

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Embesin 20 IU/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The medicinal product has a concentration of 20 IU argipressin (equating to 66.5 micrograms of argipressin acetate) per ml (20 IU/ml).

Excipient(s) with known effect:

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion. The solution is clear, colourless and free from visible particles with a pH between 2.5 - 4.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Embesin is indicated for the treatment of catecholamine refractory hypotension following septic shock in patients older than 18 years. A catecholamine refractory hypotension is present if the mean arterial blood pressure cannot be stabilised to target despite adequate volume substitution and application of catecholamines (see section 5.1).

4.2 Posology and method of administration

Method of administration

The therapy with argipressin in patients with catecholamine refractory hypotension is preferably started within the first six hours after the onset of septic shock, or within 3 hours of onset in patients on high doses of catecholamines (see section 5.1). Argipressin should be administered by continuous intravenous infusion of 0.01 IU per minute using a perfusor / motor pump. Dependent on the clinical response, the dose may be increased every 15 – 20 minutes up to 0.03 IU per minute. For intensive care patients, the usual target blood pressure is 65 – 75 mmHg. Argipressin should only be used in addition to conventional vasopressor therapy with catecholamines. Doses above 0.03 IU per minute should only be applied as emergency treatment, as this may cause gut and skin necrosis and increase the risk for cardiac arrest (see section 4.4). The treatment duration should be chosen according to the individual clinical picture but should preferably last for at least 48 hours. Treatment with argipressin must not be discontinued abruptly, but should be weaned off in accordance with the clinical course of the patient. The overall duration of treatment with argipressin is at the discretion of the responsible physician.

Posology

Infusion rates according to the recommended doses:

Dose Embesin / min	Dose Embesin / hour	Infusion rate
0.01 IU	0.6 IU	0.75 ml / hour
0.02 IU	1.2 IU	1.50 ml / hour
0.03 IU	1.8 IU	2.25 ml / hour

Paediatric population

Argipressin has been used for the treatment of vasodilatory shock in children and infants in intensive care units and during surgery. Since argipressin in comparison to the standard treatment did not result in an improvement of survival and showed higher rates of adverse events, the use in children and infants is not recommended.

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

This product should not be used interchangeably with other medicinal products containing argipressin with different expressions of strength (for example Pressor Units P.U.).

Argipressin must not be administered as bolus for therapy of catecholamine refractory shock.

Argipressin may only be administered under close and continuous monitoring of hemodynamic and organ-specific parameters.

The therapy with argipressin should only be started if no sufficient perfusion pressure can be maintained despite adequate volume substitution and application of catecholaminergic vasopressors.

Argipressin should be used with special caution in patients with heart or vascular diseases. The application of high argipressin doses for other indications has been reported to cause myocardial and gut ischaemia, myocardial and gut infarction and reduced perfusion of the extremities.

Argipressin may in rare cases cause water intoxication. The early signs of drowsiness, listlessness, and headaches should be recognised in time to prevent terminal coma and convulsions.

Argipressin should be used cautiously in the presence of epilepsy, migraine, asthma, heart failure, or any state in which a rapid increase of extracellular water may produce hazard for an already overburdened system.

In the paediatric population a positive benefit risk balance has not been demonstrated. The use of argipressin in this indication in children and neonates is not recommended (see section 5.1).

This medicine contains less than 1 mmol sodium (23 mg) per ml that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of carbamazepine, chlorpropamide, clofibrate, carbamide, fludrocortisone or tricyclic antidepressants may potentiate the antidiuretic effect of argipressin.

Concomitant use of demeclocycline, norepinephrine, lithium, heparine or alcohol may decrease the antidiuretic effect of argipressin.

Furosemide increases osmolal clearance and decreases renal clearance of vasopressin. Since plasma levels of vasopressin remain unaltered the clinical relevance of this interaction is low.

Ganglion blocking agents can cause a marked increase in sensitivity to the pressor effect of argipressin.

Tolvaptan and argipressin may both decrease their individual diuretic or antidiuretic effects.

Blood pressure elevating drugs may potentiate the blood pressure elevation induced by argipressin.

Blood pressure decreasing drugs may reduce the blood pressure elevation induced by argipressin.

4.6 Fertility, pregnancy and lactation

Pregnancy

No animal reproduction studies have been performed with argipressin. In reproductive toxicity studies with related substances abortions and malformations were observed. Argipressin may cause uterus contractions and increased intra-uterine pressure during pregnancy and may reduce uterine perfusion. Argipressin should not be used during pregnancy unless clearly needed.

Breastfeeding

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It is not known whether argipressin passes into breast milk and affect the child. Argipressin should be administered with caution in breastfeeding patients.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

No studies have been conducted to evaluate the influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions listed below, considered to be possibly or probably related to the administration of argipressin, were reported in 1,588 patients suffering from hypotension following septic shock of which 909 patients have been included in controlled clinical trials.

