VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 OVERVIEW OF DISEASE EPIDEMIOLOGY

Volume depletion takes place when fluid is lost from the extracellular space at a rate exceeding net intake. Acute haemorrhage is the leading cause of acute life-threatening intravascular volume loss requiring aggressive fluid resuscitation to maintain tissue perfusion until the underlying cause can be corrected. Other intravascular volume depletions may result from gastrointestinal disorders (e.g. vomiting, diarrhoea, or ascites), burns, environmental exposure, or renal salt wasting. Volume depletion may also result from acute sequestration in the body in a "third space" that is not in equilibrium with the intracellular fluid, as seen in septic shock (Third spacing is the unusual accumulation of fluid in a transcellular space. Transcellular, consists of those spaces in the body where fluid does not normally collect in larger amounts or where any significant fluid collection is physiologically nonfunctional).

Without adequate fluid resuscitation, tissue hypoperfusion leads to lactate production and metabolic acidosis. Once the physiologic response to hypovolemia is overwhelmed by prolonged tissue hypoxia, myocardial contractility is depressed and hypoxia and acidosis result in the loss of peripheral vasoconstriction, release of inflammatory mediators and activation of cellular apoptotic pathways, eventually leading to death.

Initial fluid resuscitation is generally accepted to begin with the infusion of crystalloids. If no acceptable hemodynamic improvement occurs after 2-3 L infusion of crystalloids in patients with shock, a blood transfusion may be needed. In the setting of massive haemorrhage, beginning blood transfusion immediately is appropriate.

VI.2.2 SUMMARY OF TREATMENT BENEFITS

Geloplasma is a modified liquid gelatine in ionic solution similar to that of extracellular fluid, to be used for vascular filling and restoration of water/electrolyte balance.

This solution enables:

- restoration of blood volume, volume by volume, without plasma expansion due to intravascular transfer of interstitial fluids;

- haemodilution with lowering of blood viscosity and improvement of the microcirculation;

- rehydration of the extravascular sector.

This solution contributes in the restoration of ionic balance and the correction of acidosis.

Liquid gelatin also slightly increases urine output.

In the presence of heavy bleeding, alternate administration of blood and liquid gelatine ensures adequate haemodilution (restoration of blood volume and maintenance of oncotic pressure).

The volume efficacy of isooncotic colloids is higher compared to crystalloid solutions. In the hypovolemic patient with normal pulmonary function, the use of colloids to maintain colloid-osmotic pressure may limit the development of peripheral as well as pulmonary oedema (Vincent 2000).

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

Geloplasma is a well-established product. There are no significant unknowns regarding the benefits of the product.

VI.2.4 SUMMARY OF SAFETY CONCERNS

Safety Concern	**What is known**	**Preventability**
Important Identified Risks		
Hypersensitivity to modified liquid gelatin	Hypersensitivity to gelatin solutions may occur	Limited, Geloplasma is contraindicated in patients with hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 of the SmPC.
Worsening conditions of fluid overload in patients with predominantly extracellular hyperhydration	The solution is contraindicated in predominantly extracellular hyperhydration situations (excessive fluids in the body). Products like Geloplasma, which are to be used for vascular filling and restoration of water/electrolyte balance are contraindicated in predominantly extracellular hyperhydration situations.	Yes, the solution is contraindicated in predominantly extracellular hyperhydration Use of this solution requires clinical and laboratory monitoring of the patient's status: - blood pressure, and possibly central venous pressure; - urine output; - haematocrit and electrolytes.
Worsening of electrolyte disturbances and cardiac dysfunction in patients with hyperkalemia	The solution is contraindicated in Hyperkalemia (high level of potassium in blood). Moreover, this solution contains potassium, it is preferable to avoid using potassium and medicinal products that may cause hyperkalemia (e.g. potassium, sparing diuretics, ACE inhibitors). Patients with reduced kidney function or on restricted potassium or sodium diet should take this information into consideration.	Yes, the solution is contraindicated in Hyperkalemia Use of this solution requires clinical and laboratory monitoring of the patient's status: - blood pressure, and possibly central venous pressure; - urine output; - haematocrit and electrolytes.
Worsening of alkalosis in patients with metabolic alkalosis	This solution may cause metabolic alkalosis because of the presence of lactate ions. Metabolic alkalosis is a pH imbalance in which the body has accumulated	Yes, the solution is contraindicated in Metabolic alkalosis Use of this solution requires clinical and laboratory monitoring of the patient's status:

