

**Scientific Evaluation Report of
the Medicines Evaluation Board
of the Netherlands on the assessment
of applications for**

**Levosimendan containing products
with a 2.5 mg/mL strength
and the pharmaceutical form
concentrate for solution for infusion
for the proposed indication
treatment of patients with acutely
decompensated severe chronic
heart failure (ADHF)**

Date: 4 February 2016

Remark

This Scientific Evaluation Report describes the results of the assessment by CBG-MEB of available information on an active substance used in medicinal products not authorised in the Netherlands. Although not authorised the subject is still known to be prescribed by healthcare professionals. The Scientific Evaluation Report is published to inform the healthcare professionals and patients about the risks when using the medicinal product. By publishing this report the CBG-MEB hopes to contribute to a sound and safe use of the medicinal product. This Scientific Evaluation Report expresses the conclusions of the CBG-MEB only.

List of abbreviations

ACE	Angiotensin-converting Enzyme
ADHF	Acutely Decompensated Heart Failure
AE	Adverse Events
AHF	Acute Heart Failure
ARB	Angiotensin II Receptor Blocker
ASMF	Active Substance Master File
ATP	Adenosine Triphosphate
BNP	B-type natriuretic peptide
CASINO	Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure Study
CHF	Chronic Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CV	Cardiovascular
EC	European Commission
ERA	Environmental Risk Assessment
ESC	European Society of Cardiology
HF	Heart Failure
HR	Hazard Ratio
ICH	International Conference on Harmonization
IV	Intravenous
JACC	Journal of the American College of Cardiology
LIDO	Levosimendan Infusion versus Dobutamine Study
LVEF	Left Ventricular Ejection Fraction
MEB	Medicines Evaluation Board of the Netherlands
NL	the Netherlands
NNT	Number Needed to Treat
NYHA	New York Heart Association
PCWP	Pulmonary Capillary Wedge Pressure
Ph.Eur.	European Pharmacopoeia
REVIVE	Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy versus Placebo in the Short Term Treatment of Decompensated Chronic Heart Failure Study
RH	Relative Humidity
RMP	Risk Management Plan
RR	Risk Ratio
RUSSLAN	Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure After an Acute Myocardial Infarction
SBP	Systolic Blood Pressure
SURVIVE	Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support
TSE	Transmissible Spongiform Encephalopathies
SmPC	Summary of Product Characteristics

I. INTRODUCTION

Levosimendan 2.5 mg/mL concentrate for solution for infusion is not currently registered in the Netherlands, nor has it been authorised in the past. The product was applied for twice, in 2001 (full dossier) and 2014 (generic application) in the context of European application procedures.

The indication applied for in the most recent application was 'short-term treatment of acutely decompensated severe chronic heart failure (ADHF) in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate. Levosimendan is indicated in adults.' The conclusion of the MEB's assessment was that the benefit/risk balance was considered negative for this product. Both applications were withdrawn in the Netherlands.

In the Netherlands levosimendan is known to be prescribed by healthcare professionals on the basis of named patient use.

This report reflects the MEB's assessment of Levosimendan 2.5 mg/mL concentrate for solution for infusion. It presents the scientific discussion of the two dossiers the applicant provided for evaluation. A list of literature references is provided on page 14.

According to the ESC guideline (acute and chronic heart failure, 2012), levosimendan may be considered in AHF to reverse the effect of beta-blockade, if beta-blockade is thought to be contributing to hypoperfusion (class IIb, level C).

For acute decompensated heart failure the following inotropes are discussed in the Dutch cardiology guideline for heart failure: dobutamine, dopamine, enoximon and milrinone (*Multidisciplinaire richtlijn Hartfalen 2010*). Although not registered, the Dutch Formulary for Children (*Kinderformularium*) includes levosimendan as one of the options in acute heart failure after failure of standard therapy. It is stated that in the Netherlands this medicine is only available with a specific doctor's declaration (*artsenverklaring*), i.e. as a 'named patient product'.

Based on the available clinical data in the literature and provided dossiers, the MEB concludes that two potential serious risks to public health exist precluding a recommendation for marketing authorisation (see section II).

In this report the MEB's assessment of the available clinical data is briefly discussed. Data on the quality and non-clinical are not included. The clinical overview of the available literature data, mostly after 2001, is discussed.