The most common serious adverse reactions (incidence below 10%) were: life threatening arrhythmia, mesenteric ischemia, digital ischemia and acute myocardial ischemia.

Tabulated listing of adverse reactions

The adverse reactions that may occur during treatment with Embesin are summarised below and are presented by system organ class and frequency category.

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

not known (cannot be estimated from the available data)

MedDRA system organ class (SOC)	Adverse reaction frequency
Metabolism and nutrition disorders	<u>Uncommon</u> : hyponatremia <u>Unknown</u> : Water intoxication, diabetes insipidus after discontinuation
Nervous system disorders	<u>Uncommon</u> : tremor, vertigo, headache
Cardiac disorders	<u>Common</u> : arrhythmia, angina pectoris, myocardial ischaemia <u>Uncommon</u> : reduced cardiac output, life threatening arrhythmia, cardiac arrest
Vascular disorders	<u>Common</u> : peripheral vasoconstriction, necrosis, perioral paleness
Respiratory, thoracic and mediastinal disorders	<u>Uncommon</u> : bronchial constriction
Gastrointestinal disorders	<u>Common</u> : abdominal cramps, intestinal ischaemia <u>Uncommon</u> : nausea, vomiting, flatulence, gut necrosis
Skin and subcutaneous tissue disorders	<u>Common</u> : skin necrosis, digital ischaemia** <u>Uncommon</u> : sweating, urticaria
General disorders and administration site conditions	<u>Rare</u> : anaphylaxis (cardiac arrest and / or shock) has been observed shortly after injection of argipressin
Investigations	<u>Uncommon</u> : in two clinical trials some patients with vasodilatory shock showed increased bilirubin and transaminase plasma levels and decreased thrombocyte counts during therapy with argipressin

** Digital ischemia may require surgical intervention in single patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

If water intoxication occurs, no fluids should be given and argipressin therapy may be temporarily interrupted until polyuria occurs. In severe cases, an osmotic diuresis may be performed using mannitol, hypertonic dextrose, urea with or without furosemide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin and analogues, ATC code: H01BA01

Mechanism of action

Argipressin (arginine vasopressin) is an endogenous hormone with osmoregulatory, vasopressor, hemostatic, and central nervous effects. Peripheral effects of arginine vasopressin are mediated by different vasopressin receptors, namely V1a-, V1b-, and V2-vasopressin-receptors. V1a-receptors have been found in arterial blood vessels, their activation induces vasoconstriction by an increase in cytoplasmatic ionized calcium via the Phosphatidyl-Inositol-Biphosphat-Cascade, which is the most prominent effect of argipressin.

During vasopressin infusion a linear blood pressure response can be seen in patients in vasodilatory shock (septic shock, vasoplegic shock and SIRS = systemic inflammatory response syndrome). Specifically, a significant correlation was demonstrated between baseline corrected mean arterial pressure (MAP) changes and the vasopressin dose. A comparable significant linear relationship was demonstrable between vasopressin doses and the increase in peripheral resistance as well as the decrease in norepinephrine requirements.

A decrease in heart rate has been observed in patients with septic shock while vasopressin was initiated and catecholamines were reduced in parallel. In a study in human volunteers, investigating the effect of vasopressin infusion after lisinopril, heart rates decreased from 67 +/- 6.5 to 62 +/- 4.5 beats/min ($P < 0.05$). A suppression of heart rate and cardiac index (CI) may only be expected at a dose range of 0.1 IU/min and higher.

Clinical efficacy

The clinical evidence for efficacy of argipressin in the claimed indication of hypotension following catecholamine-refractory septic shock is based on analysis of several clinical trials and publications. A total of 1,588 septic shock patients who have been treated with vasopressin under controlled conditions to date have been included in this analysis.

The largest investigation of vasopressin in septic shock was a multicentre, randomized, double-blind trial (VASST trial), where a total of 778 patients with septic shock were randomized to receive either low-dose vasopressin (0.01 to 0.03 IU/min) or norepinephrine (5 to 15 µg/min) in addition to open label vasopressors. Patients who were 16 years or older and had septic shock resistant to fluids, defined as lack of response to 500 ml of normal saline, or a requirement for vasopressors or low-dose norepinephrine, were considered for enrolment. Patients needed to have received ≥ 5 microgram/min of norepinephrine or equivalent for at least six consecutive hours in the preceding 24 hours and to have received at least 5 microgram/min within the last hour prior to randomization or norepinephrine equivalent > 15 microgram/hr for three consecutive hours. The primary endpoint was death of any cause and was assessed 28 days after initiation of the study drug. There was no significant difference between the vasopressin (35.4%) and the norepinephrine (39.3%) groups (95% confidence interval -2.9% to +10.7%; $p=0.26$). Similarly, there was no significant difference in the mortality rate at 90 days (43.9% and 49.6%, respectively; $p=0.11$). In a recent double blind randomised study (VANISH) comparing norepinephrine to early argipressin (up to 0.06 U/min) mortality in the argipressin group was 30.9% and in the norepinephrine group was 27.5%. One or more serious adverse events were seen in 10.7 % of argipressin and 8.3% of norepinephrine patients. Significantly less renal replacement therapy was necessary in the argipressin group compared to the norepinephrine group (25.4% vs 35.3%).

