1. NAME OF THE MEDICINAL PRODUCT

Embesin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule with 2 ml concentrate for solution for infusion contains 40 I.U. argipressin (equating 133 microgram).
1 ml concentrate for solution for infusion contains 20 I.U. argipressin (equating 66.5 microgram).

Excipients with known effect: Each ml contains less than 23 mg of sodium.
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 65 – 75 mmHg despite adequate volume substitution and application of catecholamines (see section 5.1).

4.2 Posology and method of administration

The therapy with argipressin in patients with catecholamine refractory hypotension is slowly started by a continuous intravenous infusion of 0.01 I.U. 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 I.U. 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 I.U. per minute should only be applied as emergency treatment, as this may cause gut and skin necrosis (see section 4.4).
Dose reductions of Embesin should be done in accordance with the clinical course. The treatment duration should also be chosen according to the individual clinical picture.

The solution for infusion is prepared by diluting 40 I.U. Embesin with NaCl 9 mg/ml (0.9%) solution. The total volume after dilution should be 50 ml (equivalent to 0.8 I.U. argipressin per ml).

Infusion rates according to the recommended doses:

Dose Embesin / min	Dose Embesin / hour	Infusion rate

0.01 I.U.	0.6 I.U.	0.75 ml / hour
0.02 I.U.	1.2 I.U.	1.50 ml / hour
0.03 I.U.	1.8 I.U.	2.25 ml / hour

Paediatric population
Embesin is not indicated for children under 18 years and old.

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.

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.

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, chlorpropamine, 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 urinary 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.

Tolvaptane 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
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 (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥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	Uncommon: hyponatremia Unknown: Water intoxication, diabetes insipidus after discontinuation
Nervous system disorders	Uncommon: tremor, vertigo, headache
Cardiac disorders	Common: arrhythmia, angina pectoris, myocardial ischaemia Uncommon: reduced cardiac output, life threatening arrhythmia, cardiac arrest
Vascular disorders	Common: peripheral vasoconstriction, necrosis, perioral paleness
Respiratory, thoracic and mediastinal disorders	Uncommon: bronchial constriction
Gastrointestinal disorders	Common: abdominal cramps, intestinal ischaemia Uncommon: nausea, vomiting, flatulence, gut necrosis
Skin and subcutaneous tissue disorders	Common: skin necrosis, digital ischaemia** Uncommon: sweating, urticaria
General disorders and administration site conditions	Rare: anaphylaxis (cardiac arrest and / or shock) has been observed shortly after injection of argipressin

Investigations	Uncommon: 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 suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

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. V1-receptors have been found in arterial blood vessels, and induce vasoconstriction by an increase in cytoplasmatic ionized calcium via the phosphatidyl-inositol-bisphosphonate cascade, which is the most prominent effect of argipressin.
During vasopressin infusion a linear blood pressure response can be seen in patients in vasodilatatory shock (septic, vasoplegic and SIRS = systemic inflammatory response syndrome). Specifically, a significant correlation was demonstrable between baseline corrected 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 µg/min of norepinephrine or equivalent for at least six consecutive hours in the preceding 24 hours and to have received at least 5 µg/min within the last hour prior

to randomization or norepinephrine equivalent > 15µg/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 esophageal variceal bleedings with doses more than 10 times the recommended level have been described but no final conclusions on the torsadogenic potential are possible.

5.2 Pharmacokinetic properties

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.
Vasopressin metabolism was demonstrable in human liver and kidney homogenates. Approximately 5% of a subcutaneous dose of argipressin is excreted unchanged in the urine four hours after application.

No specific studies were conducted investigating pharmacokinetics 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.

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

The expiry date of the product is indicated on the packaging materials.
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

Clear glass ampoules (Type I, with a broken ring on the narrow part of the ampoule) with 2 ml concentrate for solution for infusion.
Pack sizes: 5 and 10 ampoules.
Not all pack-sizes may be marketed.

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.

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

7. MANUFACTURER

Amomed Pharma GmbH
Leopold-Ungar-Platz 2,
1190 Vienna, Austria

8. MARKETING AUTHORISATION HOLDER

AOP ORPHAN PHARMACEUTICALS ISRAEL LTD.
10 Riza St. Aseret 7685800
Israel

9. MARKETING AUTHORISATION NUMBER

163-92-35430

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