1. NAME OF THE MEDICINAL PRODUCT

NIPRUSS®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule contains 60 mg sodium nitroprusside dihydrate (corresponding to 52.75 mg sodium nitroprusside anhydrous).

For the full list of excipients, see section 6.1.

1 ampoule of 60 mg contains 9.2 mg sodium.

3. PHARMACEUTICAL FORM

Lyophilized powder (slightly pink, hygroscopic) for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertensive crisis

Controlled intraoperative hypotension

Nipruss is not suitable for permanent therapy.

4.2 Posology and method of administration

Posology

Sodium nitroprusside infusions generally have to be started with low doses. The hypotensive effect is immediate. Baseline values are rapidly achieved after the end of the infusion. In the titration phase, an exact titration with blood pressure measurements every one to two minutes is required. Towards the end of the infusion, the infusion rate is gradually reduced.

The infusion is started at a dose of 0.2 µg/kg/min sodium nitroprusside dihydrate and is then doubled every 3-5 minutes until the desired blood pressure level is achieved. The infusion rate varies between 0.2 µg/kg/min and 10 µg/kg/min sodium nitroprusside dihydrate (see Table 1).

To achieve controlled hypotension during surgical procedures, it is recommended not to exceed the total amount of 1.0 to 1.5 mg/kg sodium nitroprusside dihydrate per case.

In case of infusions administered over several days, e.g. for the treatment of hypertensive crises, the maximum doses of Nipruss stated above are generally exceeded.

To prevent cyanide intoxication, the standard 10% sodium thiosulfate solution at a ratio of 1 : 10 (sodium nitroprusside : sodium thiosulfate) according to the weights of the active substances must be infused simultaneously via a separate venous access (volume ratio: see Table 2).

Table 1: Dosage table for perfusor (1.2 mg/mL sodium nitroprusside dihydrate)

µg/kg/min sodium nitro-prusside dihydrate	Infusion rate [ml/h]														
	Body weight (kg)														
	30	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**
0.2	0.3	0.4	0.4	0.5	0.5	0.6	0.6	0.7	0.7	0.8	0.8	0.9	0.9	1.0	1.0
0.4	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
0.8	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0	3.2	3.4	3.6	3.8	4.0
1.0	1.5	1.8	2.0	2.3	2.5	2.8	3.0	3.3	3.5	3.8	4.0	4.3	4.5	4.8	5.0
1.6	2.4	2.8	3.2	3.6	4.0	4.4	4.8	5.2	5.6	6.0	6.4	6.8	7.2	7.6	8.0
3.2	4.8	5.6	6.4	7.2	8.0	8.8	9.6	10.4	11.2	12.0	12.8	13.6	14.4	15.2	16.0
5.0	7.5	8.8	10.0	11.3	12.5	13.8	15.0	16.3	17.5	18.8	20.0	21.3	22.5	23.8	25.0
6.4	9.6	11.2	12.8	14.4	16.0	17.6	19.2	20.8	22.4	24.0	25.6	27.2	28.8	30.4	32.0
10.0	15.0	17.5	20.0	22.5	25.0	27.5	30.0	32.5	35.0	37.5	40.0	42.5	45.0	47.5	50.0

Prevention of cyanide intoxication

To effectively prevent cyanide toxicity of Nipruss, sodium thiosulfate must **always** be administered simultaneously as a continuous infusion.

Concerning the practical procedure, it is recommended to draw up 10% sodium thiosulfate pentahydrate solution into a second Perfusor syringe and to infuse it at a **volume ratio** of 10:1 (Nipruss: sodium thiosulfate· 5 H_2O) via a separate venous access. When using an Infusomat for Nipruss, the volume ratio should be 50 : 1 or 100 : 1 (see Table 2 below).

