## VI.2 Elements for a Public Summary

Terlipressin SUN is a medicine used to stop bleeding from leaking varicose veins in the foodpipe also known as esophageal varices.

### *VI.2.1 Overview of disease epidemiology*

#### *Bleeding esophageal varices*

Esophageal varices are abnormal, enlarged veins in the tube that connects the throat and stomach (esophagus). Esophageal varices develop when normal blood flow to the liver is blocked by a clot or scar tissue in the liver (cirrhosis). To go around the blockages, blood flows into smaller blood vessels that aren't designed to carry large volumes of blood. The swollen vessels can leak blood or even rupture, causing severe bleeding and life-threatening complications.

The frequency of esophageal varices varies from 30% to 70% in patients with cirrhosis, and 9–36% of cirrhotic patients have what are known as "high-risk" varices. Esophageal varices develop in patients with cirrhosis at an annual rate of 5–8%, but only in 1–2% of cases the varices are large enough to pose a risk of bleeding. Approximately 4–30% of patients with small varices will develop large varices each year and will therefore be at risk of bleeding. Bleeding from esophageal varices, can occurs at a yearly rate of 5-15%. Esophageal variceal bleeding is associated with a 15-20% early mortality. In patients who survive the initial haemorrhage, the risk of rebleeding is as high as 60% within 2 years, with a 33% mortality. Elderly patients and people with chronic medical conditions withstand acute bleeding from esophageal; varices less well than younger, fitter patients, and have a higher risk of death.[1-3]

### *VI.2.2 Summary of treatment benefits*

Terlipressin is considered the vasoactive agent of choice in acute variceal bleeding and it should be given to all patients presenting with suspected variceal bleeding prior to endoscopy and following endoscopic confirmation.

Terlipressin SUN contains the active ingredient Terlipressin acetate, which is a drug similar to a hormone found naturally in the body called antidiuretic hormone (ADH) or vasopressin. Terlipressin is broken down in the body to release a substance called lysine vasopressin, which acts on the walls of blood vessels, causing them to narrow and decrease the blood flow to affected veins. This helps to stop or slow the bleeding.

Terlipressin SUN injection is given into a vein (intravenously). The effect is achieved within 30 min and is still significant 4 h after administration. One injection can be given every four hours until the bleeding has been controlled. The treatment may be administrated for a maximum of 3 days.

Several clinical trials that compared placebo (a dummy treatment) and Terlipressin have shown that Terlipressin is more effective than placebo to control the variceal bleeding. The overall efficacy of Terlipressin in controlling variceal bleeding is 75%-80% at 48 h and 67% at 5 days Terlipressin has been shown to significantly improve control of bleeding and survival when compared to placebo and is the only drug that has shown to improve survival.

There were also studies that compared Terlipressin, Somatostatin or endoscopic sclerotherapy efficacy in controlling variceal bleeding but no statistically significant difference was observed in any of the measured outcomes. In some studies Somatostatin improve control of bleeding, but show no effects on mortality (death rate), while Terlipressin was the only vasoactive treatment that have demonstrated effects on control of bleeding and on mortality [4-6]

### *VI.2.3 Unknowns relating to treatment benefits*

Very limited information is available regarding treatment benefits of Terlipressin in children and pregnant or breastfeeding women. There are also no adequate and well controlled studies in elderly patients > 70 years old.

### *VI.2.4 Summary of safety concerns*

## Important identified risks

| Risk | What is known | Preventability |
|---|---|---|
| ***1. Problems with heart or blood vessels***<br><br>[Cardiovascular events including angina, myocardial | Terlipressin may causes narrowing of blood vessels (vasoconstriction), thereby limiting blood flow to a particular area of the body. Due to insufficient blood flow to the tissues and organs, Terlipressin may compromise heart function and induce ischemic | Terlipressin should not be used in patients with insufficient blood circulation in the heart vessels (e.g. angina), |

| Risk | What is known | Preventability |
|---|---|---|
| ischemia, , peripheral or intestinal ischemia, hypertension heart failure with or without pulmonary oedema] | events (e.g heart, small bowel or skin)<br><br>Angina (chest pain) and ECG changes, may be signs of insufficient blood circulation in the heart vessels.<br><br>Insufficient blood circulation in arms, legs and skin, may cause pale skin or bluish coloration of the skin or lips and extremity pain. Signs of insufficient blood flow to the intestines may include severe abdominal pain with gastrointestinal bleeding, nausea (feeling sick) and vomiting.<br><br>Terlipressin administration may cause only mild increase in blood pressure. Although very high blood pressure values have been observed in patients with hypertension due to kidney problems and general blood vessel sclerosis (arteriosclerosis). | previous heart attack (myocardial infarction), or in those with hardening of arteries (arteriosclerosis).<br><br>Regular monitoring of the cardiovascular system (e.g. EKG, blood pressure). Blood pressure monitoring is recommend especially in patients suffering from uncontrolled high blood pressure. |
| ***2. Imbalance of minerals in the body***<br><br>[Electrolytes disturbances (e.g. hyponatraemia, hypokalaemia, hypomagnesaemia)] | Terlipressin is promoting the water reabsorption by the kidney and formation of concentrated urine. Excessive reuptake of electrolyte-free water into the blood circulation may lead to dilution of blood electrolytes.<br><br>Therefore, fluid balance and electrolytes should be monitored carefully as hyponatraemia (low level of sodium into the blood), hypokalaemia (low level of potassium into the blood), hypomagnesaemia (low level of magnesium into the blood) and other electrolyte disturbances have been reported during treatment with Terlipressin. | Frequent monitoring of serum electrolytes and fluid balance during the course of Terlipressin use. |
| ***3. Death of the skin tissue***<br><br>[Skin necrosis] | Several cases of skin ischemia (insufficient blood circulation in into the skin) and necrosis (death of skin tissue) unrelated to the injection site have been reported with Terlipressin use. Terlipressin is known to have narrowing effect on blood vessels that can cause significant decrease in blood circulation of the skin. Skin necrosis occurs when not enough blood and oxygen are supplied to a given skin region.<br><br>Patients with venous insufficiency or morbid obesity seem to have a greater tendency to this reaction. | Extreme caution should be exercised when administering Terlipressin in patients with obesity and venous circulation disorders. |
| ***4. Narrowing of airways into the lungs***<br><br>[Bronchospasm] | Terlipressin may cause contraction of the smooth muscles in the lung walls that can lead to airways narrowing (bronchospasm).<br><br>Doctor should be informed immediately if the patient experiences severe shortness of breath, wheezing or | Patients with asthma, progressive lung diseases or other breathing problems who require Terlipressin therapy should be closely monitored and |