II. SCIENTIFIC DISCUSSION

II.1 Levosimendan full application

Levosimendan was first approved in 2000 and 2001 in several EU countries. The application was mainly based on 2 clinical studies, LIDO and RUSSLAN. On the basis of the data presented in the first submission (2001), the MEB considered that these two studies failed to show a positive effect on mortality/morbidity. A number of deficiencies in the studies precluded a positive opinion: the patient population was not well defined, dobutamine was not considered a relevant comparator, the doses used for both treatment arms were not in line with the SmPCs, the background therapy was not in line with EU standards (RUSSLAN), the shown benefits were haemodynamic or symptomatic, whereas serious adverse events were reported (hypotension, arrhythmias) which necessitate monitoring.

The indication applied for was 'short term treatment of severe congestive heart failure. Levosimendan should only be used as add-on therapy in situations where conventional therapy with e.g. diuretics, ACE-inhibitors and digitalis is not sufficient and where there is a need for inotropic support'. The MEB came to the conclusion that the benefit-risk balance for levosimendan 2.5 mg/mL for this indication is considered negative.

II.2 Levosimendan generic application

For the generic application submitted in 2014, a clinical overview was provided, which is based on scientific literature. No additional clinical data were gathered.

II.2.1 Pharmacokinetics

On infusion of levosimendan it is extensively metabolised, with a half-life of about 1 hour. Its active metabolites OR-1855 and OR-1896 are interconverted by acetylation and de-acetylation and have half-lives of about 75 to 80 hours, producing a prolonged duration of action. Metabolites and a small amount of unchanged drug are excreted in urine and faeces. More than 95% of a dose is excreted within one week. Levosimendan is about 98% bound to plasma proteins, mainly albumin, but the active metabolites have much lower protein binding of about 40%.

II.2.2 Pharmacodynamics

Levosimendan enhances the calcium sensitivity of contractile proteins by binding to cardiac troponin C in a calcium-dependent manner. It increases the contraction force but does not impair ventricular relaxation. In addition, levosimendan opens ATP-sensitive potassium channels in vascular smooth muscle, thus inducing vasodilatation of systemic and coronary arterial resistance vessels and systemic venous capacitance vessels.

Levosimendan is shown to provide haemodynamic improvement within a few hours of treatment initiation; it causes dose-dependent increases in stroke volume and cardiac index, and dose-dependent decreases in pulmonary capillary wedge pressure (PCWP) and pulmonary arterial pressure. Importantly, levosimendan increases contractile force without impairment of ventricular relaxation.

In addition to these positive inotropic and lusitropic effects, levosimendan also produces vasodilation. This effect reduces cardiac preload and afterload, improves oxygen supply to the myocardium, increases coronary blood flow and also enhances renal blood flow. These effects may account for the reductions in myocardial ischaemia, as well as the improved function of stunned myocardium observed during the treatment with levosimendan.

II.2.3 Clinical efficacy and safety

The main clinical studies discussed in the clinical overview are:

- LIDO study (Levosimendan Infusion versus Dobutamine - Follath 2002).
- RUSSLAN study (Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarction - Moiseyev 2002).

These studies were already assessed during the European application procedure in 2001.

Additionally the following studies are presented:

- CASINO study (Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure Study - Zairis 2004).
- REVIVE study (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy versus Placebo in the Short Term Treatment of Decompensated Chronic Heart Failure - Packer et al., 2013).
- SURVIVE study (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support - Mebazaa et al., 2007).

A short overview of the last two studies is given below, mainly based on the available publications.

- **REVIVE study**

The REVIVE programs consisted of 2 studies, REVIVE I was a preliminary study. Focus in this assessment is on REVIVE II: a placebo-controlled double blind study to investigate changes in clinical status during the first 5 days after randomization.

Study patients. Main **inclusion** criteria were patients hospitalized for the treatment of ADHF and remained dyspneic at rest despite treatment with IV diuretics. At randomization, patients might have also received intravenous vasodilators and/or positive inotropic drugs (except amrinone and milrinone), but the infusion rates of these drugs must have remained constant for at least 2 h before entry into the study. All patients had left ventricular dysfunction (LVEF <35% within the prior 12 months).

Main **exclusion** criteria were systolic blood pressure \leq 90 mm Hg or a heart rate \geq 120 beats/min; patients who had experienced angina within 6 h or cardioversion within 4 h (or were expected to undergo cardioversion within 5 days).

Dose. Treatment with the study medication (levosimendan or placebo) was initiated with an intravenous bolus of 12 μ g/kg over 10 min (6 μ g/kg if the patient was receiving concurrent IV vasodilator or positive inotropic agent) followed by a continuous IV infusion of 0.1 μ g/kg/min. If tolerated, the infusion was increased after 50 min to 0.2 μ g/kg/min and was maintained for 23 additional hours. If not tolerated, the infusion rate could be reduced to 0.05 or 0.1 μ g/kg/min or treatment with the study drug could be discontinued.

