence base. Enoximone shares the PDE3 mechanism with levosimendan but lacks calcium sensitization and KATP channel opening. The comparison is similar to the milrinone comparison.

12.4 Pimobendan

Mechanism: Calcium sensitizer and PDE3 inhibitor, structurally a benzimidazole-pyridazinone derivative. The compound shares the dual calcium-sensitizer/PDE3-inhibitor mechanism with levosimendan but acts through a distinct binding site on troponin C and with different PDE3 selectivity. Pimobendan is primarily used in veterinary medicine (canine dilated cardiomyopathy and myxomatous mitral valve disease) and has limited human clinical data [50].

Novelty: Moderate. The calcium-sensitizer/PDE3-inhibitor dual mechanism is shared with levosimendan, but the veterinary-specific development pathway is distinct.

Effect size: Substantial in canine heart failure, where the QUEST and EPIC trials established survival benefit. Human data are limited and the compound is not approved for human use in any major jurisdiction [50].

Promising potential: Low for human applications; high for veterinary cardiology where it is a standard of care.

Side-effect profile: In canine use, the compound is generally well tolerated. Human safety data are limited. The chronic PDE3-inhibitory component carries the same theoretical safety concern as milrinone and enoximone for long-term human use.

Overall validation: Low for human medicine; high for veterinary cardiology.

Comparison to levosimendan: Pimobendan shares the dual mechanism conceptually but is not a practical comparator for human acute heart failure. Levosimendan has the substantially larger human evidence base, the active metabolite pharmacokinetic advantage, and the KATP channel-opening mechanism that pimobendan does not possess. Pimobendan is relevant as a mechanistic comparator demonstrating that the calcium-sensitizer/PDE3-inhibitor concept translates to survival benefit in a mammalian heart failure model (canine), which indirectly supports the levosimendan pharmacological thesis.

12.5 Istaroxime

Mechanism: First-in-class agent with dual inotropic and lusitropic (relaxation-enhancing) activity. Inhibits sodium-potassium ATPase (Na^+/K^+ -ATPase, the digitalis receptor) to increase intracellular calcium (positive inotropy) and simultaneously stimulates the sarcoplasmic reticulum calcium ATPase (SERCA2a) to enhance diastolic calcium reuptake (positive lusitropy). The combined mechanism aims to improve both systolic and diastolic function, distinguishing istaroxime from all other inotropes and inodilators [51].

Novelty: High. The dual inotropic-lusitropic mechanism is unique and represents a mechanistically novel approach to heart failure pharmacotherapy. Istaroxime is the first compound to directly stimulate SERCA2a in the clinical setting.

Effect size: In the Phase 2 HORIZON-HF trial ($n=120$), istaroxime reduced pulmonary capillary wedge pressure, increased systolic blood pressure, and improved diastolic function indices in patients with acute heart failure and reduced ejection fraction. Effect sizes on diastolic parameters exceeded those achievable with levosimendan or dobutamine [51, 52].

Promising potential: Moderate to high. The compound is in active Phase 2/3 development by Windtree Therapeutics for acute heart failure. The SEISMiC trial program is advancing evaluation of the compound in heart failure with preserved ejection fraction, where the lusitropic mechanism is particularly relevant [52].

Side-effect profile: Phase 2 data demonstrate tolerability, with the principal adverse events being injection site reactions, nausea, and mild QTc prolongation. The sodium-potassium ATPase inhibition raises the theoretical concern of digitalis-like toxicity at higher doses, but clinical data to date have not demonstrated clinically significant arrhythmia [51].

Overall validation: Low to moderate. The clinical evidence base is early-phase (Phase 2) and the compound has not yet achieved registration. The mechanistic novelty and the promising Phase 2 results support continued attention.

Comparison to levosimendan: Istaroxime is mechanistically distinct from levosimendan: levosimendan enhances systolic function through calcium sensitization (without calcium loading) and produces vasodilation; istaroxime enhances both systolic function (through calcium loading via Na^+/K^+ -ATPase inhibition) and

diastolic function (through SERCA2a stimulation). The two compounds address different pathophysiological targets and may ultimately prove complementary rather than competitive. Levosimendan has the substantial advantages of extensive clinical validation, regulatory approval in 60 countries, and the sustained-effect metabolite OR-1896. Istaroxime has the potential advantage of lusitropic activity in diastolic heart failure, a setting where levosimendan has less evidence.

12.6 Comparator summary

The five comparator agents occupy distinct positions in the inotrope and inodilator landscape. **Dobutamine** is the established reference standard with extensive validation but significant oxygen-wasting and proarrhythmic liabilities. **Milrinone** shares the PDE3 mechanism with levosimendan but lacks calcium sensitization and KATP channel opening and carries chronic mortality signal. **Enoximone** is a milrinone analog with a smaller evidence base. **Pimobendan** shares the dual calcium-sensitizer/PDE3-inhibitor concept but is a veterinary agent with minimal human data. **Istaroxime** is the most mechanistically novel comparator with a unique lusitropic property but early-phase clinical evidence.

Levosimendan occupies a unique position: it is the only approved inotrope that combines calcium sensitization, PDE3 inhibition, and KATP channel opening; the only inotrope with a long-lived active metabolite that sustains hemodynamic effects for days; the only positive inotrope that does not increase myocardial oxygen consumption at clinically relevant doses; and the only inodilator with cardioprotective properties through mito-KATP channel activation. These properties collectively position levosimendan as the most pharmacologically sophisticated inotrope in clinical use. The principal limitations relative to the comparator field are the absence of FDA approval, the inability to rapidly reverse the drug effect (a disadvantage in hemodynamically unstable patients), the hypotensive liability that limits use in low-blood-pressure states, and the absence of definitive mortality benefit in the largest randomized trial (SURVIVE).

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States Food and Drug Administration. The compound is registered as a medicine in approximately 60 jurisdictions outside the United States; investigators should consult their local regulatory authority before any human research application.