TECHNICAL
DATA SHEET

1. DRUG NAME

Nitroprussiat Fides 50 mg powder and solvent for injectable solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

General description

Box containing a lyophilised phial and a solvent ampoule.

Qualitative and quantitative composition

Each phial contains 50 mg of sodium nitroprusside.
Excipients: 45 mg of sodium citrate per phial.

Each 5 ml solvent ampoule contains 250 mg of anhydroglucose and water for injections c.s.p. 5 ml.

After reconstitution, each ml of injectable solution contains around 10 mg of sodium nitroprusside.

To consult the complete list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for injectable solution.
Pinkish lyophilised powder and transparent, colourless solvent.

4. CLINICAL DATA

4.1. Therapeutic indications

- Treatment of hypertensive crisis and malignant hypertension refractory to other treatments.

- Controlled hypotension during anaesthesia to reduce bleeding in surgical procedures.
  The risk-benefit ratio must be evaluated in each case on an individual basis by the surgeon and the anaesthesiologist.

4.2. Dosage and form of administration

Dosage

Adults:

Dosage shall be adjusted in each case by the doctor in accordance with the desired hypotensive effect, controlling this by means of frequent determinations of blood pressure.

As a guideline, in patients who do not receive any antihypertensive medication, the mean dosage of Nitroprussiat Fides is 3 (0.5-8) µg/kg/minute, whilst in patients who concomitantly receive an oral antihypertensive agent, smaller doses shall be required. Generally speaking, in a

dosage of 3 µg/kg/minute, the diastolic blood pressure figures reduce by around 30-40% with regard to the values prior to treatment.

To induce hypotension during anaesthesia, the maximum recommended dosage is 1.5 µg/kg/minute.

The infusion of Nitroprussiat Fides shall be continued until the introduction of oral antihypertensive treatment which must be carried out as soon as possible.

Paediatric population:

In children who do not receive antihypertensive medication, the mean dosage of Nitroprussiat Fides is 3 (0.5-8) µg/kg/minute, whilst in patients who concomitantly receive an antihypertensive agent, smaller dosages shall be required.

The possible use of Nitroprussiat Fides in children in early childhood has not been properly determined yet.

Use in the elderly:

The elderly may be more sensitive to the hypotensive effects of sodium nitroprusside.

Form of administration

Nitroprussiat Fides must only be used in an infusion with a sterile dextrose solution with 5% in water. Direct injections should not be used.

To consult the reconstitution/dilution instructions of the medication before administration, see section 6.6.

To avoid excessive levels of thiocyanate in the blood and reduce the possibility of a rapid fall in blood pressure, it shall be avoided using an infusion rate of greater than 8 µg/kg/minute. If after 10 minutes an appropriate reduction has not been achieved in blood pressure with this infusion rate, the administration of Nitroprussiat Fides must be suspended.

Nitroprussiat Fides starts its action rapidly and hence it must be administered in the form of infusion (drop by drop) and the entry speed of the solution regulated with a view to achieving a gradual reduction in blood pressure until the desired level; this is why the administration of Nitroprussiat Fides must be supervised by specialised technical staff who must carry out parallel control of blood pressure.

4.3. Contraindications

- Compensatory hypertensions, such as arteriovenous shunts or the coarctation of the aorta.
- ASA Risk level 5, equivalent to moribund patients who are not expected to survive without surgical intervention.
- Uncorrected anaemia or hypovolemia.
- Insufficient cerebral circulation (cerebrovascular insufficiency).
- Hypotension induced by sodium nitroprusside during anaesthesia is contraindicated in patients with hepatopathy, serious kidney disease, Leber optic atrophy, tobacco amblyopia and diseases associated with vitamin B_{12} deficiency.
- During treatment with nitrates or nitric oxide donors, riociguat should not be used, the soluble guanylate cyclase stimulator (see section 4.5)
- Hypersensitivity to the active ingredient or to any of the excipients included under section 6.1.