| Risk | What is known | Preventability |
|---|---|---|
| | breathing difficulty or if patient stops breathing. | any bronchospasm should be treated symptomatically. |

## Important potential risks

| Risk | What is known |
|---|---|
| ***5. Alteration of heart rhythm called "prolongation of QT interval" and other serious irregular heart rhythm***<br><br>[QT prolongation and ventricular arrhythmias including Torsade de pointes] | Several cases of alteration the heart rhythm (QT interval prolongation) and irregular beating of the heart (ventricular arrhythmias including "torsade de pointes") have been reported with Terlipressin use. The term "prolonged QT" refers to an abnormal pattern seen on an electrocardiogram (EKG)-a test that detects and records the heart's electrical activity. Prolonged QT is sometimes associated with EKG findings called "torsade de pointes", which are known to degenerate into ventricular fibrillation, a life-threatening arrhythmia.<br><br>There are many causes of prolonged QT intervals. Some people are born with a genetic mutation that puts them at risk of long QT syndrome (LQTS). In addition, certain medications and medical conditions might cause QT prolongation.<br><br>Terlipressin can trigger sudden and dangerous arrhythmias if use in combination with other drugs that are further prolonging the QT interval such as :<br><br>• anti-arryhthmic drugs known as Class IA (quinidine, procainamide, disopyramide) and Class III (amiodarone, sotalol, ibutilide, dofetilide)<br>• erythromycin (an antibiotic)<br>• antihistamines (mainly used to treat allergies but also found in certain cough and cold remedies<br>• tricyclic antidepressants used to treat depression<br>• medicines that may alter the level of salt or electrolytes in your blood, particularly diuretics (water tablets used to treat high blood pressure and heart failure)<br><br>Therefore administration of Terlipressin should be avoided in patients with predisposing factors such as: inherited long QT syndrome, abnormal levels of salt or electrolytes in the blood, or in those taking medications with concomitant effect on QT prolongation. |
| ***6. Slow heart rate when use in combination with other medicines***<br><br>[Bradycardia when use in combination with non-selective beta blockers, Propofol Sufentanil] | Some medicines and Terlipressin may interfere with each other. These include beta blockers (medicines used to treat high blood pressure and certain heart conditions), Propofol (a short-acting anaesthetic) and Sufentanil, (a powerful opioid painkiller). The administration of Terlipressin with these medicines may cause heart to slow down. |

## Missing information

| Risk | What is known |
|---|---|
| ***7. Administration in pregnant or nursing women***<br><br>[Use in pregnancy/lactation] | Terlipressin may be harmful if used during pregnancy as it can decrease blood flow to the womb and cause contractions. Miscarriage and birth defects were observed in pregnant rabbits treated with Terlipressin at doses less than the maximum recommended daily dose in human.<br><br>Due to these potential harmful effects on the pregnancy and unborn baby Terlipressin should not be used during pregnancy.<br><br>It is not known if Terlipressin passes into breast milk. Since there are no human or animal data on the excretion of Terlipressin into milk or on the safety of Terlipressin in infants, this medicine should not be used in mothers who are breastfeeding. |
| **8.** ***Administration in children and teenagers***<br><br>[Use in paediatric population] | Safety and effectiveness of Terlipressin in children and adolescents have not been established. No data are available regarding dosage recommendation in these special patient categories. |
| **8.** ***Administration in elderly***<br><br>[Use in elderly patient >70years of age] | In clinical studies, most of elderly patients were > 65 years of age (15%) and very few patients were >75 years of age (3%). No overall differences in safety or effectiveness were observed between elderly patients and younger patients, but the number of patients treated is too small to draw definitive conclusions and greater sensitivity of some older individuals cannot be ruled out. Because of limited experience, special precaution should be taken during treatment with Terlipressin in elderly patients. |

### *VI.2.5 Summary of risk minimisation activities by safety concern*

Summary of Product Characteristics (SmPC) of Terlipressin acetate SUN 0.12 mg/ml solution for injection 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) for patients.

For all of the above mentioned risks, the routine risk minimisation measures as presented in proposed Terlipressin acetate SUN 0.12 mg/ml solution for injection SmPC and PL are considered sufficient and no additional risk minimisation measures are proposed by Sun Pharma for the safety concerns identified with Terlipressin.

### *VI.2.6 Planned post-authorization development plan*

None.

### *VI.2.7 Summary of changes to the risk management plan over time*

Not applicable. New RMP.