PROFESSIONAL INFORMATION FOR

NETVODY

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NETVODY 40 units / 100 mL, Solution for injection

NETVODY 60 units / 100 mL, Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NETVODY 40 units / 100 mL contains:

40 international units of vasopressin per 100 mL (0,4 international units vasopressin per mL)

NETVODY 60 units / 100 mL contains**:**

60 international units of vasopressin per 100 mL (0,6 international units vasopressin per mL)

Contains Sugar: Dextrose anhydrous 50,0 mg/mL

For the full list of excipients see **section 6.1**.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear colourless solution free from visible particles filled in 100 mL glass vial, sealed with laminated rubber stopper and aluminium flip-off seal.

Ready to use isotonic solution for injection has pH 3,8 and osmolality in the range of 260 mOsmol/kg to 360 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NETVODY is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines.

4.2 Posology and method of administration

Posology

NETVODY is available as 40 units / 100 mL and 60 units / 100 mL ready to use vials.

Method of administration

In general, titrate to the lowest dose compatible with a clinically acceptable response.

The recommended starting dose is:

Post-cardiotomy shock: 0,03 units/minute

Septic Shock: 0,01 units/minute

Titrate up by 0,005 units/minute at 10- to 15-minute intervals until the target blood pressure is reached. There are limited data for doses above 0,1 units/minute for post-cardiotomy shock and 0,07 units/minute for septic shock. Adverse reactions are expected to increase with higher doses.

After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper NETVODY by 0,005 units/minute every hour as tolerated to maintain target blood pressure.

Special populations

Pregnancy:

Dose adjustments during pregnancy and the postpartum period: Because of increased clearance of vasopressin in the second and third trimester, the dose of NETVODY may need to be increased).

Because of a spill over into blood of placental vasopressinase, the clearance of exogenous and endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy, the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery, the clearance of vasopressin returns to preconception baseline within two weeks.

Elderly patients:

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. (**See section 4.8)**

Paediatric use

Safety and effectiveness of NETVODY in paediatric patients aged less than 18 years with vasodilatory shock have not been established.

Renal impairment:

As no clinical studies have been carried out in patients with renal impairment, the treatment recommendations are not established for patients with renal impairment.

Hepatic impairment:

As no clinical studies have been carried out in patients with hepatic impairment, the treatment recommendations are not established for patients with hepatic impairment.

4.3 Contraindications

NETVODY is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or to any of the excipients used in the formulation of NETVODY (see **section 6.1**)**.**

4.4 Special warnings and precautions for use

- Worsening Cardiac Function

A decrease in cardiac index may be observed with the use of NETVODY.

- Reversible Diabetes Insipidus

Patients may experience reversible diabetes insipidus, manifested by the development of polyuria, a dilute urine, and hypernatremia, after cessation of treatment with NETVODY. Monitor serum electrolytes, fluid status and urine output after NETVODY discontinuation. Some patients may require re-administration of NETVODY or administration of desmopressin to correct fluid and electrolyte shifts.

- Ischemic events:

The skin condition should be monitored in patients with peripheral vascular disease for the signs of ischemia (pain, changes in color, temperature, or sensation, absence of pulse in the extremities).

- Vasopressin withdrawal:

Direct effects will resolve within minutes of withdrawal of treatment.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on **NETVODY**

- Catecholamines

Use with catecholamines is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters. Hemodynamic monitoring is recommended; adjust the dose of NETVODY as needed.

- Indomethacin

Use with indomethacin may prolong the effect of NETVODY on cardiac index and systemic vascular resistance. Hemodynamic monitoring is recommended; adjust the dose of NETVODY as needed.

- Ganglionic Blocking Medicines

Use with ganglionic blocking medicines may increase the effect of NETVODY on mean arterial blood pressure. Hemodynamic monitoring is recommended; adjust the dose of NETVODY as needed.

- Medicines Suspected of Causing Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

Use with medicines suspected of causing Syndrome of Inappropriate Antidiuretic Hormone (SIADH) (e.g., SSRIs, tricyclic antidepressants, haloperidol, chlorpropamide, enalapril, methyldopa, pentamidine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of NETVODY. Hemodynamic monitoring is recommended; adjust the dose of NETVODY as needed.

- Medicines Suspected of Causing Diabetes Insipidus

Use with *medicines suspected of causing diabetes insipidus* (e.g., demeclocycline, lithium, foscarnet, clozapine) may decrease the pressor effect in addition to the antidiuretic effect of NETVODY. Hemodynamic monitoring is recommended; adjust the dose of NETVODY as needed.

4.6 Fertility, pregnancy, and lactation

Pregnancy:

There are no available data on NETVODY use in pregnant women to inform a drug associated risk of major birth defects, miscarriage, or adverse maternal or foetal outcomes. Animal reproduction studies have not been conducted with vasopressin.

Dose adjustments during pregnancy and the postpartum perio*d:* Because of increased clearance of vasopressin in the second and third trimester, the dose of NETVODY may need to be increased.

Maternal adverse reactions*:* NETVODY may produce tonic uterine contractions that could threaten the continuation of pregnancy.

Breastfeeding:

There are no data on the presence of NETVODY in either human or animal milk, the effects on the breastfed infant, or the effects on milk production.

Fertility

No formal carcinogenicity or fertility studies with vasopressin have been conducted in animals. Vasopressin was found to be negative in the *in vitro* bacterial mutagenicity (Ames) test and the *in vitro* Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

The following adverse reactions associated with the use of vasopressin were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it

is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure. The following adverse reactions have been classified according to the following categories, frequent, less frequent and frequency unknown.