Evaluation. At 6 and 24 h and after 2, 3, and 5 days after randomization, patients were asked to evaluate changes in overall clinical status (the patient global assessment) and in dyspnea. These changes were characterized as markedly, moderately, or mildly improved; unchanged; or mildly, moderately, or markedly worse.

Primary endpoint. The primary endpoint of the study was a composite of clinically relevant measures. Patients were classified as "improved" if they considered themselves moderately or markedly improved at all pre-specified time points (6 h, 24 h, and 5 days) and showed no evidence of clinical deterioration during this period. Patients were classified as "worse" if (during the 5 days) they died; experienced persistent or unresponsive symptoms of heart failure after the first 24 h of randomized therapy or worsening heart failure at any time during the first 5 days, which required a rescue intervention specifically to relieve such symptoms; or considered themselves to have moderately or markedly worsened on global assessment at 6 h, 24 h, or 5 days.

Secondary endpoints included among others changes in plasma BNP at 24 h, changes in the patient global assessment and their perception of dyspnea at 6 h and all-cause mortality during the first 90 days.

Statistical analyses. The sample size was estimated on the basis of the following assumptions: the proportion of patients considered improved during the first 5 days would be 50% greater in the levosimendan group than in the placebo group; the proportion of patients considered worse during the first 5 days would be 33% lower in the levosimendan group than in the placebo group; the expected rates of improvement and deterioration in the placebo group would both be 25%; and the study would have >90% power to detect a treatment difference ($\alpha = 0.05$).

Results

The study enrolled 600 patients, of whom 301 were assigned to placebo and 299 were assigned to levosimendan. Enrollment took place between December 2001 and September 2004. More than 90% of the patients in the levosimendan group received the target infusion rate of 0.2 μ g/kg/min at 2 h, and 70% to 85% of the group continued to receive this dose at 24 h. Approximately 12% of the levosimendan group and 7% of the placebo group discontinued the study medication before 24 h. Main patients characteristics and co-medications are shown in table 1.

Table 1: Baseline Characteristics REVIVE II Trial

	REVIVE II	
	Levosimendan (n = 299)	Placebo (n = 301)
Age (yrs)	64 ± 15	63 ± 15
Men	73%	72%
Caucasian	61%	68%
African American	28%	20%
Prior myocardial infarction	55%	52%
LV ejection fraction	0.23 ± 0.07	0.24 ± 0.07
Systolic BP (mm Hg)	115 ± 17	116 ± 20
Diastolic BP (mm Hg)	68 ± 12	69 ± 14
Heart rate (beats/min)	82 ± 15	81 ± 15
Digoxin	53%	51%
ACE inhibitor/ARB	78%	76%
Beta-blocker	68%	69%
Spirolactone	37%	37%
IV vasodilator	13%	13%
IV inotropic drug	11%	10%
Both IV vasodilator and inotrope	2%	2%

Primary endpoint: 58 patients in the levosimendan but only 44 patients in the placebo group were improved at 6 and 24 h, and at 5 days. By contrast, 82 patients in the placebo but only 58 patients in the levosimendan group were worse ($p = 0.015$ for the overall difference between groups). The clinical features and management of worsening in the patients who deteriorated are summarized in Table 2.

Table 2: Worsening Clinical Status Requiring Rescue Therapy in REVIVE II

	REVIVE II	
	Levosimendan (n = 299)	Placebo (n = 301)
Proportion requiring rescue therapy	15%	26%
Worsening dyspnea or tachypnea	7%	13%
Increased pulmonary edema	3%	6%
Diaphoresis	1%	1%
Cool extremities and cyanosis	0%	2%
Worsening renal function	3%	5%
Decreased mental status	1%	2%
Persistent/unresponsive symptoms	6%	11%

Overall, 26% (n = 79) of patients in the placebo but only 15% (n = 45) of patients in the levosimendan group required intravenous rescue therapy for worsening heart failure. Most experienced worsening dyspnea (13% placebo, 7% levosimendan); increased pulmonary edema (6% placebo, and 3% levosimendan); and persistent or unresponsive symptoms (11% placebo and 6% levosimendan). These treatment intensifications included intravenous furosemide (placebo 47, levosimendan 23); nesiritide (placebo 24, levosimendan 17); dobutamine (placebo 19, levosimendan 12); and milrinone (placebo 18, levosimendan 12).

Secondary endpoints: Both at 24 h and at 5 days, plasma levels of BNP declined substantially in the levosimendan group compared with the placebo group (both $p < 0.001$); this effect was no longer apparent after 31 days of follow-up.