Table 2 (see section 6)

Nipruss dosage using			Dosage sodium thio-sulfate 10%
Perfusor in 50 ml	**Infusomat in 250 ml**	**Infusomat in 500 ml**	Perfusor
0.3 – 10.0 ml/h	1.5 – 50.0 ml/h	3 - 100 ml/h	1 ml/h
10.1 – 20.0 ml/h	50.5 – 100.0 ml/h	101 - 200 ml/h	2 ml/h
20.1 – 30.0 ml/h	100.5 – 150.0 ml/h	201 - 300 ml/h	3 ml/h
30.1 – 40.0 ml/h	150.5 – 200.0 ml/h	301 - 400 ml/h	4 ml/h
40.1-50.0 ml/h	200.5-250.0 ml/h	401-500 ml/h	5 ml/h

Thiocyanate toxicity

If Nipruss is infused over several days, thiocyanate levels must be monitored especially in renally impaired patients and must not exceed 6 mg/100 mL. Thiocyanate concentrations of more than 6 mg/100 mL lead to toxic symptoms such as weakness, vomiting, dizziness and tinnitus. In cases of thiocyanate intoxication, the infusion of sodium nitroprusside should be discontinued and, if necessary, thiocyanate should be removed from the body with the help of dialysis.

Special dosage instructions

Patients with hepatic impairment

Because the cyanide, which is released from sodium nitroprusside, is mainly metabolized by hepatic enzymes, it may accumulate in patients with severe hepatic impairment. Nipruss should therefore be used with caution in patients with hepatic impairment, and dose titration must be done carefully. In patients with hepatic impairment, signs of cyanide toxicity should be monitored more closely (see section 4.8).

Patients with renal impairment

If Sodium Nitroprusside is infused over several days, thiocyanate levels must be monitored especially in renally impaired patients and must not exceed 6 mg/100 mL.

Elderly patients

Elderly patients frequently require lower doses.

Children and adolescents

No special reduction in the dosage is required.

Method of administration

Intravenous use:

Nipruss is infused intravenously via a Perfusor or Infusomat. Among others, the duration of application is based on the total dose – see information in sections 4.4 and 4.9.

Precautions to be taken before and during handling or administering the medicinal product

Protection from light can be achieved by using coloured syringes and tubes. For information on the shelf life of the ready-to-use solution for infusion, see section 6.3. The solution for infusion is light yellow in colour. Strongly coloured solutions for infusion must not be used. Additional drugs must not be added to the ready-to-use solution for infusion . The safest way to administer the solution for infusion is via a separate venous catheter to prevent an accumulation of active substances in the tube system or in peripheral veins.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance ;
- Compensatory hypertension e.g. as caused by aortic isthmus stenosis or arteriovenous shunts;
- Leber's optic atrophy;
- tobaccos amblyopia;
- vitamin B12 deficiency;
- metabolic acidosis;
- hypothyroidism;
- intrapulmonary arteriovenous shunts.

4.4 Special warnings and precautions for use

In cases of patients who have previously taken PDE5-inhibitors, the application of Nipruss should only occur subject to strict risk/benefit consideration. When using PDE 5-inhibitors a significant intensification of the hypotensive effect of Nipruss may occur, if sodium nitroprusside is given in the 24 hours post-dose sildenafil or vardenafil, or 48 hours post-dose tadalafil, depending on the half-life of the PDE5-inhibitor. In this case, particularly careful dose titration is required.

Particularly careful medical supervision is necessary in case of diseases associated with increased intracranial pressure.

During the infusion of Nipruss, continuous monitoring of the ECG and, where relevant, of the most important haemodynamic parameters is required. Under surgical conditions, the best way to measure blood pressure is directly via an arterial cannula. In case of infusions administered over several days, blood pressure measurements by a non-invasive technique are sufficient.

Patients with renal impairment

If Sodium Nitroprusside is infused over several days, thiocyanate levels must be monitored especially in renally impaired patients and must not exceed 6 mg/100 mL.

Patients with hepatic impairment

Because the cyanide, which is released from sodium nitroprusside, is mainly metabolized by hepatic enzymes, it may accumulate in patients with severe hepatic impairment. Nipruss should therefore be used with caution in patients with hepatic impairment, and dose titration must be done carefully. In patients with hepatic impairment, signs of cyanide toxicity should be monitored more closely (see section 4.8).

Cyanide toxicity

To effectively prevent cyanide intoxication (owing to the possibility of an inadequate detoxification capacity of the body) see recommendations in Section 4.2. For symptoms of cyanide toxicity, see section 4.8.

Sodium Thiocyanate toxicity

To manage sodium thiocyanate toxicity, see recommendations in Section 4.2. For symptoms of sodium thiocyanate toxicity, see section 4.8.