Tabulated summary of adverse reactions

MedDRA System Organ Class (SOC)	Frequency	**Adverse reaction**
Blood and lymphatic system disorders	*frequency unknown*	Haemorrhagic shock, decreased platelets, intractable bleeding.
Cardiac disorders	*frequency unknown*	Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia.
Gastrointestinal disorders	*frequency unknown*	Mesenteric ischemia.
Hepatobiliary disorders	*frequency unknown*	Increased bilirubin levels.
Renal and urinary disorders	*frequency unknown*	Acute renal insufficiency.
Vascular disorders	*frequency unknown*	Distal limb ischemia.
Metabolism and nutrition disorders	*frequency unknown*	Hyponatremia.
Skin and subcutaneous tissue disorders	*frequency unknown*	Skin and subcutaneous tissue disorders.

frequency unknown (cannot be estimated from the available data).

Postmarketing Experience: Reversible diabetes insipidus

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Overdosage with NETVODY can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.2 Vasoconstrictors, pressor medicines.

Pharmacotherapeutic group: Vasopressin and analogues

ATC code: H01BA01

Mechanism of action

Vasopressin causes vasoconstriction by binding to V_1 receptors on vascular smooth muscle coupled to the Gq/11-phospholipase C-phosphatidyl-inositol-triphosphate pathway, resulting in the release of intracellular calcium. In addition, vasopressin stimulates antidiuresis via stimulation of V_2 receptors which are coupled to adenyl cyclase.

Pharmacodynamic effects

At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, vasopressin at pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V_1-receptors and release of prolactin and ACTH via V_3 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V_2 receptors. In addition, vasopressin has been demonstrated to cause vasodilation in numerous vascular beds that are mediated by V_2, V_3, oxytocin and purinergic P_2 receptors.

In patients with vasodilatory shock vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine (noradrenaline). Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous vasopressin. The pressor effect reaches its peak within 15 minutes. After stopping the infusion, the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of vasopressin in patients.

Clinical efficacy

Increases in systolic and mean blood pressure following administration of vasopressin were observed in studies in septic shock and studies in post-cardiotomy vasodilatory shock.

5.2 Pharmacokinetic properties

Absorption

Vasopressin plasma concentrations increase linearly with increasing infusion rates from 10 to 200 µU/kg/min. Steady state plasma concentrations are achieved after 30 minutes of continuous intravenous infusion.

Distribution:

Vasopressin does not appear to bind plasma protein. The volume of distribution is 140 mL/kg.

Elimination:

At infusion rates used in vasodilatory shock (0,01 to 0,1 units/minute), the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent t1/2 of vasopressin at these levels is ≤10 minutes.

Biotransformation:

Serine protease, carboxypeptidase and disulphide oxido-reductase cleave vasopressin at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Excretion:

Vasopressin is predominantly metabolized and only about 6 % of the dose is excreted unchanged into urine.

Specific Populations

Pregnancy: Because of a spill over into blood of placental vasopressinase, the clearance of exogenous and endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy, the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery, the clearance of vasopressin returns to pre-conception baseline within two weeks.

Drug Interactions

Indomethacin more than doubles the time to offset for vasopressin's effect on peripheral vascular resistance and cardiac output in healthy individuals.

The ganglionic blocking agent tetra-ethyl ammonium increases the pressor effect of vasopressin by 20 % in healthy individuals.

Halothane, morphine, fentanyl, alfentanil and sufentanil do not impact exposure to endogenous vasopressin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrose anhydrous,

Succinic acid,

Sodium succinate hexahydrate

Water for injection

Sodium hydroxide (for pH-adjustment)

Hydrochloric acid (for pH-adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Ideal Storage: Store between 2 °C and 8 °C (36 °F and 46 °F). Store in a refrigerator. Do not freeze. Shelf life of the product is 24 months when stored at 2 to 8 °C from the date of manufacturing.

Vials may be held up to 6 months upon removal from refrigeration to room temperature storage conditions (20 °C to 25 °C [68 °F to 77 °F], USP Controlled Room Temperature), anytime within the labelled shelf life.

6.4 Special precautions for storage

Once removed from refrigeration, unopened vial should be marked to indicate the revised 6-months expiration date. If the manufacturer’s original expiration date is shorter than the revised

expiration date, then the shorter date must be used. Do not use NETVODY, beyond the manufacturer's expiration date stamped on the vial.

The storage conditions and expiration periods are summarized in the following table.

Pack	***Unopened Refrigerated 2 °C to 8 °C (36 °F to 46 °F)***	***Unopened Room Temperature 20 °C to 25 °C (68 °F to 77 °F) Do not store above 25 °C (77 °F)***	***Opened (After First Puncture)***
100 mL Vial	Until manufacturer expiration date	6 months or until manufacturer expiration date, whichever is earlier	Not applicable

6.5 Nature and contents of container

NETVODY is available in 100 mL Din Exim Flint moulded glass vial with 32 mm rubber stopper and 32 mm al flip off seal 12 bridges (white) both side colourless lacquer. 10 such vials are packed in a carton.

6.6 Special precautions for disposal and other handling

For single use only. If only part used, discard the remaining solution. No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap,

Mispel Street,

Belville, 7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBERS

NETVODY 40 units / 100 mL: 57/7.2/0400

NETVODY 60 units / 100 mL: 57/7.2/0401

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

First authorisation: 08 April 2025

Renewal of the authorisation: Not applicable

10. DATE OF REVISION OF THE TEXT

Not applicable