There were no differences between the groups in the number of days alive and out of the hospital over 14 days. However, patients in the levosimendan group were discharged from the hospital earlier than those in the placebo group. The NYHA functional class at 5 days was not significantly different between treatment groups ($p = 0.196$).

Safety. Both systolic and diastolic blood pressure decreased significantly during the 24-h infusion of levosimendan (by 4 mm Hg and by 6 mm Hg, respectively, when compared with placebo); the hypotensive effects of the drug dissipated within 12 h after withdrawal of the drug at the end of the 24-h infusion. By contrast, heart rate increased during the 24-h infusion of levosimendan (by 2 to 8 beats/min), and this effect was still statistically significant at the end of 5 days. Adverse events reported in REVIVE II during the first 31 days of the study are listed in Table 3.

Table 3: Adverse Events Occurring With a Frequency \geq 5% in REVIVE II

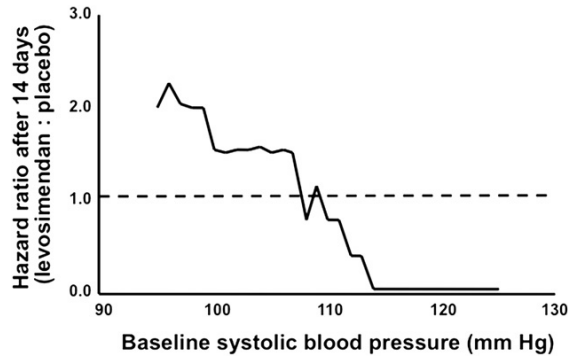
REVIVE II		
	Levosimendan (n = 293)	Placebo (n = 294)
Hypotension	147 (50.2%)	107 (36.4%)
Headache	88 (30.0%)	44 (15.0%)
Cardiac failure	98 (33.5%)	108 (36.7%)
Ventricular tachycardi	72 (24.6%)	51 (17.3%)
Nausea	53 (18.1%)	46 (15.6%)
Dizziness	38 (13.0%)	35 (11.9%)
Hypokalemia	35 (11.9%)	36 (12.2%)
Renal failure	36 (12.3%)	40 (13.6%)
Insomnia	32 (10.9%)	37 (12.6%)
Constipation	34 (11.6%)	35 (11.9%)
Vomiting	27 (9.2%)	22 (7.5%)
Hyperkalemia	21 (7.2%)	19 (6.5%)
Diarrhea	21 (7.2%)	20 (6.8%)
Back pain	13 (4.4%)	20 (6.8%)
Urinary tract infection	20 (6.8%)	21 (7.1%)
Muscle cramp	20 (6.8%)	11 (3.7%)
Anxiety	17 (5.8%)	18 (6.1%)
Pain in extremity	14 (4.8%)	18 (6.1%)
Anemia	16 (5.5%)	15 (5.1%)
Angina pectoris	18 (6.1%)	18 (6.1%)
Atrial fibrillation	25 (8.5%)	6 (2.0%)
Pyrexia	16 (5.5%)	18 (6.1%)
Cough	13 (4.4%)	15 (5.1%)
Ventricular extrasysto	22 (7.5%)	6 (2.0%)
Dyspnea exacerbated	10 (3.4%)	15 (5.1%)
Hypoglycemia	15 (5.1%)	8 (2.7%)

An excess of adverse events (AE) was apparent both during the first 24 h and from 24 h to 5 days, except for hypotension, the occurrence of which was increased only within the first 24 h. The most common adverse event leading to discontinuation of treatment was hypotension, which was the cause of withdrawal in 8.1% of the levosimendan group and 2.3% of the placebo group.

By the protocol-specified time point of 90 days, 35 patients in the placebo group and 45 in the levosimendan group had died in the REVIVE II trial. The hazard ratio for all-cause mortality was 1.33 (95% CI: 0.85 to 2.06) for the REVIVE II trial ($p = 0.21$). An excess risk of death in the levosimendan

group (vs. placebo) was apparent as early as 5 days; was nominally significant at 14 days; and was largely seen in subgroups at highest risk of death before entry into the study (e.g., patients with systolic blood pressure <100 mm Hg). After 14 days, an inverse relation between baseline systolic pressure and the magnitude and direction of the treatment-related difference in the risk of death was observed, with an excess hazard in the levosimendan group when the baseline systolic pressure was <100 to 110 mm Hg. After 90 days, the relative risk of death (levosimendan/ placebo) was 1.9 in patients with a pre-treatment systolic blood pressure <100 mm Hg but was 1.1 in patients with a systolic blood pressure \geq 100 mm Hg (figure 1).

