℞ *For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.*

Terlipressin Injection 1 mg/10 ml
GLYCIPRESIN

Each 10 ml contains:

Terlipressin (Synthetic) BP	1.0 mg
Excipients	q.s.
Water for Injections IP	q.s.

DESCRIPTION:
Chemical name of Terlipressin is a Glycyl-glycyl-glycyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-lysylglycinamide cyclic (4→9)-disulfide. Molecular formula: of terlipressin is $C_{52}H_{74}N_{16}O_{15}S_2$ Average molecular weight: 1227 g/mol.

THERAPEUTIC INDICATIONS:
Terlipressin injection is indicated in for the treatment of:
Treatment of bleeding oesophageal varices. (BOV)
Type 1 Hepatorenal Syndrome, characterized by spontaneous acute renal insufficiency, in patients suffering from severe cirrhosis, with ascites.

POSOLOGY AND METHOD OF ADMINISTRATION
The administration of terlipressin serves the emergency care for acute bleeding oesophageal varices until endoscopic therapy is available. Afterwards the administration of terlipressin for the treatment of oesophageal varices is usually an adjuvant therapy to the endoscopic haemostasis.
Adults
Initially 1-2 mg terlipressin acetate (equivalent to 1-2 ampoules of Terlipressin Acetate 1 mg solution for injection) are administered.
Depending on the patient's body weight the dose can be adjusted as follows:
- weight less than 50 kg: 1 mg (1 ampoule of 8.5 ml)
- weight 50 kg to 70 kg: 1.5 mg (1.5 ampoules of 8.5 ml)
- weight exceeding 70 kg: 2 mg (2 ampoules of 8.5 ml).

After the initial injection, the dose can be reduced to 1 mg every 4 to 6 hours.
The approximate value for the maximum daily dose of Terlipressin Acetate 1 mg solution for injection is 120 µg/kg body weight.
The therapy is to be limited to 2 – 3 days in adaptation to the course of the disease.
Terlipressin Acetate 1 mg solution for injection is injected intravenously and should be given during the period of one minute.
Do not use, if any particle, leakage or breakage is found.
Elderly
Terlipressin Acetate 1 mg solution for injection should only be used with caution in patients over 70 years (see section Special warnings and precautions for use)
Children and adolescents
Terlipressin Acetate 1 mg solution for injection is not recommended in children and adolescents due to insufficient experience on safety and efficacy (see section Special warnings and precautions for use)
Renal insufficiency
Terlipressin Acetate 1 mg solution for injection should only be used with caution in patients with chronic renal failure (see section Special warnings and precautions for use).
Hepatic insufficiency
A dose adjustment is not required in patients with liver failure.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients being used in formulation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
In principle the use of the product should be confined to specialist supervision in units with facilities for regular monitoring of the cardiovascular system, haematology and electrolytes.
Terlipressin Acetate 1 mg solution for injection should only be used with caution and under strict monitoring of the patients in the following cases:
- septic shock
- bronchial asthma, respiratory deficiencies
- uncontrolled hypertension
- cerebral or peripheral vascular diseases
- cardiac arrhythmias
- cardiac insufficiency
- coronary deficiencies or previous myocardial infarction
- chronic renal insufficiency
- elderly patients > 70 years as experience is limited in this group
- pregnancy (see section Fertility, pregnancy and lactation).

Also hypovolaemic patients often react with an increased vasoconstriction and atypical cardiac reactions.
Due to the weak antidiuretic effect of terlipressin (only 3% of the antidiuretic effect of native vasopressin) especially patients with already disturbed electrolyte metabolism should be monitored for a possible hyponatraemia and hypokalaemia.
In emergency situations which require an immediate treatment before sending the patient to a hospital, symptoms of hypovolaemia have to be considered.
Terlipressin has no effect on arterial bleeding.
To avoid local necrosis at the injection site, the injection must be administered intravenously exclusively.
Skin necrosis: Several cases of cutaneous ischemia and necrosis unrelated to the injection site have been reported (see section Undesirable effects). Patients with peripheral venous hypertension or morbid obesity seem to have a greater tendency to this reaction. Therefore, extreme caution should be exercised when administering terlipressin in these patients.
Torsade de pointes: In most cases, patients had predisposing factors such as basal prolongation of the QT interval, electrolyte abnormalities (hypokalemia, hypomagnesemia) or medications with concomitant effect on QT prolongation. (See section Undesirable effects) Therefore, extreme caution should be exercised in the use of terlipressin in patients with a history of QT interval prolongation, electrolytic anormalities, concomitant medications that can prolong the QT interval, such as class IA and III antiarrhythmics, erythromycin, certain antihistamines and tricyclic antidepressants or medications that can cause hypokalaemia or hypomagnesemia (e.g. some diuretics) (see section Interaction with other medicinal products and other forms of interaction).
Special populations: Particular caution should be exercised in the treatment of children, adolescents and elderly patients, as experience is limited and there is no data available regarding dosage recommendation in these special patient categories.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:
Terlipressin increases the hypotensive effect of non-selective β-blockers on the portal vein. The reduction in heart rate and cardiac output caused by the treatment can be attributed to the inhibition of the reflexogenic activity of the heart through the vagus nerve as a result of increased blood pressure. Concomitant treatment with drugs known to induce bradycardia (e.g. propofol, sufentanil) can cause severe bradycardia.
Terlipressin can trigger ventricular arrhythmias including "torsade de pointes" (see sections Special warnings and precautions for use and Undesirable effects). Therefore, extreme caution should be exercised in the use of terlipressin in patients with concomitant medications that can prolong the QT interval, such as class IA and III antiarrhythmics, erythromycin, certain antihistamines and tricyclic antidepressants or medications that may cause hypokalaemia or hypomagnesemia (e.g. some diuretics).

