可利新注射液 0.1 毫克/毫升

Glypressin® 0.1mg/mL Solution for Injection

衛署藥輸字第025557號
本藥限由醫師使用

【成份】

1安瓿的8.5毫升藥液含0.85毫克terlipressin，相當於每毫升含0.1毫克terlipressin。1安瓿含1毫克terlipressin acetate。

每安瓿含有1.33毫莫耳(或30.7毫克)的鈉。

賦型劑：詳見【賦形劑】。

【藥物劑型】

注射液

澄清無色液體

【適應症】

出血性食道靜脈曲張，第一型肝腎症候群。

說明：治療第一型肝腎症候群。其特性是罹患嚴重肝硬化且有腹水的病患，出現自發的急性腎功能不全，依據International Ascites Club的診斷標準。

【用量和施打方式】

出血性食道靜脈曲張：

成年人：

一開始每4小時靜脈注射2安瓿GLYPRESSIN®注射液(2毫克terlipressin acetate，相當於1.7毫克terlipressin)，直到出血獲得控制，最多可使用到48小時。如果病患體重< 50公斤，可以將劑量調整為每4小時靜脈注射1安瓿GLYPRESSIN®注射液(1毫克terlipressin acetate，相當於0.85毫克terlipressin)。

維持劑量(如果需要時)是每4小時注射1安瓿GLYPRESSIN®注射液，最長 3 天。

治療期間不能超過5天。

對於第一型肝腎症候群：

每24小時，3到4安瓿GLYPRESSIN®注射液(3到4毫克terlipressin acetate，相當於2.55到3.4毫克terlipressin)，分成3或4次注射。

如果治療3天後血清肌酸酐(creatinine)沒有下降，建議要停止GLYPRESSIN®治療。

至於其他病例，則繼續GLYPRESSIN®治療，直到血清肌酸酐的數值低於130 μmol/litre，或血清肌酸酐值與診斷為肝腎症候群時的數值相比下降至少30%為止。

標準平均治療期間是10天。

【禁忌】

禁忌使用於懷孕婦女。

對terlipressin或其任一種賦型劑過敏。

敗血性休克：低心搏輸出的敗血性休克病患，不能使用terlipressin。

【警告及注意事項】

治療期間要監測血壓、心率和體液平衡。

假使治療持續數天，必須監測尿量及血液電解質。為了避免注射部位局部壞死，一定要靜脈注射。

高血壓、已知有心臟病冠狀動脈功能不全、腎功能不全、腦血管或周圍血管疾病、呼吸衰竭的病患治療時要特別小心。

兒童和老年人：因為對兒童和老年人的經驗有限，所以治療時要特別小心。

目前對於這些特殊病患族群，沒有建議劑量相關的數據。

本品每安瓿含有1.33毫莫耳(或30.7毫克)的鈉，對於正在控制鈉飲食之患者須特別注意。

【藥物交互作用】

與terlipressin一起使用時，非選擇性的beta阻斷劑對門靜脈的降壓作用會增強。與已知有降低心率作用的藥物製劑(例如：propofol、sufentanil)同時使用時，心率和心搏輸出可能會降低。這些作用是因為血壓升高後經由迷走神經的反射性抑制心臟活性所造成。

【生殖、懷孕和哺乳】

懷孕

懷孕期間terlipressin治療是禁忌(請參閱禁忌及臨床前安全性數據)。目前已經顯示，於懷孕初期，terlipressin會造成子宮收縮和增加子宮內壓，以及降低子宮血流。Terlipressin可能對懷孕及胎兒有害。