Figure 1: Hazard ratio for all-cause mortality (levosimendan/placebo) at 14 days as a function of the systolic blood pressure at randomization.



- **SURVIVE study**

The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support study was a randomized, double-blind trial comparing the efficacy and safety of IV levosimendan or dobutamine in 1327 patients hospitalized with ADHF who required inotropic support. The trial was conducted at 75 centers in 9 countries (EU, Israel and Russia) and patients were randomized between March 2003 and December 2004.

Main **inclusion** criteria were LVEF \leq 30% within the previous 12 months and required IV inotropic support, as evidenced by an insufficient response to IV diuretics and/or vasodilators, and at least 1 of the following at screening: (1) dyspnea at rest or mechanical ventilation for ADHF; (2) oliguria; or (3) PCWP \geq 18 mm Hg and/or cardiac index \leq 2.2 L/min per m².

Main **exclusion** criteria were SBP persistently < 85 mm Hg or heart rate persistently \leq 130/min; IV inotrope use during the index hospitalization (except dopamine \leq 2 μ g/kg/min or digitalis).

Study treatment. A loading dose of levosimendan (12 μ g/kg) was administered over 10 minutes, followed by an infusion (0.1 μ g/kg/min) for 50 minutes; the rate was increased to 0.2 μ g/kg/min for an additional 23 hours as tolerated. Dobutamine was initiated at a rate of 5 μ g/kg/min and could be increased at the discretion of the investigator to a maximum rate of 40 μ g/kg/min. The infusion was maintained as long as clinically appropriate (minimum of 24 hours) and was tapered according to each patient's clinical status.

Primary endpoint was all-cause mortality during the 180 days following randomization.

Statistical plan. The sample size was based on the objective of assessing differences in all-cause mortality between the levosimendan and dobutamine groups at 180 days. The trial was event-rate driven until 330 deaths had occurred, providing 85% power ($\alpha=.05$) to detect a 25% relative risk reduction in mortality rates between the treatment groups, assuming the 180-day mortality rate was 25.3%. The originally targeted number of patients, based on LIDO study was 700 but was increased to 1320 following a blinded review of mortality after 131 deaths to achieve the target number of 330 deaths.

Results. Patients randomized to levosimendan (n=664) or dobutamine (n=663) were similar with respect to pretreatment characteristics (table 4) and concomitant medications.

Table 4: Baseline Patient Demographics and Characteristics

	Levosimendan (n = 664)	Dobutamine (n = 663)
Male sex	493 (74)	463 (70)
White race	627 (94)	625 (94)
Age, mean (SD), y	67 (12)	66 (12)
Weight, mean (SD), kg	79 (18)	79 (16)
Vital signs, mean (SD)		
Systolic BP, mm Hg	116 (18)	116 (19)
Diastolic BP, mm Hg	70 (12)	70 (12)
Heart rate, beats/min	84 (17)	83 (17)
Cardiovascular history		
History of heart failure	586 (88)	585 (88)
Myocardial infarction	453 (68)	455 (69)
Mitral insufficiency	412 (62)	419 (63)
Hypertension	405 (61)	429 (65)
Atrial fibrillation/flutter	324 (49)	308 (46)
Tricuspid insufficiency	317 (48)	308 (46)
Stable angina pectoris	310 (47)	318 (48)
Type 2 diabetes	205 (31)	223 (34)
Initial hospitalization characteristics		
Ischemic etiology for acute heart failure	503 (76)	502 (76)
NYHA class IV	572 (86)	562 (85)
LVEF, mean (SD), %†	24 (5)	24 (5)
BNP level, pg/mL‡		
Mean (SD)	1581 (1490)	1667 (1670)
Median (range)	1178 (573-2066)	1231 (583-2084)
Cardiovascular medications prior to infusion		
β-Blocking agents	336 (51)	333 (50)
ACE inhibitor or ARB	463 (70)	451 (68)
Aldosterone antagonists	336 (51)	366 (55)
Intravenous diuretics	523 (79)	523 (79)
Intravenous nitrates	241 (36)	252 (38)
Intravenous dopamine§	50 (8)	34 (5)

After the initial hour that includes loading dose, levosimendan was continuously infused at a mean (standard deviation) rate of 0.2 (0.02) µg/kg/min for 23.4 (2.9) hours; dobutamine was infused at a rate of 5.9 (2.6) µg/kg per minute for 39.3 (44.4) hours. The results of the primary and secondary endpoints are summarised in table 5, and show no significant differences between levosimendan and dobutamine.

