SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sodium Nitroprusside 50 mg/2 mL Concentrate For Solution For Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg sodium nitroprusside dihydrate, equivalent to 44 mg anhydrous sodium nitroprusside.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear reddish-brown solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sodium Nitroprusside is indicated for:

- treatment of hypertensive crises in adults
- controlled intraoperative hypotension in adults.

Sodium Nitroprusside is not suitable for permanent therapy.

4.2 Posology and method of administration

Sodium Nitroprusside is a concentrated aqueous solution (50 mg/2 mL), which has to be diluted with 5% glucose solution prior to administration. The final concentration of the diluted Sodium Nitroprusside (1.0 mg/mL) may differ from the final concentration of other reconstituted products on the market, which is due to different amounts of nitroprusside sodium per unit. However,

the administered dosage is the same, when the infusion rates recommended in Table 1 for Sodium Nitroprusside are followed. The volume ratios of sodium nitroprusside to sodium thiosulfate solution provided in the section "Prevention of cyanide toxicity" and in Table 2 should be used.

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 sodium nitroprusside dihydrate/kg/min and is then doubled every 3 to 5 minutes until the desired blood pressure level is achieved. The infusion rate varies between 0.2 and 10 µg sodium nitroprusside dihydrate/kg/min.

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

In case of sodium nitroprusside infusions administered over several days, e.g. for the treatment of hypertensive crises, the maximum doses stated above are generally exceeded. For Sodium Nitroprusside application, a syringe pump (Perfusor) or an Infusomat might be used. Further details are given in section 6.6.

Table 1: Dosage table for 1 mg/mL sodium nitroprusside dihydrate using a 50 mL syringe pump (see section 6.6)

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	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.8	0.8	0.9	1.0	1.0	1.1	1.1	1.2
0.4	0.7	0.8	1.0	1.1	1.2	1.3	1.4	1.6	1.7	1.8	1.9	2.0	2.2	2.3	2.4
0.8	1.4	1.7	1.9	2.2	2.4	2.6	2.9	3.1	3.4	3.6	3.8	4.1	4.3	4.6	4.8
1.0	1.8	2.1	2.4	2.7	3.0	3.3	3.6	3.9	4.2	4.5	4.8	5.1	5.4	5.7	6.0
1.6	2.9	3.4	3.8	4.3	4.8	5.3	5.8	6.2	6.7	7.2	7.7	8.2	8.6	9.1	9.6
3.2	5.8	6.7	7.7	8.6	9.6	10.6	11.5	12.5	13.4	14.4	15.4	16.3	17.3	18.2	19.2
5.0	9.0	10.5	12.0	13.5	15.0	16.5	18.0	19.5	21.0	22.5	24.0	25.5	27.0	28.5	30.0
6.4	11.5	13.4	15.4	17.3	19.2	21.1	23.0	25.0	26.9	28.8	30.7	32.6	34.6	36.5	38.4
10.0	18.0	21.0	24.0	27.0	30.0	33.0	36.0	39.0	42.0	45.0	48.0	51.0	54.0	57.0	60.0

Prevention of cyanide toxicity

To effectively prevent cyanide intoxication, it is strongly recommended to administer the sodium nitroprusside infusion always with a simultaneous continuous infusion of a sodium thiosulfate solution via a separate venous access at a ratio of approx. 1:10 (sodium nitroprusside dihydrate: sodium thiosulfate) based on the weights of the active substances.

Concerning the practical procedure, it is recommended to draw up sodium thiosulfate solution 100 mg/mL into a second Perfusor syringe and to infuse it at a volume ratio of approx. 12:1 (sodium nitroprusside dihydrate: sodium thiosulfate) via a separate venous access as indicated in Table 2 below.

When using an Infusomat for Sodium Nitroprusside , the volume ratio should be 60:1 or 120:1 (see also table 2).

As an antidote in the event of suspected or observed cyanide toxicity (e.g., when no thiosulfate is available for co-administration), hydroxocobalamine and/or methaemoglobin-forming agents might be required. The respective safety information of these medications must be followed.