Safety Concern	What is known	Preventability
	too much of an alkaline substance, such as bicarbonate, and does not have enough acid to effectively neutralize the effects of the alkali.	- blood pressure, and possibly central venous pressure; - urine output; - haematocrit and electrolytes.
Foetal and neonatal distress when used at the end of pregnancy (during labor/delivery) in women presenting with anaphylactic/anaphylactoid reaction to modified liquid gelatin	Due to possible allergic reaction, this medicinal product must not be given to pregnant women at the end of pregnancy (during labor/delivery). It should not be used for the prophylaxis of hypovolemia during delivery with analgesia or epidural anaesthesia; however it can be used to treat hypovolemia when plasma volume replacement is needed during pregnancy.	Yes, this product is contraindicated at the end of pregnancy (during labor/delivery). Due to this possible allergic reaction, this medicinal product must not be given to pregnant women at the end of pregnancy.
Risk to foetus during delivery with analgesia or epidural anaesthesia	As with all drugs, the benefits and risks of use should be assessed in the light of the patient's condition: under these circumstances this preparation should only be prescribed when the potential advantage outweighs the potential risk to the foetus. It should not be used for the prophylaxis of hypovolemia during delivery with analgesia or epidural anaesthesia; however it can be used to treat hypovolemia when plasma volume replacement is needed during pregnancy.	Limited, the product should only be prescribed after assessing the benefits and risks of use in the light of the patient's condition: under these circumstances this preparation should only be prescribed when the potential advantage outweighs the potential risk to the foetus. It should not be used for the prophylaxis of hypovolemia during delivery.
Important Potential Risks		
None	None	None
Missing Information		
Use in breast-feeding and pregnant women	There are limited amount of data from the use of this product in pregnant or lactating women. No embryotoxic effect has, however, until this time been observed, but there is a risk of severe anaphylactic/anaphylactoid reactions, with consequential foetal and neonatal distress secondary to maternal hypotension.	

Safety Concern	What is known	Preventability
	It is unknown whether this product/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.	

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.

The Summary of Product Characteristics and the Package leaflet for Geloplasma can be found in Annex 2 of this RMP.

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
2.0	15/07/2015	Missing information: Use in breast-feeding and pregnant women	The existing RMP was updated to the applicable template with the mentioned safety concern.
3.0	20/06/2016	Risks are re-worded as per the RMP assessment report FR/H/290/01/II/017 Allergic reaction removed as an identified risk which is to be merged with the important identified risk of "hypersensitivity to active substance or any of the excipients listed in section 6.1". Use during delivery with analgesia or epidural	Stated changes are made to be in compliance with the assessment report (variation FR/H/290/01/II/017).

Version	Date	Safety Concerns	Comment
		anaesthesia (risk to foetus) added as potential risk	
4.0	31/08/16	Rewording as per the Risk Management Plan (RMP) Final assessment report FR/H/290/01/II/017 The identified risk are re-worded to "Hypersensitivity to modified liquid gelatin", "Worsening conditions of fluid overload in patients with predominantly extracellular hyperhydration", "Worsening of electrolyte disturbances and cardiac dysfunction in patients with hyperkalemia", "Worsening of alkalosis in patients with metabolic alkalosis" and "Foetal and neonatal distress when used at the end of pregnancy (during labor/delivery) in women presenting with anaphylactic/anaphylactoid reaction to modified liquid gelatin" The important potential risk "Use during delivery with analgesia or epidural anesthesia (risk to foetus) is recategorized as an important identified risk and reworded as "Risk to foetus during delivery with analgesia or epidural anaesthesia".	Stated changes are made to be in compliance with the Risk Management Plan (RMP) Final assessment report (variation FR/H/290/01/II/017