Part VI Summary of the risk management plan

Part VI: Summary of risk management plan for GLYPRESSIN/REMESTYP (terlipressin)

This is a summary of the risk management plan (RMP) for GLYPRESSIN/REMESTYP. The RMP details important risks of GLYPRESSIN/REMESTYP, how these risks can be minimised, and how more information will be obtained about GLYPRESSIN/REMESTYP's risks.

GLYPRESSIN/REMESTYP's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how GLYPRESSIN/REMESTYP should be used.

Important new concerns or changes to the current ones will be included in updates of GLYPRESSIN/REMESTYP's RMP.

I. The medicine and what it is used for

GLYPRESSIN/REMESTYP is authorised for indications bleeding oesophageal varices (BOV) and for type 1 hepatorenal syndrome (type 1 HRS) (see the SmPC for the full indication). GLYPRESSIN/REMESTYP contains terlipressin as the active substance and it is administered by injection or as continuous IV infusion (only for indication type 1 HRS).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of GLYPRESSIN/REMESTYP, together with measures to minimise such risks and the proposed studies for learning more about GLYPRESSIN/REMESTYP's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

In the case of GLYPRESSIN/REMESTYP these measurements are supplemented with additional risk minimisation measures mentioned under relevant important risks below.

II.A List of important risks and missing information

Important risks of GLYPRESSIN/REMESTYP are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of GLYPRESSIN/REMESTYP. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information for GLYPRESSIN/REMESTYP for indication type 1 HRS	
Important identified risks	Sepsis/septic shock Respiratory failure Increased mortality in patients with baseline serum creatinine (sCr) ≥442 µmol/L (5.0 mg/dL) at treatment initiation Increased mortality in patients with severe liver disease defined as acute-on-chronic liver failure (ACLF) grade 3 and/or model for end-stage liver disease (MELD) score ≥39
Important potential risks	None
Missing information	None

There are no safety concerns for indication BOV.

II.B Summary of important risks

Important Identified Risk: Sepsis/septic shock	
Evidence for linking the risk to the medicine	Data from terlipressin trials and from the company post-marketing safety database, literature.
Risk factors and risk groups	Risk factors for sepsis include young or old age, compromised immune system, diabetes, malignancy, chronic kidney or liver disease and history of previous sepsis. Patients with decompensated cirrhosis have a high baseline risk of sepsis/septic shock, and bacterial infections and sepsis are recognized as a distinct stage in the natural progression of

	chronic liver disease.[23] In addition to the factors predisposing the general population to the development of sepsis, the severity of the underlying liver disease also makes cirrhotic patients more susceptible to the development of sepsis.[24]
Risk minimisation measures	Routine risk minimisation measures: CCDS sections 4.8 and 4.4. Other routine risk minimisation measures beyond the product information: Legal status: Prescription only medicine for administration at hospital setting. Additional risk minimisation measures: Communication Plan (DHPC letter).

Important Identified Risk: Respiratory failure	
Evidence for linking the risk to the medicine	Data from terlipressin trials and from the company post-marketing safety database, literature.
Risk factors and risk groups	Infection, neurologic failure and older age (>65 years) has been recognised as risk factors for developing acute respiratory failure.[27] Patients with decompensated cirrhosis and type 1 HRS may develop respiratory failure due to factors specific to the advanced liver disease including hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax.[28] Additional pulmonary complications seen in these patients and resulting in acute respiratory failure include aspiration, pneumonia, volume overload, transfusion-related acute lung injury (TRALI), atelectasis, pleural effusion, acute respiratory distress syndrome (ARDS). In patients receiving terlipressin for type 1 HRS, ACLF grade 3 and/or a MELD score ≥39, and baseline sCr ≥442 µmol/L (5.0 mg/dL) may present additional risk factors for respiratory failure or other adverse events.[29]
Risk minimisation measures	Routine risk minimisation measures: CCDS sections 4.2, 4.4 and 4.8. Other routine risk minimisation measures beyond the product information: Legal status: Prescription only medicine for administration at hospital setting.

	Additional risk minimisation measures: Communication Plan (DHPC letter).

Important Identified Risk: Increased mortality in patients with baseline serum creatinine (sCr) ≥442 µmol/L (5.0 mg/dL) at treatment initiation	
Evidence for linking the risk to the medicine	Data from terlipressin trials and from the company post-marketing safety database, literature.
Risk factors and risk groups	Patients with baseline sCr ≥442 µmol/L (5.0 mg/dL) receiving terlipressin.
Risk minimisation measures	Routine risk minimisation measures: CCDS sections 4.2 and 4.4. Other routine risk minimisation measures beyond the product information: Legal status: Prescription only medicine for administration at hospital setting. Additional risk minimisation measures: Communication Plan (DHPC letter).

Important Identified Risk: Increased mortality in patients with severe liver disease defined as acute-on-chronic liver failure (ACLF) grade 3 and/or model for end-stage liver disease (MELD) score ≥39	
Evidence for linking the risk to the medicine	Data from terlipressin trials and from the company post-marketing safety database, literature.
Risk factors and risk groups	Patients with ACLF grade 3 and/or MELD score ≥39 receiving terlipressin.
Risk minimisation measures	Routine risk minimisation measures: CCDS sections 4.2 and 4.4. Other routine risk minimisation measures beyond the product information: Legal status: Prescription only medicine for administration at hospital setting. Additional risk minimisation measures: Communication Plan (DHPC letter).

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of GLYPRESSIN/REMESTYP.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for GLYPRESSIN/REMESTYP.