VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Septic shock is a serious medical condition which starts with an infection somewhere in the body. Failure of the immune system allows the infection to spread and enter the bloodstream. The immune system goes into overdrive attempting to fight the infection, secreting substances which dilate blood vessels. As the blood vessels expand, blood pressure drops, and the bloodflow to the body is drastically reduced.

Due to the decreased blood supply and the rising acid level, the organs in the body begin to fail. When bloodflow fails to reach crucial organs like the brain and heart, the patient can fall into a coma and eventually die. The death rate ranges from 20% to 50%.

This condition most commonly occurs in the young, the elderly, and people with compromised immune systems. Men have a higher risk for developing sepsis than women, regardless of age.

VI.2.2 Summary of treatment benefits

Argipressin 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. Argipressin is used in states of

septic shock after unsuccessful use of other adequate methods when blood pressure values of 65-75 mmHg are not to be obtained.

The evidence for treatment benefits of argipressin in the above-mentioned indication is based on the analysis of several clinical studies and publications. A total of 1588 septic shock patients who have been treated with argipressin under controlled conditions have been included in this analysis.

Argipressin has been proven to successfully stabilize the dynamics of blood flow in septic shock. Additionally, latest data suggest a survival benefit for argipressin in patients with less severe septic shock. The use of argipressin is included in the 2012 Surviving Sepsis Campaign guidelines.

Overall, it may be concluded that argipressin is effective and safe in the treatment of low blood pressure in septic shock after unsuccessful use of other adequate methods.

VI.2.3 Unknowns relating to treatment benefits

Use in patients with liver problems (hepatic impairment)
No specific studies were conducted investigating the movements of argipressin, including biotransformation and excretion, in patients with liver problems.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Heart-related side effects (cardiac adverse events)	Empressin may cause side effects affecting the heart, especially at higher doses. Circulatory discorders of the heart muscle (myocardial ischaemia), abnormal heart beat and chest tightness are common side effects, whereas sudden stopping of heart (cardiac arrest), life-threathening change in the heart beat and reduced cardiac output are uncommon side effects of treatment with argipressin.	Yes, Empressin should be used with special caution in patients with heart diseases
Circulatory side effects (vascular adverse events)	Circulatory side effects are common with Empressin. They might affect the finger tips or the intestine and lead to death of tissue.	Yes, Empressin should be used with special caution in patients with vascular diseases
Death of skin tissue (skin necrosis)	Empressin may lead to peripheral narrowing of blood vessels and eventually death of skin tissue.	Yes, by closely controlling vital parameters and watching out for early signs such as pale areas of skin.
Allergic reactions / life-threatening allergic reaction (Hypersensitivity / Anaphylactic reaction)	Some people might be allergic to argipressin. Severe, life-threatening allergic reactions to argipressin are rare.	No. Do not use Empressin if you are hypersensitive to argipressin or any of the other ingredients of Empressin.
Hyperhydration and water intoxication	Water intoxication is a known side effect of Empression. Special precautions for use of Empressin is mandatory, 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.	Yes, by closely controlling vital parameters and watching out for early signs of drowsiness, listlessness, and headaches.

Important potential risks

None

Missing information

Use in patients with liver problems (hepatic impairment)	No specific studies were conducted investigating the movements of argipressin, including biotransformation and excretion, in patients with liver problems.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	**Date**	**Safety Concerns**	**Comment**
1.0	At time of authorisation dd/mm/yyyy	*Important Identified Risks:* - Adverse cardiac events *Important Potential Risks:* - Ischemic skin lesions - Adverse events on gastrointestinal tract - Decrease in platelet count *Missing information:* N/A	-
2.0	27/03/2017	*The following changes are proposed to the*	As the template of the RMP was revised in 2012

Version	Date	Safety Concerns	Comment
		important identified risks: Addition of: - Vascular adverse events - Skin necrosis (formerly classified as important potential risk under the term "ischemic skin lesions") - Hypersensitivity / Anaphylactic reaction - Hyperhydration and Water intoxication Adverse cardiac events were rephrased to "cardiac adverse events". *The following changes are proposed to the important potential risks:* Addition of: - Harmful effects on pregnancy and foetus - Torsade de pointes - Use in paediatric population Adverse events on gastrointestinal tract were rephrased to "gastrointestinal tract adverse events". "Ischemic skin lesions" were reclassified from potential to identified risk (see above). *The following changes are proposed to missing information:* Addition of:	the RMP was updated using the current valid version of the template of the RMP (Guidance on format of the risk management plan (RMP) in the EU – in integrated format; EMA/465932/2013 Rev.1). The safety concerns were updated taking into consideration the definitions quoted in the Guideline on good pharmacovigilance practices (GVP) Annex I – Definitions (EMA/876333/2011 Rev 3) as well as other guidance documents (GVP Module V – Risk management systems and Guidance on format of the risk management plan (RMP) in the EU – in integrated format). The information provided in the Risk Management Plan was adapted to the approved SmPC.

Version	Date	Safety Concerns	Comment
		- Use in patients with hepatic impairment	
2.3	01-Feb-2018	The important Identified Risks were deleted and information regarding "Adverse events on gastrointestinal tract" integrated into the vascular adverse events (important identified risks). -	According to Assessment Report of MRP procedure DE/H/4530/01/MR