Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information may 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.

Amendments to relevant sections of the Product Information

For all products in Annex I, the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below:

Summary of product characteristics

4.2 Posology and method of administration

[The following wording should be added, as appropriate]

Method of administration

As an alternative to bolus injection, terlipressin can be administered as a continuous intravenous (IV) infusion with a starting dose of 2 mg of terlipressin acetate/24 hours and increased to a maximum of 12 mg of terlipressin acetate/24 hours. Administration of terlipressin as continuous IV infusion may be associated with lower rates of severe adverse events than with administration by IV bolus (see section 5.1).

Special populations

Type 1 hepatorenal syndrome

Renal impairment

Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442µmol/L (5.0 mg/dL), unless the benefit is judged to outweigh the risks (see section 4.4).

Hepatic impairment

Terlipressin should be avoided in patients with severe liver disease defined as Acute-on-Chronic Liver Failure (ACLF) grade 3 and/or a Model for End-stage Liver Disease (MELD) score ≥39, unless the benefit is judged to outweigh the risks (see section 4.4).

Method of Administration

Type 1 hepatorenal syndrome: (…) or IV infusion

4.4 Special warnings and precautions for use

[This following wording should be reflected in this section]

Monitoring during treatment

During treatment, regular monitoring of blood pressure, heart rate, oxygen saturation, serum levels of sodium and potassium, as well as fluid balance are required. Particular care is required in management of patients with cardiovascular or pulmonary disease since terlipressin may induce ischemia and pulmonary vascular congestion.

Type 1 hepatorenal syndrome

Renal impairment

Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442µmol/L (5.0 mg/dL), when treated with terlipressin

for type 1 hepatorenal syndrome, unless the benefit is judged to outweigh the risks. Reduced efficacy in reversal of hepatorenal syndrome, increased risk of adverse events, and increased mortality in this patient group have been observed in clinical trials (see section 4.2).

Hepatic impairment

Terlipressin should be avoided in patients with severe liver disease defined as Acute-on-Chronic Liver Failure (ACLF) grade 3 and/or a Model for End-stage Liver Disease (MELD) score ≥ 39, when treated with terlipressin for type 1 hepatorenal syndrome, unless the benefit is judged to outweigh the risks. Reduced efficacy in reversal of hepatorenal syndrome, increased risk of respiratory failure, and increased mortality in this patient group have been observed in clinical trials (see section 4.2).

Respiratory events

Fatal cases of respiratory failure, including respiratory failure due to fluid overload, have been reported in patients treated with terlipressin for type 1 hepatorenal syndrome.

Patients with a new onset of breathing difficulties or worsening of respiratory disease should be stabilised prior to receiving their first dose of terlipressin.

Caution should be exercised when terlipressin is administered together with human albumin as part of the standard of care for type 1 hepatorenal syndrome. In case of signs or symptoms of respiratory failure or fluid overload, dose reduction of human albumin should be considered. If respiratory symptoms are severe or do not resolve, treatment with terlipressin should be discontinued.

Sepsis/ septic shock

Cases of sepsis/septic shock, including fatal cases, have been reported in patients treated with terlipressin for type 1 hepatorenal syndrome. Patients should be monitored daily for any signs or symptoms suggestive of infection.

4.8 Undesirable effects

[This following wording should be reflected in this section]

There are adverse reactions that appear twice in the table, as the estimated frequencies differ between indications.

[The following adverse reaction(s) should be added or revised as follows:]

SOC Respiratory, thoracic and mediastinal disorders:

Very common: Respiratory failure[a]

Very common: Dyspnoea[a]

Common: Pulmonary oedema[a]

Common: Respiratory distress[a]

Uncommon: Respiratory failure[b]
Uncommon: Pulmonary oedema[b]
Uncommon: Respiratory distress[b]
Rare: Dyspnoea[b]

SOC Infections and infestations:

Common: Sepsis/septic shock[a]

[a] Applicable to type 1 hepatorenal syndrome. Frequencies are calculated based on the pooled safety population in the OT-0401, REVERSE and CONFIRM clinical trials.

[b] Applicable to <other approved indications apart from type 1 hepatorenal syndrome>

Description of selected adverse reactions:

Safety related to method of administration

Based on results from a dedicated randomised controlled multicentre trial, administration of terlipressin as continuous IV infusion may be associated with lower rates of severe adverse events than with administration by IV bolus (see section 4.2 and 5.1).