Thiocyanate toxicity
If Sodium Nitroprusside infused over several days (in case of high doses already within 24 hours), 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.

Table 2 (see section 6.6)

Dosage Sodium Sodium Nitroprusside			**Dosage sodium thiosulfate 100 mg/mL**
Perfusor in 50 mL	**Infusomat in 250 mL**	**Infusomat in 500 mL**	**Perfusor**
1 - 12 mL/h	6 - 60 mL/h	12 - 120 mL/h	1 mL/h
13 - 24 mL/h	61 - 120 mL/h	121 - 240 mL/h	2 mL/h
25 - 36 mL/h	121 - 180 mL/h	241 - 360 mL/h	3 mL/h
37 - 48 mL/h	181 - 240 mL/h	361 - 480 mL/h	4 mL/h

Elderly patients
Elderly patients frequently require lower doses.

Paediatric population
The safety and efficacy of Sodium Nitroprusside in children and adolescents have not been demonstrated so far. No data are available. Therefore, Sodium Nitroprusside should not be administered to children and adolescents.

Patients with renal impairment
If sodium nitroprusside is infused over several days (in case of high doses already within 24 hours), 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. Sodium Nitroprusside 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). If necessary, administration of sodium nitroprusside is to be gradually reduced or discontinued, and the instructions for treatment of cyanide toxicity must be followed.

Method of administration
For infusion.

Sodium Nitroprusside is infused intravenously via a syringe pump (see Table 1) or Infusomat. Among others, the duration of application is based on the total dosage – therefore, 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. The solution for infusion is clear colourless to faint brownish. 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 dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to the excipient listed in section 6.1
- Compensatory hypertension, e.g., as caused by coarctation of the aorta (aortic isthmus stenosis) or arteriovenous shunt
- Leber’s optic atrophy
- tobacco 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 PDE 5 inhibitors, the application of Sodium Nitroprusside should only occur subject to strict

risk/benefit consideration. For PDE 5 inhibitors, a significant intensification of the hypotensive effect of Sodium Nitroprusside 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 PDE_5 inhibitor. In this case, particularly careful dose titration of Sodium Nitroprusside is required.

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

During the infusion of Sodium Nitroprusside, 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 (in case of high doses already within 24 hours), thiocyanate levels must be monitored, especially in renally impaired patients and must not exceed 6 mg/100 mL.

Patients with hepatic impairment
Since the cyanide, which is released from sodium nitroprusside, is mainly metabolized by hepatic enzymes, it may accumulate in patients with severe hepatic impairment. Sodium Nitroprusside 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). If necessary, administration of sodium nitroprusside is to be gradually reduced or discontinued, and the instructions for treatment of cyanide toxicity must be followed.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The blood pressure lowering effect of Sodium Nitroprusside can be increased by the concomitant administration of

- vasodilators,
- antihypertensive drugs
- antihypertensives for treatment of pulmonary arterial hypertension,

- sedatives and
- anesthetics.

This applies in particular to patients who have previously taken PDE 5 inhibitors (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy and breastfeeding
Since there is insufficient experience with the administration of sodium nitroprusside during pregnancy and breast-feeding, sodium nitroprusside should not be administered during these periods (only following strictest medical indication).

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 ranked according to system organ class and frequency:

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
Not known: bright red venous blood.

Metabolism and nutrition disorders
Not known: metabolic acidosis, lactate increased, appetite loss, hypothyroidism.

Psychiatric disorders
Not known: psychosis.

Nervous system disorders

Not known: headache, dizziness, sleep disorders, nervousness, tinnitus, miosis, hyperreflexia, confusion, hallucinations, seizures, paralysis, coma.

Cardiac disorders
Not known: tachycardia, cardiac arrhythmia, palpitations.

Vascular disorders
Not known: severe hypotension, rebound effects.

Respiratory, thoracic and mediastinal disorders
Not known: hypoventilation, decreased oxygen uptake, respiratory paralysis.