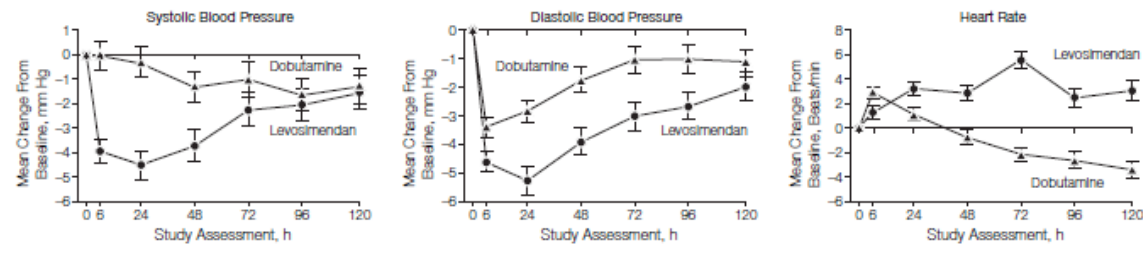
Table 5: Primary, Secondary, and Post Hoc All-Cause Mortality End Points

	No. (%) of Patients†		HR (95% CI)	P Value
	Levosimendan (n = 664)	Dobutamine (n = 663)		
Primary end point				
All-cause mortality at 180 d	173 (26)	185 (28)	0.91 (0.74-1.13)	.40‡
Secondary end point				
All-cause mortality at 31 d	79 (12)	91 (14)	0.85 (0.63-1.15)	.29‡
Mean change in BNP at 24 h from baseline, pg/mL	(n = 628) -631	(n = 611) -397		<.001§
Mean No. of days alive and out of the hospital during 180 d	120.2	116.6		.30
Dyspnea assessed at 24 h; ≥mild improvement¶	544 (82)	550 (83)		.96
Global assessment at 24 h; ≥mild improvement¶	531 (80)	537 (81)		>.99
Cardiovascular mortality during 180 d	157 (24)	171 (26)	0.90 (0.72-1.12)	.33‡
Post hoc all-cause mortality				
5 d	29 (4)	40 (6)	0.72 (0.44-1.16)	.17‡
14 d	59 (9)	69 (10)	0.84 (0.59-1.19)	.33‡
90 d	139 (21)	138 (21)	0.99 (0.78-1.25)	.91‡

The pre-specified subgroup analyses showed no interactions, except a prior history of heart failure at baseline showing influence at 31 days (treatment prior heart failure interaction, $P=.05$) but not at 180 days.

Safety. Systolic and diastolic blood pressure initially declined more in the levosimendan group than in the dobutamine group; with differences subsiding after cessation of infusion. However, the increase in heart rate observed with levosimendan was maintained through 5 days (figure 2).

Figure 2. Mean Change From Baseline in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate Through 5 Days by Treatment Group



Treatment emergent adverse events reported in more than 5% of the patients are shown in table 6.

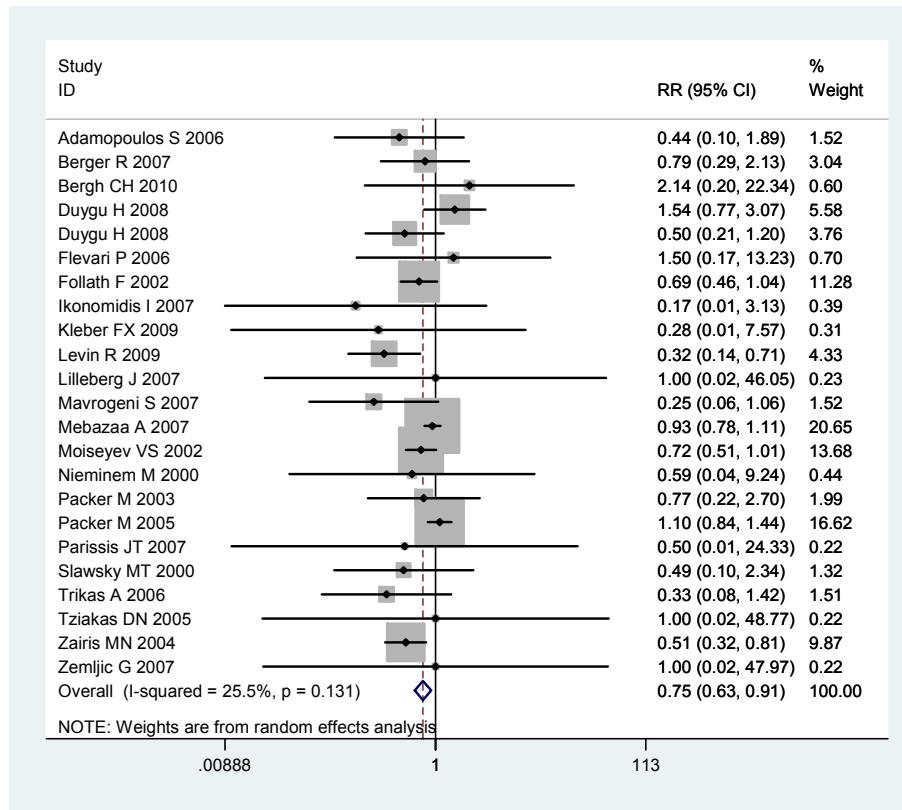
Table 6. Treatment-Emergent Adverse Events