Effects on QT and QTc

Experimentally high doses of vasopressin were shown to induce ventricular arrhythmias in animals. In the intended dose range and application form (chronic infusion) QT and QTc prolongation is not described. Single cases of torsade de point tachycardias in patients receiving vasopressin for the treatment of oesophageal variceal bleedings with doses more than 10 times the recommended level have been described but no final conclusions on the torsadogenic potential are possible.

Paediatric population

In a double blind randomised placebo controlled study (Choong et al, 2009) including 69 paediatric patients with vasodilatory shock (age range 4 – 14 years, 54 with septic shock), 35 patients received vasopressin (starting dose of 0.0005 U/kg/min uptitrated up to 0.002 U/kg/min) and 34 placebo. There was no difference between vasopressin and placebo in the primary efficacy parameter (time vasoactive free hemodynamic stability, 49.7 hours in the vasopressin group and 47.1 hours in the placebo group) and in secondary efficacy parameter such as ventilator free days etc. 10 patients (30.3 %) died in the

vasopressin group, 5 (15.6 %) in the placebo group. It is unclear, to which degree this result was related to baseline differences.

5.2 Pharmacokinetic properties

Absorption

Steady state plasma levels were achieved after 30 min of continuous infusion of doses between 10 and 350 µU/kg/min (i.e. 0.007-0.0245 IU/min) which corresponds to a half-life of less than 10 minutes. Plasma exposure was close to dose-linearity in this dose range.

Biotransformation

Vasopressin metabolism was demonstrable in human liver and kidney homogenates.

No specific studies were conducted investigating pharmacokinetics (PK) in patients with renal or hepatic impairment.

There is no information on the influence of age, gender and race on pharmacokinetic effects. No PK data are available for the paediatric population.

Elimination

Approximately 5% of a subcutaneous dose of argipressin is excreted unchanged in the urine four hours after administration.

5.3 Preclinical safety data

Systematic research results on the preclinical safety, repeated dose toxicity, reproduction toxicity, genotoxicity and carcinogenic potential are not available. The clinical experiences with the use of argipressin do not show any particular risk to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, glacial acetic acid for pH adjustment, water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

36 months.

Once opened, dilute and use immediately.

6.4 Special precautions for storage

Store refrigerated (2°C – 8°C).

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Embesin is supplied in clear, type I glass ampoules containing a sterile concentrate for solution for infusion.

- **1 ml ampoule:** Type I clear – glass ampoule (One Point Cut ampoule).
- **2 ml ampoule:** Type I clear – glass ampoule (Colour Break Ring ampoule).

Pack sizes:

- **1 ml ampoule:** Boxes of 10 ampoules
- **2 ml ampoule:** Boxes of 5 or 10 ampoules

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Embesin concentrate must not be administered without dilution.

The solution should be checked for visible particles and discolouration prior to the use. Only clear and colourless solutions should be used.

Prepare a solution for infusion by performing the following dilution:

- **1 ml ampoule:** Dilute 1 ml of the concentrate with 24 ml of sodium chloride 9 mg/ml (0.9%) solution (equivalent to 0.8 IU argipressin per ml). The total volume after dilution should be 25 ml.
- **2 ml ampoule:** Dilute 2 ml of the concentrate with 48 ml of sodium chloride 9 mg/ml (0.9%) solution (equivalent to 0.8 IU argipressin per ml). The total volume after dilution should be 50 ml.

Single use ampoules, discard any remaining solution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.6 Special precautions for disposal and other handling

Embesin concentrate must not be administered without dilution.

The solution should be checked for visible particles and discolouration prior to the use. Only clear and colourless solutions should be used.

Prepare a solution for infusion by diluting 2 ml of the concentrate with 48 ml of sodium chloride 9 mg/ml (0.9%) solution (equivalent to 0.8 I.U. argipressin per ml). The total volume after dilution should be 50 ml.

Single use ampoules, discard any remaining solution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Orpha-Devel Handels und Vertriebs GmbH
Wintergasse 85/1B
A-3002 Purkersdorf
Austria

8 MARKETING AUTHORISATION NUMBER

PA1353/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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