Gastrointestinal disorders
Not known: vomiting, nausea, diarrhoea, incontinence.

General disorders and administration site conditions
Not known: 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
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.

Cyanide intoxication symptoms
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).

Thiocyanate intoxication symptoms
Cyanide together with thiosulphate is metabolized to thiocyanate, which is approximately 100 times less toxic compared to cyanide. 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 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In case of an acute myocardial infarction, an excessive reduction of aortic pressure bears the risk of a decrease in diastolic coronary 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 Sodium Nitroprusside . This depends on the duration of treatment and on 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.

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

In case of cyanide intoxication, 4-Dimethylaminophenol Hydrochloride (4-DMAP) 3 to 4 mg/kg i.v. (produces methemoglobin) is recommended as a short-acting antidote. This is followed by an infusion of sodium thiosulfate, 50 to 100 mg/kg body weight.

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

Pharmacotherapeutic group: antihypertensives, agents acting on arteriolar smooth muscle, ATC code: C02DD01.

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 characterized 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 refractory 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*.

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 metabolized to cyanide; 30 to 50% are detected in the blood, the rest in tissues. Cyanide binds partly to hemoglobin. 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 optimum 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 is lower in patients with renal impairment.

5.3 Preclinical safety data

Following single intravenous dosing, the LD_{50} is 9 mg/kg in rats and 1.8 mg/kg in rabbits.

The toxicity is characterized 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.

Based on specific investigations 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

Water for injection.

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

Vial in the outer carton: 36 months

Chemical and physical in-use stability of the solution for infusion has been demonstrated for 24 hours at 25 °C ± 2°C when protected from light (using a light-protective Perfusor syringe). From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, the storage time and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 25 °C ± 2 °C, unless dilution has taken place at controlled and validated conditions.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

2 mL type I amber-coloured glass vial with a rubber stopper and aluminium-plastic overseal.

Pack size: each carton contains 1 vial of 2 mL.

A light-protecting sleeve is included in the unit pack for overwrapping the infusion bag containing the solution for infusion with added sodium nitroprusside solution.

6.6 Special precautions for disposal

The solution in vials before diluting has a reddish brownish colour and should **never be injected directly**. For further dilution only a solution of 5% glucose may be used. The solution for infusion containing the sodium nitroprusside must be prepared immediately prior to the administration.

The ready-to-use solution for infusion is sensitive to light; see section 6.3. Protection against light is possible by using coloured syringes and hoses. The infusion bags should be overwrapped with the light-protective sleeve included in the unit packs.

It should be noted that the vials contain an overage that allows the removal of not less than 2.0 mL of Sodium Nitroprusside using a syringe. Therefore, the dilution procedures (see below) should not assume that the vials contain exactly 2.0 mL but measure 2.0 mL using a syringe.

<u>Syringe pump (see also dosing Table 1 in section 4.2)</u>
When using a perfusor, add 2.0 mL of Sodium Nitroprusside to 48 mL of a 5% glucose solution to obtain 50 mL of a 1 mg/mL solution of sodium

nitroprusside. 48 mL of the 5% glucose solution is first drawn up into a 50 mL Perfusor syringe. Then 2.0 mL of the Sodium Nitroprusside is added to the Perfusor syringe using a 2 mL syringe. To prevent overdoses, the content of the perfusor syringe must be homogeneously mixed by shaking.

Infusomat (see also Table 2 in section 4.2)
When using an infusomat, 2.0 mL of solution from one vial of Sodium Nitroprusside is injected into 250 mL or 500 mL of a 5% glucose solution. For controlled intraoperative hypotension, the dilution in 250 mL is recommended. The dose conversion is detailed in the dosage table (Table 1). The infusion rates indicated in Table 1 in mL per hour are multiplied by a factor 5 when diluting in 250 mL of glucose solution, and with a factor 10 when diluting in 500 mL. To prevent a high fluid load, the perfusor is the preferred method for prolonged infusions.

Any unused medicinal product or waste material should be discarded in accordance with local regulations.

7 MARKETING AUTHORISATION HOLDER

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