Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflet

Note:

The relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information shall be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

I. Summary of Product Characteristics

<▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.>

[...]

Section 4.1 Therapeutic indications

[The wording of this section should be read as below]

Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. (see sections 4.2, 4.3 and 4.4)

Section 4.2 Posology and method of administration

[This section should be amended to reflect the following wording]

Use of HES should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h.

The first 10-20 ml should be infused slowly and under careful monitoring of the patient so that any anaphylactoid reaction can be detected as early as possible.

The maximum daily dose is *<30ml/kg for 6% HES (130/0.40) and 6% HES (130/0.42); for other HES products the maximum daily dose should be recalculated accordingly>*.

The lowest possible effective dose should be applied. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved. The maximum recommended daily dose must not be exceeded.

Paediatric population:
Data are limited in children therefore it is recommended not to use HES products in this population.

[...]

Section 4.3 Contraindications

[This section should be amended to include the following contraindications]

- hypersensitivity to the active substances or to any of the other excipients listed in section 6.1
- sepsis
- burns
- renal impairment or renal replacement therapy
- intracranial or cerebral haemorrhage
- critically ill patients (typically admitted to the intensive care unit)
- hyperhydration
- pulmonary oedema
- dehydration
- hyperkalaemia *[only applicable to products containing potassium]*
- severe hypernatraemia or severe hyperchloraemia
- severely impaired hepatic function
- congestive heart failure
- severe coagulopathy
- organ transplant patients

[...]

Section 4.4 Special warnings and precautions for use

[This section should be amended to reflect the following wording]

Because of the risk of allergic (anaphylactoid) reactions, the patient should be monitored closely and the infusion instituted at a low rate (see section 4.8).

Surgery and trauma:
There is a lack of robust long term safety data in patients undergoing surgical procedures and in patients with trauma. The expected benefit of treatment should be carefully weighed against uncertainty with regard to this long term safety. Other available treatment options should be considered.

The indication for volume replacement with HES has to be considered carefully, and haemodynamic monitoring is required for volume and dose control. (See also section 4.2.)

Volume overload due to overdose or too rapid infusion must always be avoided. The dosage must be adjusted carefully, particularly in patients with pulmonary and cardiocirculatory problems. Serum electrolytes, fluid balance and renal function should be monitored closely.

HES products are contraindicated in patients with renal impairment or renal replacement therapy (see section 4.3). The use of HES must be discontinued at the first sign of renal injury.
An increased need for renal replacement therapy has been reported up to 90 days after HES administration. Monitoring of renal function in patients is recommended for at least 90 days.

Particular caution should be exercised when treating patients with impaired hepatic function or in patients with blood coagulation disorders.
Severe haemodilution resulting from high doses of HES solutions must also be avoided in the treatment of hypovolaemic patients.
In the case of repeated administration, blood coagulation parameters should be monitored carefully.
Discontinue the use of HES at the first sign of coagulopathy.
In patients undergoing open heart surgery in association with cardiopulmonary bypass the use of HES products is not recommended due to the risk of excess bleeding.

Paediatric population:
Data are limited in children therefore it is recommended not to use HES products in this population. (see section 4.2)

[...]

Section 4.8 Undesirable effects

[This following wording should be reflected in this section]

[...]

Hepatic injury < frequency not known (cannot be estimated from the available data)>
Renal injury < frequency not known (cannot be estimated from the available data)>

[...]

II. Package Leaflet

< ▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects. >

[…]

1. What <*Product name*> is and what it is used for

[This section should be amended to include the below wording]

<*Product name*> is a plasma volume substitute that is used to restore the blood volume when you have lost blood when other products called crystalloids are not considered sufficient alone.

[…]

2. What you need to know before you use <*Product name*>

Do not use <*Product name*> if you:

[This section should be amended to include the below wording]

- are allergic to any of the active substances or any of the other ingredients of this medicine
- suffer from serious generalised infection (sepsis)
- suffer from burn injury
- have kidney impairment or receive dialysis
- have severe liver disease
- suffer from bleeding in the brain (intracranial *or cerebral* bleeding)
- are critically ill (e.g. you need to stay in an intensive care unit)
- have too much fluid in your body and you have been told that you have a condition known as hyperhydration
- have fluid in the lungs (pulmonary oedema)
- are dehydrated
- have been told that you have a severe increase of potassium [Note: only for products which contain potassium], sodium or chloride in your blood
- have severely impaired liver function
- have severe heart failure
- have severe problems with your blood clotting
- have received an organ transplant

[…]

Warnings and precautions

[This section should be amended to include the below wording]

It is important to tell your doctor if you have:
- impairment of your liver function
- problems with your heart or circulation
- blood clotting (coagulation) disorders
- problems with your kidneys

Because of the *risk of allergic* (anaphylactic/anaphylactoid*) reactions*, you will be monitored closely to detect early signs of an allergic reaction when you receive this medicine.

Surgery and trauma:
Your doctor will consider carefully if this medicine is suitable for you.

Your doctor will adjust the dose of <*Product name*> carefully in order to prevent fluid overload. This will be done especially if you have problems with your lungs or with your heart or circulation.

The nursing staff will also take measures to observe your body's fluid balance, blood salt level, and kidney function. If necessary you may receive additional salts.

In addition it will be ensured that you receive enough fluids.

<Product name> is contraindicated if you have kidney impairment or of kidney injury requiring dialysis.
If impaired kidney function occurs during therapy:
If the doctor detects first signs of kidney impairment he/she will stop giving you this medicine. In addition your doctor may need to monitor your kidney function for up to 90 days.

If you are given *<Product name>* repeatedly your doctor will monitor the ability of your blood to clot, bleeding time and other functions. In case of an impairment of the ability of your blood to clot, your doctor will stop giving you this medicine.

If you are undergoing open heart surgery and you are on a heart-lung machine to assist in pumping your blood during the surgery, the administration of this solution is not recommended.

[...]

3. How to use <Product name>

[This section should be amended to include the below wording]

Dosage
Your doctor will decide on the correct dose for you to receive.
Your doctor will use the lowest possible effective dose and will not infuse *<Product name>* for more than 24 hours.
The maximum daily dose is *<30ml/kg for 6% HES (130/0.40) and 6% HES (130/0.42); for other HES products the maximum daily dose should be recalculated accordingly>*.

Use in children
There is only limited experience of the use of this medicine in children. Therefore it is not recommended to use this medicine in children.

[...]

4. Possible side effects

[This section should be amended to include the below wording]

[...]

Frequency not known (cannot be estimated from the available data)
- Kidney injury
- Liver injury

Reporting of side effects
If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

[...]