	No. (%) of Patients		P Value†
	Levosimendan (n = 660)	Dobutamine (n = 660)	
Any adverse event	518 (78.5)	502 (76.1)	.32
Any serious adverse event‡	195 (29.5)	217 (32.9)	.21
Hypotension	102 (15.5)	92 (13.9)	.48
Cardiac failure§	81 (12.3)	112 (17.0)	.02
Hypokalemia	62 (9.4)	39 (5.9)	.02
Atrial fibrillation	60 (9.1)	40 (6.1)	.05
Headache	55 (8.3)	31 (4.7)	.01
Ventricular tachycardia	52 (7.9)	48 (7.3)	.76
Nausea	45 (6.8)	49 (7.4)	.75
Ventricular extrasystoles	40 (6.1)	24 (3.6)	.05
Insomnia	37 (5.6)	29 (4.4)	.38
Tachycardia	33 (5.0)	33 (5.0)	>.99

- **Meta analysis (Landoni et al, 2012)**

In support of efficacy, reference was also made to this meta analysis. Data from 5,480 patients in 45 randomised controlled trials were analysed. The analysis included all the pivotal studies and several smaller trials in HF patients as well as studies in cardiac surgery patients. The overall mortality rate was 17.4% among levosimendan-treated patients and 23.3% in the control group (RR 0.80, 95% CI 0.72–0.89, $p<0.001$, number needed to treat 17). These results were also shown in the cardiology setting (441 of 2207 [20.0%] in the levosimendan group vs. 484 of 1893 [25.6%] in the control group, RR 0.67 [0.51; 0.86], $p=.002$, RR 0.75 [0.63; 0.91], $p=.003$, $I^2=29.51$, p for heterogeneity .131, $I^2=25.5\%$ with 23 studies included, NNT 18) (figure 3).

Figure 3: Forrest plot of mortality for studies performed in the setting of cardiology showing a statistically significant reduction in mortality in the levosimendan group.



The above meta-analysis is presented for completeness, and was not methodologically assessed. However, the studies that contribute most weight to this analysis are discussed in this report, or have been assessed in the past (Follath 2002, Mebazaa 2007, Moiseyev 2002 and Packer 2005 are LIDO, SURVIVE, RUSSLAN and REVIVE II respectively).

II.3 Discussion on the clinical aspects

The MEB considers that the previously identified deficiencies are not solved.

REVIVE study

REVIVE II was conducted in 2001-2004, but the full results were only published in 2013 in the Journal of the American College of Cardiology (JACC). This delay in publishing of the data was heavily criticized in the accompanying editorial (Califf, 2013). The study did not recruit patients from the EU, with obvious differences in the standard of care, but that could also be related to the time of the study, e.g. around 50% of the patients on digoxin and 77% on ACE-I/ARBs. Recruited patients also had a systolic blood pressure of around 115 mmHg, which is in line with the labeling of levosimendan, but not in line with the indication of inotropic therapy, that is patients with hypotension (systolic blood pressure <85 mmHg) and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion. The chosen endpoint is a mixture of signs and symptoms, and is not well validated. The method of measurement of dyspnea is not further described in the publication, precluding assessment. Measuring the main endpoint at 5 days is chosen in line with the average hospital stay in the US but is considered to be on the shorter side. Results show significant symptomatic improvement in the levosimendan group at 5 days, accompanied with significant reduction of BNP; the latter parameter was neutral at 31 days. There was no improvement in the NYHA classification, no differences in the days alive but out of hospital over 14 days, but shorter hospital stays (5 days) were more common in levosimendan arm than placebo (10 days). This mostly symptomatic improvement was accompanied with significantly higher incidence of hypotension, ventricular tachycardia, atrial fibrillation and ventricular extrasystoles. Importantly, there is a higher risk

of death reported at 90 days (HR: 1.33, 95% CI: 0.85 to 2.06) with observed difference that started to emerge already at day 5.