PREGNANCY, LACTATION AND FERTILITY:
Pregnancy: The use of terlipressin is not recommended during pregnancy as it has been shown to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow. Terlipressin may have harmful effects on pregnancy and foetus.
Terlipressin Acetate 1 mg solution for injection should therefore only be used at vital indication on a case by case decision especially in the first trimester, when bleeding cannot be controlled with endoscopic therapy.
Lactation: It is not known whether terlipressin is excreted in human breast milk. A risk to the suckling child cannot be excluded. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with terlipressin should be made taking into account the benefit of breast-feeding to the child and the benefit of terlipressin therapy to the woman.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
No studies on the effects on the ability to drive and use machines have been performed.

UNDESIRABLE EFFECTS:
Metabolism and nutrition disorders
hyponatraemia if fluid not monitored, hyperglycaemia
Nervous system disorders
Headache, triggering of a convulsive disorder, stroke
Cardiac disorders
ventricular and supra-ventricular arrhythmia, bradycardia, signs of ischaemia in the ECG, angina pectoris, acute hypertension rise, in particular in patients already suffering from hypertension (generally, it decreases spontaneously), atrial fibrillation, ventricular extrasystoles, tachycardia, chest pain, myocardial infarction, fluid overload with pulmonary oedema, cardiac failure, Torsade de Pointes, myocardial ischemia
Vascular disorders
hypertension, hypotension, peripheral ischaemia, peripheral vasoconstriction, facial pallor, intestinal ischaemia, peripheral cyanosis, hot flushes
Respiratory, thoracic and mediastinal disorders
pain in the chest, bronchospasm, respiratory distress, respiratory failure, dyspnoea
Gastrointestinal disorders
transient abdominal cramps, transient diarrhoea, transient nausea, transient vomiting
Skin and subcutaneoustissue disorders
Paleness, lymphangitis, skin necrosis unrelated to the site of administration
Reproductive system and breast disorders
abdominal cramps (in women)
Pregnancy, puerperium and perinatal conditions
uterine hypertonus, uterine ischemia, uterine constriction, decreased uterine blood flow

General disorders and administration site conditions:
injection site necrosis

OVERDOSE:
The recommended dose should not be exceeded in any case, since the risk of severe circulatory adverse effects is dose-dependent. An acute hypertensive crisis, especially in patients with recognized hypertension, can be controlled with a vasodilator-type alpha-blocker, e.g. 150 micrograms clonidine intravenously. Bradycardia requiring treatment should be treated with atropine.

PHARMACOLOGICAL PROPERTIES:
Pharmacotherapeutic group: Systemic hormonal preparations, posterior pituitary lobe hormones, vasopressin and analogues
ATC code: H01BA04.
Pharmacodynamic properties:
Terlipressin inhibits portal hypertension with simultaneous reduction of blood circulation in portal vessels. Terlipressin contracts smooth oesophageal muscle with consecutive compression of oesophageal varices.
The inactive pre-hormone terlipressin slowly releases bioactive lysine-vasopressin. Metabolic elimination takes place concomitantly and within a period of 4-6 hours. Therefore, concentrations remain continuously above the minimal effective dose and below toxic concentrations.
Specific effects of terlipressin are assessed as follows:
Gastrointestinal system: Terlipressin increases the tone of vascular and extravascular smooth muscle cells. The increase in arterial vascular resistance leads to decrease of splanchnic hypervolemia. The decrease of the arterial blood supply leads to reduction of pressure in the portal circulation. Intestinal muscles contract concomitantly which increases intestinal motility. The muscular wall of the esophagus also contracts which leads to closure of experimentally induced varices.
Kidneys: Terlipressin has only 3% antidiuretic effect of the native vasopressin. This residual activity is of no clinical significance. Renal blood circulation is not significantly effected in normovolemic condition. Renal blood circulation is increased, however, under hypovolemic condition.
Blood pressure: Terlipressin induces a slow haemodynamic effect which lasts 2-4 hours. Systolic and diastolic blood pressure increase mildly. More intense blood pressure increase has been observed in patients with renal hypertension and general blood vessel sclerosis.
Heart: Influences on the heart, such as bradycardia, arrhythmia, coronary insufficiency, occur possibly because of reflex or direct vascular constrictive effects of terlipressin.
Uterus: Terlipressin causes significant decrease in myometrial and endometric blood flow.
Skin: The vasoconstrictive effect of terlipressin causes significant decrease in blood circulation of the skin.
In conclusion, the main pharmacological properties of terlipressin are its haemodynamic effects and its effects on smooth muscle. The centralization effect under hypovolemic condition is a desired side effect in patients with bleeding oesophageal varices.

Pharmacokinetic properties:
After bolus intravenous injection terlipressin elimination follows second order kinetics. Plasma halflife was calculated as 8-12 minutes during the distribution phase (0-40 minutes) and 50-80 minutes during the elimination phase (40-180 minutes). The release of lysine-vasopressine is maintained for at least 180 minutes. Due to cleavage of the glycyl rests from terlipressin lysine-vasopressin is slowly released and reaches maximal concentrations after 120 minutes. Urine contains only 1% of the injected terlipressin, which indicates almost complete metabolism by endo- and exopeptidases of liver and kidneys.

STORAGE:
Store between 2ºC - 8ºC, protect from light. Do not freeze.
Keep out of reach of children.

PRESENTATION:
Primary Packing: 10 ml amber glass ampoule USP type-I
Secondary Packing: Such a one ampoule kept in Transparent PVC tray packed in Monocarton along with package insert.

Marketed by:
VARENYAM®
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