Proposed packaging material		
Code	GLYINJ-I-ID-03.01	
Size	N/A	
Submission	☐ NDA ☐Renewal ☒ Variation change detail no.: 186724	
Code of previous version	GLYINJ-I-ID-02.01	
Changes	CCDS Update V.4 and V.5	
Reference	☐CCDS version: V.5 ☐ Core PIL version:	☒SPC country/version/date: EU, Version 3.1, 06/2015 ☐LAC no.:
Name & Date	HINI, 30 Jan 2023	

GLYPRESSIN®
Terlipressin acetate
Powder and solvent for solution for injection 1mg

QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains 1 mg terlipressin acetate, corresponding to 0.86 mg terlipressin. The concentration of the reconstituted solution is 0.2 mg terlipressin acetate/ml.

Excipients:
Powder: Mannitol (E 421), Hydrochloric acid.
Solvent: Sodium chloride, Hydrochloric acid, Water for injections.

PHARMACEUTICAL FORM
Powder and solvent for solution for injection.
Powder (vial): White lyophilized powder.
Solvent (ampoule): Clear, colourless liquid.

THERAPEUTIC INDICATIONS
Glypressin® is indicated in the treatment of bleeding oesophageal varices.

POSOLOGY AND METHOD OF ADMINISTRATION
Adults:
Initially an i.v. injection of 2 mg GLYPRESSIN® is given every 4 hours. The treatment should be maintained until bleeding has been controlled for 24 hours, but up to a maximum of 48 hours. After initial dose, the dose can be adjusted to 1 mg i.v. every 4 hours in patients with body weight < 50 kg or if adverse effects occur.

Paediatric and geriatric population:
No data are available regarding dosage recommendations in these patient populations.

Method of Administration
i.v. injection

CONTRAINDICATIONS
Contraindicated in pregnancy.
Hypersensitivity to the active substance or to any of the excipients of the product.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Monitoring during treatment
During treatment, regular monitoring of blood pressure, ECG or heart rate, oxygent 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 ischaemia and pulmonary vascular congestion. Caution should also be exercised in treating patients with hypertension.

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

Injection site reaction
To avoid local necrosis at the injection site, the injection must be given i.v.

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Name & Date	HINI, 30 Jan 2023	

Skin necrosis

During post-marketing experience with terlipressin several cases of cutaneous ischaemia and necrosis unrelated to the injection site have been reported. Patients with diabetes mellitus and obesity seem to have a greater tendency to this reaction. Therefore, caution should be exercised when administering terlipressin in these patients.

Torsade de pointes

During clinical trials and post-marketing experience, several cases of QT interval prolongation and ventricular arrhythmias including “Torsade de pointes” have been reported (see section Undesirable effects). 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. Therefore, extreme caution should be exercised in the use of terlipressin in patients with a history of QT interval prolongation, electrolyte abnormalities, or concomitant medications that can prolong the QT interval (see section interaction with other medicinal products and other forms of interaction).

Children and the elderly

Particular caution should be exercised in the treatment of children and elderly patients, as experience is limited in these group

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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.

Terlipressin can trigger “torsade de pointes” (see section Special Warning 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).

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Reference	☐CCDS version: V.5 ☐ Core PIL version:	☒SPC country/version/date: EU, Version 3.1, 06/2015 ☐LAC no.:
Name & Date	HINI, 30 Jan 2023	

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Treatment with terlipressin during pregnancy is contraindicated (see Contraindications and Preclinical safety data). terlipressin 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.

Spontaneous abortion and malformation have been shown in rabbits after treatment with terlipressin

Breastfeeding

It is not known whether terlipressin is excreted in human breast milk. The excretion of terlipressin in milk has not been studied in animals. 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.

Fertility

No human data on the effects of terlipressin on fertility is available. Animal studies do not indicate harmful effects of terlipressin on male fertility (see section Precilinical Safety Data)

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 terlipressin may cause hyponatraemia unless the fluid balance is controlled.