REVIVE II showed symptomatic improvement in the levosimendan group compared to placebo. There were also short term benefits in terms of improvement in BNP in both studies. According to the investigators, some of the haemodynamic benefits seen in the earlier studies may have been missed as unlike the older studies, the current studies did not use invasive monitoring. This questions if such methods should be employed to better identify the target patients and mitigate the risks like hypotension and arrhythmia.

The most important issue in this application is the lack of long term benefit, or at least a robust exclusion of harm. According to the draft CHMP guideline for acute heart failure (CHMP/EWP/2986/03 Rev. 1) symptomatic improvement might be acceptable as primary endpoint provided no deleterious effects are shown as regards mortality. Symptomatic improvements were shown in the REVIVE II study against placebo, however the mortality data of this study are not presented or discussed in the application. The full publication of the study shows a higher mortality risk compared to placebo. Likewise the failure of superiority against dobutamine does not mean that these products are equal, or that the risks are comparable. Failure to prove superiority precludes interpretation of the data, and leaves the issues of the long term benefit, and the comparability to dobutamine unanswered.

An important factor that almost doubles the mortality risk as shown in the REVIVE study was low SBP (SBP<100 mm Hg; RR: 1.9). Considering that inotropes are mainly reserved for patients with severe reduction in cardiac output, that vital organ perfusion is compromised and that such patients are almost always hypotensive, the target group of levosimendan appears quite limited. Even for patients with higher systolic blood pressure the risk is 1.1 at 90 days, which is not acceptable. Overall, results of REVIVE II indicate a negative benefit-risk balance for levosimendan for the recruited patients.

SURVIVE study

The SURVIVE study recruited patients with documented LVEF <35%, however, only 88% gave a history of CHF, indicating that not all patients showed acute decompensation on top of chronic HF, as indicated in the SmPC. Also the medications prior to the IV infusion do not indicate an EU standard of care with only 70% and 50% administered ACE-I and beta-blockers respectively. A mean baseline SBP of 116 mm Hg questions the need for inotropic therapy. Dobutamine is a valid comparator considering its pharmacological mechanism of action as an inotrope and its long established use in AHF, with the caveat that the long term benefits of inotropes are not investigated, and actually doubted. Accordingly the failure of levosimendan to show superiority over dobutamine in all-cause mortality is worrisome and casts doubts about possible long term risks. For other CV risks, hypotension and tachycardia are more pronounced with levosimendan than dobutamine but did not reflect in a significant difference in AEs. However, the longer half-life of levosimendan could probably necessitate a long recovery time from any AE. Other important AE reported significantly more with levosimendan are ventricular extrasystoles and atrial fibrillation. Considering SURVIVE is a dedicated mortality study, the results are not reassuring.

A specific subgroup which could benefit according to the SURVIVE data are patients with a previous history of heart failure, explained by the counteraction of levosimendan to the beta blockers. This is so far the only possible use for levosimendan according to the ESC guideline (McMurray et al., 2012) and is pharmacologically plausible.

The posology of levosimendan is still debated. According to the REVIVE/SURVIVE investigators, the use of bolus dose in these studies could have contributed to the deleterious effects as hypotension and AF. They advocate to stop using the bolus, which is the clinical practice according to them. This bolus dose is still recommended in the SmPC.

Overall, the additional clinical data available in the public domain for levosimendan does not solve the concerns raised in 2001. Based on the available literature the MEB of the Netherlands considers that:

- The results from study REVIVE II point to an increased mortality risk in patients administered levosimendan. A discussion on the causality of levosimendan should be performed taking into consideration the patients characteristics, comorbidities and co-medications.
- The SURVIVE study failed to show superiority of levosimendan over dobutamine. These results question any long term benefits of levosimendan and preclude an assessment of its role as an inotrope.

III. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the available clinical data in the literature and provided application dossiers, the MEB came to the conclusion that the benefit/risk balance for levosimendan is negative. The clinical studies submitted failed to show a positive effect on mortality/morbidity. A number of deficiencies in the studies preclude a positive opinion.

The study results available in literature indicate that besides the demonstrated haemodynamic and symptomatic improvements, there are serious risks associated with levosimendan use, including hypotension and cardiac arrhythmias. These may negatively affect mortality. Although for a number of endpoints beneficial effects have been shown, these do not outweigh the observed adverse effects. Therefore the benefit-risk balance remains negative, taking into account the nature of the identified risks and the potential benefit in the proposed indication and target patient population.

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