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.

3. PHARMACEUTICAL FORM

Lyophilized powder for solution for infusion
Slightly pink, hygroscopic lyophilizate

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.

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

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). 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.

Table 1: Dosage table for Perfusor

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

<u>Prevention of cyanide intoxication</u>

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

Concerning the practical procedure, it is recommended to draw up the standard 10% sodium thiosulfate solution into a second Perfusor syringe and to infuse it at a **volume ratio** of 10:1 (Nipruss: sodium thiosulfate) 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

Nipruss dosage using			Dosage sodium thio-sulfate 10%
Perfusor in 50 ml	**Infusomat in 250 ml**	**Infusomat in 500 ml**	Perfusor
1 - 10 ml/h	5 - 50 ml/h	10 - 100 ml/h	1 ml/h
11 - 20 ml/h	51 - 100 ml/h	101 - 200 ml/h	2 ml/h
21 - 30 ml/h	101 - 150 ml/h	201 - 300 ml/h	3 ml/h
31 - 40 ml/h	151 - 200 ml/h	301 - 400 ml/h	4 ml/h

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. 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.

Elderly patients

Elderly patients frequently require lower doses.

Paediatric population

No special reduction in the dosage is required in children

Method of administration

Intravenous infusion:

Nipruss is infused intravenously via a Perfusor or Infusomat. The duration of administration is based, among other things, on the overall dose – see information in sections 4.4 and 4.9.

Precautions to be taken before 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. Strong coloured solution for infusion must not be used. The solution for infusion must not be mixed with other medicinal products. 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.

Aortic coarctation, 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 Sildenafil, the application of Nipruss should only occur subject to strict risk/benefit consideration, as this may result in a significant intensification of the hypotensive effect of Nipruss. In this case, particularly careful dose titration is required.

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

To effectively prevent cyanide intoxication (owing to the possibility of an inadequate detoxification capacity of the body), sodium nitroprusside infusion may only be administered with a simultaneous infusion of a sodium thiosulfate solution at a ratio of 1 : 10 (sodium nitroprusside : sodium thiosulfate) based on

the weights of the active substances (see Table 2 under Dosing instructions for details of the volume ratio).
The thiocyanate level must be monitored in case of prolonged infusions and especially in renally impaired patients.
Thiocyanate concentrations of more than 6 mg/100 mL lead to toxic symptoms such as weakness, vomiting, dizziness and tinnitus. This is not the case with concomitant dialysis, which eliminates thiocyanate from the body.

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 according to Riva-Rocci are sufficient.

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 and
- anaesthetics.

This applies in particular in patients who have previously taken sildenafil (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 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 frequency of all effects is Not known (cannot be estimated from the available data):

Blood and lymphatic system disorders

Bright red venous blood

Metabolism and nutrition disorders

Metabolic acidosis, lactate increase, appetite loss, hypothyroidism

Psychiatric disorders

Psychosis

Cardiac disorders

Tachycardia, cardiac arrhythmia, palpitations

Vascular disorders

Severe hypotension, rebound effect

Respiratory, thoracic and mediastinal disorders

Hypoventilation, decreased oxygen uptake, respiratory paralysis

Gastrointestinal disorders

Vomiting, nausea, diarrhoea, incontinence

Nervous system disorders

Headache, dizziness, sleep disorders, nervousness, tinnitus, miosis, hyperreflexia, confusion, hallucinations, seizures, paralysis, coma

General disorders and administration site conditions

Weakness, insufficient lowering of blood pressure, tachyphylaxis, and 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

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 intoxication 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

Symptoms of thiocyanate intoxication that can occur in case of an 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.

Also, the symptoms of thiocyanate intoxication are 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

Excessive reduction of aorta pressure in case of infarction can lead to risk of a decreased diastolic corona perfusion. The cardiac output per minute can further decrease in case of acute cardiac insufficiency with low filling pressures.

Tachyphylaxis and rebound are possible.

Cyanide intoxication may occur during the treatment with Nipruss. This depends on the length of treatment and dosage. Short-term treatment with 2.5 µg/kg/min is harmless.
On the other hand,

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

may lead to life-threatening cyanide levels.

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 (methaemoglobin producer) is recommended as a fast-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/Pharmacodynamic properties

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.

Clinical efficacy

Hypertensive crisis:

Regarding the scientific basis for treatment decisions there have been no large clinical studies, no randomised and 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 vaso-dilatating 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.

Paediatric population

The safety and efficacy of sodium nitroprusside in children and adolescents under the age of 18 years has been established by adult studies and 2 clinical studies in children under 17 years of age for the indication severe hypertension. 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. No new safety concerns were identified in studies in children and adolescents compared to adults.

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 an increase 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, chicken, 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, thus sections 4.2 and 4.4 should be considered.

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

Based on special examinations 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. 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 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 container

packs cotaining 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 preparing the 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 powder 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 dosing table. The infusion rates indicated in the 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

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8. RIGHTS OWNER

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