Tabulated List of Adverse Reaction

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Metabolism and nutrition disorders		Hyponatraemia	
Nervous system disorders	Headache		
Cardiac disorders	Bradycardia	Atrial fibrillation Ventricular extracystoles Tachycardia Myocardial infarction Torsade de pointes Cardiac failure Cyanosis	

Vascular disorders	Vasoconstriction Peripheral ischemia Pallor Hypertension	Hot flush	
Respiratory, thoracic and mediastinal disorders		Respiratory distress Respiratory failure Pulmonary oedema	Dyspnoea
Gastrointestinal disorders	Abdominal Pain Diarrhoea	Nausea Vomiting Intestinal Ischaemia	
Skin and subcutaneous tissue disorders		Skin necrosis (unrelated to the site of administration*)	
Pregnancy, puerperium and perinatal conditions		Uterine hypertonus Uterine ischaemia	
General disorders and administration site disorders		Injection site necrosis Chest Pain	

*See section Special Warning and Precautions for Use for further information

OVERDOSE

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

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Posterior pituitary lobe hormones (vasopressin and analogues) (H 01 BA 04)
Glypressin® may be regarded as a circulating depot of lysine vasopressin. Following intravenous injection, three glycyl moieties are enzymatically cleaved from the N- terminus to release lysine vasopressin.
The slowly released vasopressin reduces blood flow in the splanchnic circulation in a prolonged manner, thereby helping to control bleeding from ruptured oesophageal varices.

PHARMACOKINETIC PROPERTIES

Glypressin® is administered by bolus iv injection. It shows a biphasic plasma level curve which indicates that a two compartment model can be applied.
The half-life of distribution (T1/2) is about 8 -10 minutes.
The half-life of elimination (T1/2) is about 50 -70 minutes.
Lysine vasopressin reaches maximum plasma levels about 1 - 2 hours following iv administration and has a duration of activity of 4-6 hours.

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 but as the route of administration was intravenous, systemic

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Name & Date	HINI, 27 Feb 2023	

exposure at multiples of the maximum human dosages 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.

In a rat fertility study, mating of terlipressin-treated males with untreated females had no effect on the number of matings and frequency of insemination but led to decreased post-natal litter size. Testicular atrophy and disturbances of spermiogenesis observed in male rats treated with terlipressin for 3 weeks could not be confirmed. Likewise no testicular effects were seen in any other repeat-dose toxicity study in rats and dogs.

No carcinogenicity studies have been performed with terlipressin.

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

SHELF LIFE
2 years.
The product should be used immediately after reconstitution.

STORAGE
Do not stored above 30°C. Store in original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product (See section Shelf Life).

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
Mix solvent with powder for injection via the rubber stopper in the vial. The clear reconstituted solution must be injected i.v. immediately after reconstitution.
Any unused medicinal product or waste materials should be disposed of in accordance with local requirements.

PACKING SIZE
Box of 1 vial @ 1 mg powder for injection and 1 ampoule@ 5 ml solvent for injection
(Reg. No.: DKI2151700844A1)

MANUFACTURED AND RELEASED BY
Glypressin powder injection manufactured by:
Ferring GmbH
Germany

Sterile Diluent manufactured by:
Haupt Pharma Wulfing GmbH
Germany

Secondary Packaging and released by:
Zuellig Pharma Specialty Solutions Group Pte. Ltd. Singapore.

IMPORTED BY
PT Ferring Pharmaceuticals Industry
BSD – Indonesia

HARUS DENGAN RESEP DOKTER

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Size	N/A	
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Code of previous version	GLYINJ-I-ID-02.01	
Changes	CCDS Update V.4 and V.5	
Reference	☒CCDS version: V.5 ☐ Core PIL version:	☐SPC country/version/date: EU, Version 3.1, 06/2015 ☐LAC no.:
Name & Date	HINI, 27 Feb 2023	

DATE OF REVISION
27 Feb 2023

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Code of previous version	GLYINJ-I(PIL)-ID-02.01	
Changes	MA Transfer	
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Name & Date	HINI, 27 Feb 2023	

Informasi untuk pasien
Glypressin 1 mg Serbuk dan Cairan untuk Larutan Injeksi
Terlipressin Acetate

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini mengandung informasi penting untuk Anda.
- Simpanlah leaflet ini, sebab Anda mungkin perlu membacanya lagi dikemudian hari.
- Apabila Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter Anda.
- Jika Anda mengalami efek samping, bicarakan dengan dokter Anda. Termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Lihat bagian 4.

Apa isi leaflet ini?

1. Apa itu GLYPRESSIN dan apa kegunaannya

GLYPRESSIN berisi serbuk dan pelarut untuk larutan injeksi. Serbuk berwarna putih, beku-kering mengandung komponen aktif terlipressin.

