Package leaflet: Information for the user
Embesin 40 IU/2 ml concentrate for solution for infusion
Argipressin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:
1. What Embesin is and what it is used for
2. What do you need to know before you use Embesin
3. How to use Embesin

Embesin is an artificially produced active substance equivalent to the natural hormone vasopressin. It regulates the water balance of the body and reduces the urinary excretion. Embesin is used in states of septic shock after unsuccessful use of other adequate methods to obtain target blood pressure values set by treating physicians.

2. What do you need to kno
w before you use Embesin
Do not
ecautions for use of Embesin is mandatory,
- if it i **use Embesin**
- if you are hypersensitive to argipressin or any of the other excipients of Embesin.

Special pr s used for increasing the blood pressure in cases of shock following the use of other methods. The administration must be carried out under close control of vital parameters.
- if it is used in patients with cardiovascular diseases.
- if it is administered in patients with epilepsy, migraine, asthma, heart failure, or with a disease in which a rapid increase of extracellular water represents a risk.
- if the patient suffers from chronic nephritis.

Children and adolescents
The use of Embesin in this indication in children and neonates is not recommended

Other medicines and Embesin
Embesin should be administered with care together with carbamazepine, chlorpropamide, clofibrate, urea, fludrocortisone or tricyclic antidepressants since these agents can enhance the effect of Embesin. Embesin should be administered with care together with demeclocycline, noradrenaline, lithium, heparin or alcohol, since its effects can thereby be

reduced. The concomitant use of Embesin with blood pressure altering medicines may increase or decrease respectively the blood pressure elevation induced by Embesin. Tell your doctor or pharmacist if you are taking/using or have recently taken/used any other medicines, even if this involves over-the-counter pharmaceuticals.

Embesin with food and drinks
Embesin may not be used in combination with alcohol.

Pregnancy and breast-feeding
Embesin may cause uterus contractions and increased intra-uterine pressure during pregnancy and may reduce uterine perfusion. Embesin should not be used during pregnancy unless clearly needed.
Whether Embesin is excreted in human milk is not known.

The use of Embesin during pregnancy and during lactation is not recommended.
Please ask your doctor or pharmacist for advice before taking any medications.

Driving and using machines
No studies have been performed on the effects of ability to drive or to use machines.

Important information about certain excipients of Embesin
This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, i.e. it is nearly sodium-free.

3. How to use Embesin

Embesin will be administered by a physician.

Embesin should only be used in addition to conventional treatment. Initially, 0.01 IU of Embesin per minute are administered as an infusion. This dose can be increased every 15-20 minutes by up to 0.03 IU Embesin per minute. Higher doses should only be used in the event of an emergency.

Embesin is administered as a long-term infusion and must be diluted with physiological saline solution.

Use in children and adolescents
Embesin has been used to treat certain conditions of shock in infants, toddlers and children in the intensive care unit and in the operating room. However, the general use of Embesin in this indication in children and neonates is not recommended.

If you use more Embesin than you should
This medication will be administered by a physician. If you believe that you were administered too high a dose of this medicine, talk to your doctor immediately.

If you stop using Embesin

The discontinuation of treatment with this medicine must occur gradually, which means the treatment must not be stopped abruptly. If you believe that the use of the medicine was stopped too early, talk to your doctor immediately. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medications, Embesin may cause side effects, although not everybody gets them.

Common (may affect up to 1 in 10 people):

- abnormal heartbeat
- chest tightness
- circulatory disorders of the myocardium the intestine or the finger tips
- narrowing of peripheral blood vessels
- death of tissue
- abdominal cramps
- paleness around the mouth
- death of skin tissue

Uncommon (may affect up to 1 in 100 people): low blood sodium level

- shakiness
- dizziness
- headache
- reduced cardiac output
- life threatening change in the heart beat
- cardiac arrest
- breathing distress caused by narrowing of the airways
- nausea
  vomiting
- flatulence
- death of gut tissue
- sweating
- rash
- changes in certain blood laboratory values

Rare (may affect up to 1 in 1,000 people)

- severe, life-threatening allergic reaction

Not known (frequency cannot be estimated from the available data):

- Water intoxication, diabetes insipidus after discontinuation.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2

Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Embesin

Keep this medicine out of the sight and reach of children.

Store in a refrigerator (2°C - 8°C).

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

Once opened, dilute and use immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Embesin contains
The active substance is argipressin.
1 ampoule with 2 ml concentrate for solution for infusion contains argipressin acetate corresponding to 40 I.U. argipressin (equal to 133 microgram).
The other excipients are: sodium chloride, glacial acetic acid to adjust the pH value, water for injection.

What Embesin looks like and contents of the pack
Embesin is a clear, colorless concentrate for solution for infusion .
Each pack contains 5 or 10 ampoules.
Not all pack-sizes may be marketed.

Marketing Authorization Holder
Orpha-Devel Handels und Vertriebs GmbH
Wintergasse 85/1B
3002 Purkersdorf
Austria

Manufacturer
AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2

1190 Vienna
Austria

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Empesin 40 I.E./2 ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Reverpleg 40 I.E./2 ml concentraat voor oplossing voor infusie
Bulgaria	Емпресин 40 IU/2ml Концентрат за инфузионен разтвор Embesin 40 IU/2ml concentrate for solution for infusion
Czech Republic	Embesin
Germany	Embesin 40 I.E./2 ml Konzentrat zur Herstellung einer Infusionslösung
Denmark	Embesin
Estonia	Empesin
Greece	Embesin 40 I.U./2 ml Πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Spain	Embesin 40 I.U./2 ml concentrado para solución para perfusión
Finnland	Embesin 40 I.U./2 ml infuusiokonsentraatti, liuosta varten
France	Reverpleg 40 U.I./2ml solution á diluer pour perfusion
Hungary	Embesyn 40 N.E./2ml koncentrátum oldatus infúzióhoz
Italy	Embesin 40 I.U./2 ml concentrato per soluzione per infusione
Lithuania	Empesin
Luxembourg	Reverpleg 40 I.U./2 ml solution à diluer pour perfusion
Latvia	Empesin 40 SV/2 ml koncentrāts infūziju šķīduma pagatavošanai
Netherlands	Embesine 40 I.E./2ml, concentraat voor oplossing voor infusie
Norway	Embesin
Poland	Empesin
Portugal	Embesin 40 U.I./2ml concentrado para solução para perfusão
Romania	Reverpleg
Sweden	Embesin 40 I.E./2 ml koncentrat till infusionsvätska, lösning
Slovenia	Empesin 40 I.E./2 ml koncentrat za raztopino za infundiranje
Slovak Republic	Embesin 40 IU/2 ml infúzny koncentrát

This leaflet was last revised in 09/2021

The following information is intended for healthcare professionals only:

Posology and 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 of the SmPC). Argipressin should be administered by 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 and increase the risk for cardiac arrest (see section 4.4 of the SmPC). 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.

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.

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

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.

Contraindications

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

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 of the SmPC).