動物試驗結果顯示兔子接受terlipressin治療後，出現自發性流產和畸形。

哺乳

關於terlipressin進入到人乳汁的情況，目前並沒有足夠的資料。哺乳的婦女不能使用terlipressin。

【服用後對駕駛及操作機械的影響】

沒有對駕駛及操作機械影響的相關研究。

【藥品不良反應】

臨床試驗中最常報告的不良作用(頻率1-10%)是：蒼白、血壓升高、腹痛、噁心、腹瀉和頭痛。

除非能控制體液平衡，terlipressin的抗利尿作用可能導致低血鈉症。

表：不良作用的頻率

藥事管理的標準醫學術語集(MedDRA)			
系統器官類別異常	**常見 (≥1/100 到 <1/10)**	**不常見 (≥1/1000 到 <1/100)**	**罕見 (≥1/10000 到 <1/1000)**
新陳代謝和營養異常		低血鈉症 (如果沒有監控體液)	
神經系統異常	頭痛		
心臟異常	心率過緩	心房顫動 心室期外收縮 心率過快 胸痛 心肌梗塞 體液過量且肺水腫 Torsade de pointes 心臟衰竭	
血管異常	周邊血管收縮 周邊缺血 臉蒼白 高血壓	腸道缺血 周邊發紺 熱潮紅	
呼吸、胸腔和縱隔異常		呼吸急迫 呼吸衰竭	呼吸困難
胃腸道異常	暫時性腹痙攣 暫時性腹瀉	暫時性噁心 暫時性嘔吐	
皮膚和皮下組織異常		皮膚壞死	
懷孕、分娩和出生前後情況		子宮劇烈收縮 子宮缺血	
全身異常和注射部位異常		注射部位壞死	

【藥物過量】

不可超過建議劑量(2 mg terlipressin acetate或1.7 mg terlipressin/4小時)，因為嚴重的循環性不良作用的風險與劑量相關。

已知有高血壓病患的血壓升高可使用150 mcg clonidine靜脈注射控制。

治療期間發生心率過緩可使用atropine治療。

【藥物藥效學】

藥物治療分類：腦下垂體後葉賀爾蒙(血管加壓素 [vasopressin]及類似藥物)。

ATC 碼：H 01 BA 04。

Terlipressin一開始自己會產生作用，然後會被酵素切斷轉變成離胺酸血管加壓素(lysine vasopressin)。1和2毫克的terlipressin acetate能有效地降低門靜脈壓，並造成顯著的血管收縮。門靜脈壓和奇靜脈血流的降低與劑量有關。低劑量時，作用3小時後會下降，血液動力學數據顯示，terlipressin acetate 2毫克比1毫克有效，因為較大的劑量能在整個治療期間(4小時)產生比較可靠的作用。

【藥物動力學】

本藥物動力學是遵照二房室模型。研究發現半衰期約40分鐘，代謝清除率約9毫升/公斤/分鐘，而分布體積約0.5升/公斤。

研究發現，GLYPRESSIN®施打後，於血漿中，約30分鐘後達到理想的離胺酸血管加壓素濃度，60到120分鐘後達到最高濃度。因為terlipressin和離胺酸血管加壓素之間有100%交互作用，所以這兩種物質沒有專一性的放射免疫分析(RIA)方法。

【臨床前安全性數據】

根據單劑量和重複劑量以及基因毒性等臨床前數據顯示對人類沒有特別的危險性。在相對於人類暴露劑量下，從動物觀察到的只有terlipressin藥理作用所造成的一些作用。對於發生這些作用，目前沒有動物的藥物動力學數據可以和人類做比較，但因為施打的途徑是靜脈，所以可以假設在動物研究中，實質上為全身性暴露。

一項大鼠的致畸胎之藥物血漿濃度研究證實，terlipressin無不良作用，但會造成兔子流產發生，或許與母兔的毒性作用有關，有少數胎兒有骨化異常，及一項單一獨立的顎裂病例。

Terlipressin沒有執行致癌性的研究。

【賦形劑】

Sodium chloride、acetic acid、sodium acetate trihydrate及water for injections

【不相容性】

因為沒有相容性研究，所以本藥物製劑不能與其他藥物製劑混合。

【有效期間】

2年

【儲存】

存放在冰箱 (2 °C - 8 °C)。安瓿要放在紙盒內以防日曬。

【包裝】

透明無色玻璃安瓿(第 I 類玻璃)內含8.5毫升藥液。

包裝：1盒含5安瓿(每安瓿含8.5毫升)。

【丟棄時注意事項】

任何未使用的藥品或廢棄物須遵照當地要求進行處理。

製造廠：

ZENTIVA k.s.,
U Kabelovny 130, 102 37 Praha 10
Dolní Měcholupy, Czech Republic

藥商：輝凌藥品股份有限公司
地址：台北市松江路111號11樓
電話：(02)25158277

GLYPRESSIN® 0.1 mg/ml Solution for Injection

COMPOSITION

One ampoule of 8.5 ml contains 0.85 mg terlipressin (as acetate) equivalent to 0.1 mg terlipressin/ml. One ampoule contains 1 mg terlipressin acetate.