GLYPRESSIN digunakan dalam pengobatan pendarahan varises esofagus.
Varises esofagus adalah pembesaran pembuluh darah yang terbentuk pada esofagus (kerongkongan) sebagai suatu komplikasi penyakit liver. Pembuluh darah tersebut bisa pecah dan berdarah yang merupakan suatu kondisi yang serius dan mengancam jiwa.
Ketika terlipressin disuntikkan ke dalam aliran darah, komponen aktif tersebut akan terurai dan melepaskan suatu zat yang disebut lysine vasopressin. Zat ini bekerja pada dinding pembuluh darah dan menyebabkan pembuluh tersebut menyempit, sehingga membatasi aliran darah ke pembuluh darah yang pecah.

2. Apa yang perlu Anda ketahui sebelum menggunakan GLYPRESSIN

Jangan gunakan GLYPRESSIN:
- Jika Anda alergi terhadap terlipressin atau zat lain yang terkandung dalam obat ini (lihat bagian 6)
- Jika Anda sedang hamil

Peringatan dan tindakan pencegahan
Bicaralah dengan dokter Anda sebelum menggunakan GLYPRESSIN
- Jika Anda memiliki tekanan darah tinggi
- Jika Anda menderita penyakit jantung
- Pada anak-anak dan pasien lanjut usia karena pengalaman yang terbatas pada kedua kelompok usia ini
- Jika Anda mengalami syok septik dengan curah jantung rendah, terlipressin disarankan untuk tidak digunakan
- Untuk mencegah kerusakan jaringan kulit, injeksi harus dilakukan secara i.v. (intravena)
- Pada pasien dengan diabetes melitus dan obesitas tampaknya memiliki kecendrungan lebih

besar terhadap kejadian nekrosis dan iskemia pada kulit. Oleh karena itu, pemberian Terlipressin harus diberikan secara hati-hati pada pasien tersebut.

- Torsade de pointes (Gangguan Irama Jantung). Hati-hati penggunaan Terlipressin pada pasien dengan riwayat gangguan irama jantung, elektrolit abnormal dan penggunaan obat-obatan yang dapat memperpanjang gangguan irama jantung.

Selama pengobatan dengan GLYPRESSIN, tekanan darah, denyut jantung, saturasi oksigen, kadar sodium dan pottasium serta keseimbangan cairan Anda harus selalu dipantau. Perhatian khusus dibutuhkan pada tatalaksana pasien dengan penyakit kardiovaskular dan paru-paru dikarenakan terlipressin dapat menyebabkan iskemia dan sumbatan pembuluh darah paru-paru.

Obat lain dan GLYPRESSIN
Beritahukan dokter apabila Anda sedang menggunakan, baru saja menggunakan atau mungkin menggunakan obat lain, termasuk obat yang dibeli tanpa resep dokter.

Beritahukan dokter anda jika menggunakan obat-obatan golongan beta-blocker non selektif, karena efek obat tersebut dapat meningkat jika digunakan bersamaan dengan GLYPRESSIN.

Beritahukan dokter anda jika menggunakan obat-obatan yang memiliki efek bradikardi (contoh propofol, sufentanil) karena dapat menurunkan detak dan curah jantung.

Terlipressin dapat memicu “gangguan irama jantung”, harus berhati-hati dalam penggunaan terlipressin untuk pasien yang menggunakan obat antiaritmia kelas IA dan III, eritromisin, antihistamin tertentu dan antidepresan trisiklik atau obat yang dapat menyebabkan hipokalemia atau hipomagnesemia (misalnya beberapa diuretik).

Kehamilan dan menyusui
GLYPRESSIN tidak boleh digunakan selama kehamilan
GLYPRESSIN tidak boleh digunakan selama menyusui karena tidak diketahui apakah GLYPRESSIN akan masuk ke ASI.

Mengemudi dan menggunakan mesin
Tidak boleh digunakan karena GLYPRESSIN adalah obat yang hanya digunakan di rumah sakit.

3. Bagaimana cara pemberian GLYPRESSIN

GLYPRESSIN adalah obat yang digunakan di rumah sakit dan hanya boleh diberikan oleh staf yang kompeten.
Pelarut dicampur dengan serbuk untuk injeksi melalui penyumbat karet vial kaca.
Segera setelah pencampuran larutan bening disuntikkan secara intravena (langsung ke aliran darah).
Dosis awal GLYPRESSIN yang digunakan pada perdarahan mendadak dari varises esofagus adalah 2 mg. Dosis lebih lanjut biasanya 1-2 mg setiap 4 jam sampai perdarahan terkontrol selama 24 jam. Maksimal pengobatan yang diperbolehkan adalah 48 jam. Setelah dosis awal, dosis Anda berikutnya dapat disesuaikan menurut berat badan Anda atau jika Anda mengalami efek samping.