5.1 Pharmacodynamic properties

[This following wording should be reflected in this section]

Clinical efficacy and safety

Continuous intravenous infusion versus intravenous boluses in the treatment of type 1 hepatorenal syndrome in patients with cirrhosis

The safety of continuous intravenous infusion of terlipressin has been compared with intravenous bolus in an open-label randomised controlled multicentre trial. Seventy-eight patients with type 1 hepatorenal syndrome were randomly assigned to either continuous intravenous infusion of terlipressin acetate at the initial dose of 2 mg/day or intravenous boluses of terlipressin acetate at the initial dose of 0.5 mg every 4 hours. In case of no response, the dose was progressively increased to a final dose of 12 mg/day in both groups. Albumin was given at the same dose in both groups. The primary endpoint was defined as the prevalence of treatment-related adverse events (AEs) between the two groups. Both the total rate of treatment-related AEs as well as severe treatment-related AEs were lower in the continuous infusion group than in the bolus group (all treatment-related AEs: 12/34 patients (35%) vs 23/37 patients (62%), p<0.025. Severe treatment-related AEs: 7/34 patients (21%) vs 16/37 patients (43%); p<0.05). The rate of response to terlipressin was not statistically significantly different between the continuous infusion and bolus groups (76% vs 65%). The probability of 90-day transplant-free survival was not significantly different between the continuous infusion group and the bolus group (53% vs 69%).

Package leaflet

2. What you need to know before you <take> <use> X

Warnings and precautions

[This following wording should be reflected in this section]

<PRODUCT NAME> can increase your risk of developing respiratory failure that may be life-threatening. If you experience difficulty breathing, or symptoms of fluid overload, before <PRODUCT NAME> is given or during treatment immediately inform your doctor.

If you are treated for very severe liver and kidney disease (type 1 hepatorenal syndrome), your doctor should ensure that your heart function and fluid and electrolyte balance are monitored during the treatment. Particular care is required if you have prior heart or lung disease since <PRODUCT NAME> can induce heart ischemia (decrease in the amount of blood flow to the heart) and respiratory failure (severe breathing difficulties). Treatment with <PRODUCT NAME> should be avoided if you have liver failure with multiple organ failures and/or kidney failure with very high levels of creatinine (a waste product) in the blood, as it increases your risk of adverse outcomes.

If you are treated for very severe liver and kidney disease, <PRODUCT NAME> can increase your risk of developing sepsis (bacteria in the blood and the body's extreme response to an infection) and septic shock (a serious condition that occurs when a major infection leads to low blood pressure and low blood flow). Your doctor will take additional precautions should this apply to you.

3. How to <take> <use> X

[The following wording should be added, as appropriate]

<X> is [injected] **or infused** intravenously.

Type 1 hepatorenal syndrome

You may also be given <PRODUCT NAME> as a drip (continuous intravenous infusion) usually starting with 2 mg terlipressin acetate per day and increased in a stepwise manner to a maximum of 12 mg terlipressin acetate per day.

4. Possible side effects

[The following wording should be added, as appropriate]

Tell your doctor or other healthcare professional straight away:

- If you develop breathing difficulties or experience a worsening of breathing ability (signs or symptoms of respiratory failure). This side effect is very common if you are treated for type 1 hepatorenal syndrome - may affect more than 1 in 10 people.

- If you develop signs or symptoms of infection of the blood (sepsis/septic shock), which may include fever and chills or very low body temperature, pale and/or bluish skin, severe breathlessness, urinating less than usual, fast heartbeat, nausea and vomiting, diarrhoea, fatigue and weakness, and feeling dizzy. This side effect is common if you are treated for type 1 hepatorenal syndrome - may affect up to 1 in 10 people.

Other side effects that may occur with different frequencies depending on the disease that you have.

Very common: may affect more than 1 in 10 people
If you have type 1 hepatorenal syndrome:
Shortness of breath (dyspnoea)

Common: may affect up to 1 in 10 people
If you have type 1 hepatorenal syndrome:
Fluid in the lungs (pulmonary oedema)
Difficulties in breathing (respiratory distress)

Uncommon: may affect up to 1 in 100 people
If you have < diseases relative to the other approved indications apart from type 1 hepatorenal syndrome>:
Fluid in the lungs (pulmonary oedema)
Difficulties in breathing (respiratory distress)

Rare: may affect up to 1 in 1,000 people
If you have < diseases relative to the other approved indications apart from type 1 hepatorenal syndrome>:
Shortness of breath (dyspnoea)