One ampoule contains 1.33 mmol (or 30.7 mg) sodium.

For the full list of excipients, see section List of excipients.

PHARMACEUTICAL DOSAGE FORM

Solution for injection

Clear, colourless liquid

INDICATIONS

Bleeding oesophageal varices

Treatment of type 1 hepatorenal syndrome, characterised by spontaneous acute renal insufficiency, in patients suffering from severe cirrhosis, with ascites

DOSAGE AND ADMINISTRATION

Bleeding oesophageal varices:

Adults:

Initially an i.v. injection of 2 ampoules of GLYPRESSIN® solution for injection (2 mg terlipressin acetate, equivalent to 1.7 mg terlipressin) is given every 4 hours. The treatment should be maintained until bleeding has been controlled but up to a maximum of 48 hours. The dose can be adjusted to 1 ampoule of GLYPRESSIN® solution for injection (1 mg terlipressin acetate, equivalent to 0.85 mg terlipressin) i.v. every 4 hours in patients with body weight < 50 kg.

For maintenance dosage (if necessary), bolus injection of 1 ampoule of GLYPRESSIN® solution for injection every 4 hours for a maximum of 3 days.

Duration of treatment must not exceed 5 days.

In type 1 hepatorenal syndrome:

3 to 4 ampoules of GLYPRESSIN® solution for injection (3 to 4 mg terlipressin acetate, equivalent to 2.55 to 3.4 mg terlipressin) every 24 hours as 3 or 4 administrations.

In the absence of any reduction of the serum creatinine after 3 days of treatment, cessation of GLYPRESSIN® treatment is advised.

In the other cases, GLYPRESSIN® treatment is to be pursued until the obtaining either of a serum creatinine less than 130 µmol/litre or of a drop of at least 30 % in the serum creatinine with respect to the value measured at the time of diagnosis of hepatorenal syndrome.

The standard average duration of treatment is 10 days.

CONTRAINDICATIONS

Contraindicated in pregnancy.

Hypersensitivity to terlipressin or to any of the excipients.

In patients with septic shock with a low cardiac output terlipressin should not be used.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Blood pressure, heart rate and fluid balance should be monitored during treatment. To avoid local necrosis at the injection site, the injection must be given i.v. Caution should be exercised in treating patients with hypertension or recognised heart disease like coronary insufficiency, renal dysfunction, cerebral or peripheral vascular disease, respiratory failure.

Children and the elderly: Particular caution should be exercised in the treatment of children and elderly patients, as experience is limited in these groups.

There is no data available regarding dosage recommendation in these special patient categories.

This medicinal product contains 1.33 mmol (or 30.7 mg) of sodium per ampoule. To be taken into consideration in patients on a controlled sodium diet.

INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTIONS

The hypotensive effect of non-selective beta-blockers on the portal vein is increased with terlipressin. Concomitant treatment with medicinal products with a known bradycardic effect (e.g. propofol, sufentanil) may lower the heart rate and cardiac output. These effects are due to reflexogenic inhibition of cardiac activity via the vagus nerve due to the elevated blood pressure.

PREGNANCY AND LACTATION

Pregnancy

Treatment with GLYPRESSIN® during pregnancy is contraindicated (please refer to Contraindications and Preclinical safety data). GLYPRESSIN® has been shown to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow. GLYPRESSIN® may have harmful effects on pregnancy and foetus.

Spontaneous abortion and malformation has been shown in rabbits after treatment with GLYPRESSIN®.

Breastfeeding

It is not known whether terlipressin is excreted in human breast milk. GLYPRESSIN® should not be used in breast feeding women.

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

The most commonly reported undesirable effects in clinical trials (frequency 1-10%) are paleness, increased blood pressure, abdominal pain, nausea, diarrhoea and headache.