4. Efek samping yang mungkin terjadi

Seperti obat lainnya, obat ini dapat memberikan efek samping, yang mungkin tidak semua orang akan mendapatkannya.
Efek samping yang sering dilaporkan (dapat mempengaruhi hingga 1 dari 10 orang yang diobati):

- Sakit kepala
- Bradikardia (denyut jantung lambat)
- Vasokonstriksi (penyempitan pembuluh darah)
- Iskemi perifer (kekurangan oksigen pada jaringan)
- Muka pucat

- Hipertensi (tekanan darah tinggi)
- Nyeri Abdomen
- Diare

Efek samping yang tidak sering dilaporkan (dapat mempengaruhi hingga 1 dari 100 orang yang diobati):

- Kadar natrium yang rendah
- Fibrilasi Atrium (gangguan jantung)
- Ventricular extracystoles (gangguan jantung)
- Takikardia (Denyut jantung cepat)
- Infark miokard (serangan jantung)
- Torsade de pointes (gangguan irama jantung)
- Gagal jantung.
- Sianosis (perubahan warna kebiru-biruan pada kulit yang disebabkan oleh kekurangan oksigen)
- Kemerahan pada kulit yang menimbulkan rasa panas
- Gangguan pernapasan dan gagal napas
- Edema Paru (terdapat banyak cairan pada paru-paru)
- Mual
- Muntah
- Iskemia usus (kekurangan aliran darah di usus)
- Nekrosis kulit (kerusakan jaringan)
- Penyempitan uterus (penyempitan rahim)
- Penurunan aliran darah uterus
- Nekrosis di tempat injeksi (kerusakan jaringan)
- Nyeri dada

Efek samping yang jarang dilaporkan (dapat mempengaruhi hingga 1 dari 1.000 orang yang diobati):

- Dispnea (kesulitan bernafas)

Pelaporan efek samping
Jika Anda mendapatkan efek samping diatas, hubungi dokter atau perawat Anda. Hal yang sama berlaku untuk efek samping yang tidak tercantum dalam leaflet ini.

5. Bagaimana cara penyimpanan GLYPRESSIN

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
Jangan gunakan obat ini setelah tanggal kadaluwarsa yang tercantum di kemasannya. Tanggal kadaluwarsa mengacu pada hari terakhir bulan itu.
Larutan yang telah dicampur memiliki warna yang jernih dan harus segera digunakan setelah mencampur serbuk dengan pelarutnya.
Simpan dalam kemasan aslinya agar terlindung dari cahaya dan pada suhu di bawah 30^{o}C.

6. Isi kemasan dan informasi lainnya

Apa isi GLYPRESSIN?

- Satu vial berisi 1 mg terlipressin asetat, setara dengan 0,86 mg terlipressin. Konsentrasi larutan hasil pelarutan adalah 0,2 mg terlipresin asetat/ ml.
- Bahan lainnya adalah:
  Serbuk: Mannitol (E 421) dan asam klorida
  Pelarut: Sodium klorida, asam klorida dan air untuk injeksi

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Name & Date	HINI, 27 Feb 2023	

Tampilan GLYPRESSIN dan isi dari kemasan
Produk ini berupa serbuk dan pelarut untuk larutan injeksi. Serbuk berwarna putih. Bila sudah dilarutkan dalam pelarut yang disediakan, maka harus diperoleh larutan jernih yang tidak berwarna.
GLYPRESSIN tersedia dalam satu ukuran kemasan:
Dus yang berisi 1 vial @ 1 mg serbuk untuk injeksi dan 1 ampul @ 5 ml larutan untuk rekonstitusi
No.Reg: DKI2151700844A1

Pemegang Hak Pemasaran dan Produsen
Produsen Glypressin Serbuk Injeksi:
Ferring GmbH
Germany
Produsen Pelarut Steril:
Haupt Pharma Wulfing GmbH
Germany
Produsen Pengemas Sekunder dan perilis
Zuellig Pharma Specialty Solutions Group Pte. Ltd. Singapore.

Diimpor oleh:
PT Ferring Pharmaceuticals Industry
BSD – Indonesia

HARUS DENGAN RESEP DOKTER

Leaflet ini terakhir direvisi pada 27 Feb 2023