Nipruss contains less than 1 mmol sodium (23 mg) per ampoule (60 mg), i.e. it is almost “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

The blood pressure-lowering effect of Nipruss can be increased by the concomitant administration of

- vasodilators;
- antihypertensive drugs;
- antihypertensive drugs for the treatment of pulmonary arterial hypertension;
- sedatives;
- anaesthetics.

This applies in particular in patients who have previously taken PDE5-inhibitors (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate, well-controlled studies on sodium nitroprusside with animals or during pregnancy available. It is not known, if sodium nitroprusside leads to foetal damages in a pregnant woman or affects fertility. Sodium nitroprusside should not be used during pregnancy.

Lactation

There is no information available if sodium nitroprusside passes into breast milk, in which way the unborn child may be affected or if there are any effects on lactation. Its metabolite thiocyanate passes into breast milk. Alternative medication is preferred during lactation. Sodium nitroprusside should not be applied during lactation.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

During administration of sodium nitroprusside, the following undesirable effects may be observed. The undesirable effects are listed below according to system organ class (SOC). Within each system organ class they are ranked by frequency starting with the most common. Within each frequency group, the undesired effects are listed in order of decreasing severity. In addition, the appropriate frequency category for each side effect is based on the following frequency definitions:

Very common (≥ 1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥1/1.000 to < 1/100)
Rare (≥ 1/10.000 to < 1/1.000)
Very rare (< 1/10.000)
Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Frequency not known: Bright red venous blood

Metabolism and nutrition disorders
Frequency not known: Metabolic acidosis, lactate increase, loss of appetite, hypothyroidism

Psychiatric disorders
Frequency not known: Psychosis

Nervous system disorders
Frequency not known: Headache, dizziness, sleep disorders, nervousness, tinnitus, miosis, hyperreflexia, confusion, hallucinations, seizures, paralysis, coma

Cardiac disorders
Frequency not known: Tachycardia, cardiac arrhythmia, palpitations

Vascular disorders
Frequency not known: Severe hypotension, rebound effect

Respiratory, thoracic and mediastinal disorders

Frequency not known: Hypoventilation, decreased oxygen uptake, respiratory paralysis

Gastrointestinal disorders

Frequency not known: Vomiting, nausea, diarrhoea, incontinence

General disorders and administration site conditions

Frequency not known: Weakness, insufficient lowering of blood pressure, tachyphylaxis, tolerance (more likely in younger patients than in elderly); infusion site reactions (e.g.: pain, reddening of the skin, itching)

Injury, poisoning and procedural complications

Frequency not known: Cyanide intoxication, thiocyanate intoxication

Description of selected adverse reactions:

Insufficient blood pressure reduction and the occurrence of tachyphylaxis and/or tolerance are to be expected in younger rather than older hypertension patients.

Symptoms of cyanide intoxication

Cyanide toxicity may manifest as bright red venous blood, hypoventilation, increased lactate, decreased oxygen uptake, palpitations, cardiac arrhythmias, headache, metabolic acidosis, coma, respiratory paralysis and seizures. Deaths have been reported.

Such signs of toxicity can occur if the dose of 0.05 mg CN^-/kg/min, which corresponds to the detoxification capacity of the human body, is exceeded without a simultaneous administration of thiosulfate.

Cyanide intoxication is completely avoidable by simultaneously administering a thiosulfate infusion at a molar ratio of 5 : 1 (thiosulfate : sodium nitroprusside).

Symptoms of thiocyanate intoxication

Cyanide together with thiosulfate is metabolised to thiocyanate, which is approximately 100 times less toxic compared to cyanide. However, it should be

taken into account that thiocyanate is only eliminated slowly and can therefore lead to severe intoxication if sodium nitroprusside is infused for a long time. Symptoms of thiocyanate toxicity that can occur in case of overdose – earlier in renally impaired patients than in renally healthy patients – include: dizziness, headache, loss of appetite, sleep disorders, nervousness, hypothyroidism, diarrhoea, vomiting, incontinence, psychosis, paralysis and coma. Very high serum concentrations can lead to death.

The symptoms of thiocyanate intoxication are also avoidable when the dosing instructions are observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form /https://sideeffects.health.gov.il

4.9 Overdose

Signs and symptoms
In case of acute myocardial infarction , an excessive reduction of aortic pressure bears the risk of a decrease in diastolic corona perfusion. In case of acute cardiac failure with decreased filling pressures the cardiac output may continue to drop.