The antidiuretic effect of GLYPRESSIN® may cause hyponatraemia unless the fluid balance is controlled.

Table: Frequency of undesirable effects

MedDRA			
System Organ Class Disorder	**COMMON (≥1/100 to <1/10)**	**UNCOMMON (≥1/1000 to <1/100)**	**RARE (≥1/10000 to <1/1000)**
Metabolism and nutrition disorders		Hyponatraemia if fluid not monitored	
Nervous system disorders	Headache		
Cardiac disorders	Bradycardia	Atrial Fibrillation Ventricular Extracystoles Tachycardia Chest pain Myocardial Infarction Fluid overload with pulmonary oedema Torsade de pointes Cardiac failure	
Vascular disorders	Peripheral vasoconstriction Peripheral ischemia Facial pallor Hypertension	Intestinal ischaemia Peripheral cyanosis Hot flushes	
Respiratory, thoracic and mediastinal disorders		Respiratory distress Respiratory failure	Dyspnoea
Gastrointestinal disorders	Transient abdominal cramps Transient diarrhoea	Transient nausea Transient vomiting	
Skin and subcutaneous tissue disorders		Skin necrosis	
Pregnancy, puerperium and perinatal conditions		Uterine hypertonus Decreased uterine blood flow	
General disorders and administrative site conditions		Injection site necrosis	

OVERDOSAGE

The recommended dose (2 mg terlipressin acetate or 1.7mg terlipressin/4 hours) should not be exceeded as the risk of severe circulatory adverse effects is dose-dependent.

Elevated blood pressure in patients with recognised hypertension can be controlled with 150 mcg clonidine i.v.

Bradycardia requiring treatment should be treated with atropine.

PHARMACODYNAMICS

Pharmacotherapeutic group: Posterior pituitary lobe hormones (vasopressin and analogues). ATC-code: H 01 BA 04.

Terlipressin initially has an effect of its own, but is converted by enzymatic cleavage to lysine vasopressin. Doses of 1 and 2 mg terlipressin acetate effectively reduce the portal venous pressure and produce marked vasoconstriction. The lowering of portal pressure and azygos blood flow is dependent on dose. The effect of the low dose is reduced after 3 hours, while haemodynamic data show that 2 mg terlipressin acetate is more effective than 1 mg as the higher dose produces a dependable effect throughout the period of treatment (4 hours).

PHARMACOKINETICS

The pharmacokinetics follows a two-compartment model. It has been found that the half-life is approximately 40 min., metabolic clearance is approximately 9 ml/kg/min and the distribution volume is approximately 0.5 l/kg.

The desired concentration of lysine vasopressin in plasma is found initially after approximately 30 min. and reaches a peak value of 60 to 120 min. after administration of GLYPRESSIN®. Because of 100% cross-reaction between terlipressin and lysine vasopressin, there is no specific RIA method for these substances.

PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of single- and repeat-dose toxicity, and genotoxicity. At dosages relevant to humans, the only effects observed in animals were those attributable to the pharmacological activity of terlipressin. No pharmacokinetic data are available from animals to compare with humans the plasma concentrations at which these effects occurred, but as the route of administration was intravenous, a substantial systemic exposure can be assumed for the animal studies.

An embryo-fetal study in rats demonstrated no adverse effects of terlipressin, but in rabbits abortions occurred, probably related to maternal toxicity, and there were ossification anomalies in a small number of fetuses and a single isolated case of cleft palate.

No carcinogenicity studies have been performed with terlipressin.

LIST OF EXCIPIENTS

Sodium chloride, acetic acid, sodium acetate trihydrate, water for injections

INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

SHELF-LIFE

2 years

STORAGE

Store in a refrigerator (2 °C - 8 °C). The ampoules are stored in the outer carton in order to protect from light.

PACKING SIZES

8.5 ml solution in clear colourless glass ampoules (Type I glass).

Box of 5 ampoules x 8.5 ml

SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused drug or waste materials should be disposed of in accordance with local requirements.

Manufacturer:

ZENTIVA k.s.,

U Kabelovny 130, 102 37 Praha 10

Dolní Měcholupy, Czech Republic