Tachyphylaxis and rebound phenomenon are possible.

Cyanide intoxication may occur during the treatment with Nipruss. This depends on the duration of treatment and the dose level. Short-term treatment with 2.5 µg/kg/min is safe.
By contrast,

- 5 µg/kg/min after 10 hours,
- 10 µg/kg/min after 4 hours and
- 20 µg/kg/min after as early as 1.5 hours

can lead to life-threatening cyanide levels.

Treatment:
Therapeutic countermeasures include reducing the infusion dose or administering an antidote.

In case of cyanide intoxication, 4-dimethyl-aminophenol-hydrochloride (4-DMAP) 3 to 4 mg/kg IV (produces methaemoglobin) is recommended as a short-acting antidote. This is followed by an infusion of sodium thiosulfate, 50-100 mg/kg BW. In cases of thiocyanate intoxication, the infusion of sodium nitroprusside should be discontinued and, if necessary, thiocyanate should be removed from the body via dialysis.

For further information, see also sections 4.2 and 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: C02DD01
Pharmacotherapeutic group: anti-hypertensives, agents acting on arteriolar smooth muscle.

Mechanism of action
Sodium nitroprusside has a dilating effect on the muscles of the precapillary arterioles and of the venous capacitance vessels. The tone-decreasing effect on veins and arteries is roughly the same. Venodilation causes venous pooling with a decrease in cardiac preload and a reduction in increased filling pressures. Arteriolar dilation leads to a reduction in blood pressure, a decrease in peripheral arterial resistance and a reduction in the cardiac afterload. Sodium nitroprusside leads to dilation of the major coronary arteries.

Smooth muscles with a predominantly phasic activity – such as the duodenum and uterus – are not very sensitive to the effect of sodium nitroprusside.

The antihypertensive effect is characterised by an unusually steep dose-response curve. In a healthy heart, the cardiac output remains practically unchanged. In

patients with cardiac insufficiency it is significantly increased depending on the initial situation.

Sodium nitroprusside causes reflectory stimulation of the sympathetic nervous system with tachycardia and stimulation of renin secretion, especially in the alert state.

Sodium nitroprusside inhibits platelet aggregation triggered in vitro by collagen, ADP and adrenaline and decreases the number of circulating platelet aggregates in vivo.

Pharmacodynamic properties

See "mechanism of action".

Clinical efficacy

Hypertensive crisis:

Regarding the scientific basis for treatment decisions there have been no large clinical studies, no randomised nor placebo-controlled studies. The treatment is usually dictated by consensus and expert opinions. The particular features of the clinical situation and the end-organ complications and not the absolute value of blood pressure therefore should be considered.

Controlled hypotension:

Baseline-controlled clinical studies have uniformly shown that sodium nitroprusside has an immediate vasodilating effect in all populations. With increasing rates of infusion, sodium nitroprusside has been able to lower blood pressure without an observed limit of effect.

Clinical studies have also shown that the hypotensive effect of sodium nitroprusside is associated with reduced blood loss in a variety of major surgical procedures.

Safety and efficacy in children / adolescents

The safety and efficacy of sodium nitroprusside in children and adolescents under 18 years of age have been determined from adult studies and 2 clinical studies in children under 17 years of age. No new safety concerns were identified in the studies in children and adolescents versus adults. Two clinical studies in the USA with intravenous sodium nitroprusside for the indication "severe hypertension" have also proven the effectiveness, tolerability and safety in the patient subpopulation of children and adolescents (under 17 years of age). The first study included 203 individuals and was conducted as a phase 2 multicentre randomised, double-blind, parallel group, dose-ranging, effect-controlled study. A second phase 2 multicentre interventional randomised, double-blind, placebo-controlled safety-related study was conducted from 2008 to 2011 in 45 patients.

5.2 Pharmacokinetic properties

Absorption

Sodium nitroprusside is administered by intravenous infusion only and is thus 100% bioavailable.

Distribution

Owing to the exceedingly short life of sodium nitroprusside, protein binding and distribution are not known. There is no accumulation of the substance in specific tissues (e.g. the vascular walls).

Biotransformation

Sodium nitroprusside is rapidly metabolised to cyanide, 30 - 50% are detected in the blood, the rest in tissues. Cyanide binds partly to haemoglobin. Cyanide is converted to thiocyanate by means of sulphur donors, first and foremost thiosulfate. The availability of substrates containing sulphur is the speed-limiting factor.

Elimination

For thiosulfate, the optimal substrate concentration is around 3 mol thiosulfate per 1 mol cyanide. The conversion rate of cyanide to thiocyanate in humans is around 0.05 mg CN^-/kg/min. Higher sodium nitroprusside doses lead to a cumulation in the serum concentration of thiocyanate, because this metabolite is formed faster than it is excreted by the kidneys. The thiocyanate clearance is

2.2 mL/kg/min in renally healthy patients and lower in patients with renal impairment.

5.3 Preclinical safety data

Acute toxicity tests were performed in mice, rats, pigeons, rabbits, dogs and cats. LD50 ranges from 9 mg/kg in mice after intraperitoneal administration to 100 mg/kg in rat after per oral application. The toxic action is rapid.
The toxicity is characterised by the cyanide effect and the reduction in blood pressure, which is why the instructions provided in sections 4.2 and 4.4 must be strictly observed.

The doses used in acute and repeated toxicity studies were significantly higher than used in humans (max. 10 µg / kg / min).

Based on special investigation on rats and rabbits, no signs of a teratogenic effect were found, including at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Reconstituted solution:

The reconstituted solution has to be diluted for solution for infusion immediately

Ready –for-use-solution:

Chemical and physical in-use stability of the solution for infusion has been demonstrated for 16 hours at 25°C protected from light (using light protection Perfusor syringe). From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use

storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution / dilution has taken place in controlled and validated conditions.

6.4 Special precautions for storage

Store below 30°C. Keep out of the sight and reach of children.

Keep the ampoules in the outer carton in order to protect from light.

Protect the solution for infusion from light by using coloured syringes and tubes.

6.5 Nature and contents of the container

packs containing 5 ampoules with lyophilized powder for solution for infusion.

6.6 Special precautions for disposal and other handling

Preparation of the solution for infusion

The powder for solution for infusion (the content of the brown ampoule is equivalent to 60 mg of sodium nitroprusside dihydrate) is dissolved in water for injections or in a 5% glucose solution. **This concentrated solution has a reddish-brownish colour and must never be injected directly**. Only 5% glucose solution may be used for the further dilution. The solution for infusion containing the sodium nitroprusside must be prepared immediately prior to the administration.

In order to avoid injection of particles of more than 5 µm in size, it is recommended to filter the reconstituted solution using a filter with a maximum pore size of 5 micrometres or alternatively to filter the solution for infusion with an inline filter with a maximum pore size of 5 micrometres prior to use.

The ampoule is already serrated below the white dot. It is thus not necessary to saw the ampoule. Break open the ampoule as usual.

Perfusor® (see also dosing table in section 4.2)

When using a Perfusor, 50 mL of a 5% glucose solution are first drawn into a 50 mL Perfusor syringe. The Nipruss ampoule is opened and filled up to around three quarters of the volume with glucose solution from the Perfusor syringe. Once the powder is dissolved, the thus concentrated solution is drawn into the

Perfusor syringe. To prevent overdoses, the content of the syringe must be homogeneously mixed by shaking.

Infusomat®

When using an Infusomat, the content of one ampoule, after dissolution in water for injections or in 5% glucose solution, is injected into 250 or 500 mL of a 5% glucose solution. For controlled intraoperative hypotension, dilution in 250 mL is recommended. The conversion of the dosing is detailed in the dosage table. The infusion rates indicated in the dosage table in mL per hour are multiplied by a factor of 5 when diluting in 250 mL of glucose, and with a factor of 10 when diluting in 500 mL. To prevent a high fluid load, the Perfusor is the preferred method for prolonged infusions.

7. MANUFACTURER

BAG Health Care GmbH, Amtsgerichtsstraße 1-5, D-35423 Lich, Germany

8. RIGHTS OWNER

Altamedics GmbH, Josef-Lammerting-Allee 16, D-50933 Köln, Germany

9. MARKETING AUTHORIZATION HOLDER

A.L. Medi-Market Ltd., 3 Hakatif St. , Emek Hefer Industrial Park , 3877701, Israel

10. REGISTRATION NUMBER

164-33-35970-00

Revised in June 2023 according to MoH's guidelines