4.4. Special warnings and precautions for use

- Sodium nitroprusside must never be administered directly, but rather in the form of intravenous infusion diluted in glucose solution (see section 4.2. *Dosage and form of administration*).
- Constantly monitor blood pressure (every 5 minutes at the start of infusion and after every 15 minutes).
- Control heart rate, the acid-base balance and blood concentration of cyanides. In the presence of kidney and/or liver failure, or when the treatment exceeds 3 days or the dosages exceed 4 μg/kg/minute, the blood levels of thiocyanates shall be controlled.
- The sharp interruption of the infusion could produce a rebound hypertension. Interrupt it progressively during 15-30 minutes.
- If the drop in blood pressure is too rapid, the typical symptoms of hypotension may be observed (see section 4.8., *Adverse reactions*) which gradually disappear by reducing the infusion speed and they totally disappear by interrupting it. If they are maintained in poorly monitored patients, irreversible ischemic lesions may appear; for this reason, **the administration of** Nitroprussiat Fides **must be supervised by specialised staff and only carried out in places that have equipment for the constant monitoring of blood pressure**.
- Hypertensive patients are more sensitive to the effect of the sodium nitroprusside than normotensive ones.
  Those patients receiving antihypertensive drugs are also more sensitive to the hypotensive effect of the sodium nitroprusside. In these cases, the dosage of nitroprusside must be reduced.
- Except in short treatments at low infusion rates (<2 μg/kg/minute), the injection of sodium nitroprusside gives rise to major quantities of cyanide ion which may reach toxic, potentially lethal levels. So, if blood pressure is not properly controlled 10 minutes after infusion has begun with 8 μg/kg/minute, the infusion must be interrupted (see section 4.2 Dosage and form of administration).
- Cyanide and thiocyanate are nitroprusside metabolism derivative products; the former may cause manifestations of histotoxic anoxia and the thiocyanate may inhibit the iodine concentration capacity of the thyroid gland and produce symptoms of hypothyroidism which could worsen the condition of patients affected by this alteration. In view of the fact that the thiocyanate inhibits the consumption and union of iodine, care should be taken in patients with hypothyroidism and in those suffering from serious kidney failure.
- When sodium nitroprusside is used (or any other vasodilator) to control hypotension during anaesthesia, the patient's capacity to compensate the anaemia or hypovolemia may be reduced. For this reason, before giving sodium nitroprusside, the anaemia or hypovolemia must be corrected as far as proves possible.

Warnings about excipients

This medication contains 13.6 mmol (313.6 mg) of sodium per maximum daily dosage which must be borne in mind in the treatment of patients with sodium-poor diets.

4.5. Interaction with other drugs and other forms of interaction

Interaction with other drugs

The joint use of sodium nitroprusside and other antihypertensive drugs may cause an increase in the hypotensive effect.
The use of Nitroprussiat Fides with riociguat, a soluble guanylate cyclase stimulator, is contraindicated (see section 4.3) as concomitant usage may cause hypotension.

Other forms of interaction

Nitroprussiat Fides is totally incompatible with other drugs and so it should always be administered by itself. It should not be given directly, but rather in the form of an intravenous infusion diluted with an isotonic dextrose solution (a sterile solution of glucose in water 4.7-5%).

4.6. Fertility, pregnancy and breastfeeding

Pregnancy

The possible use of Nitroprussiat Fides in pregnant women has not been properly determined yet. It shall thus only be used when the potential benefits outweigh the possible risks.

Breastfeeding

It is not known whether sodium nitroprusside is excreted in significant quantities in maternal milk so its use is not recommended during breastfeeding.

4.7. Effects on the capacity to drive and use machines

No studies have been carried out on the effects on the capacity to drive and use machines. It may cause disorientation, dizziness and blurred vision. If any of these adverse effects appears, it is recommended to avoid driving vehicles or using machines.

4.8. Adverse reactions

Some of the adverse effects of Nitroprussiat Fides are a consequence of intravenous infusion which is too rapid.

Adverse reactions are listed in descending order of seriousness within each frequency interval.

Classification of organs and systems	**Very frequent (≥1/10)**	**Infrequent (≥1/1000 <1/100)**	**Rare (≥1/10,000 <1/1000)**	**Frequency unknown**
Lymphatic system and blood disorders			Metahemobine-mia*	
Endocrine disorders		Hypothyroidism*		
Disorders of the metabolism and nutrition		Metabolic acidosis *		
Mental disorders		Confusion*, psychosis*		
Disorders of the nervous system	Nervousness, agitation, disorientation, headache	Ataxia*	Sleepiness, hyperreflexia	
Ocular disorders		Blurred vision*	Myosis	
Disorders of the ear and the labyrinth		Tinnitus*		
Heart disorders	Hypotension, ECG alterations, palpitations, precordial pain, bradycardia		Tachycardia, Arrhythmias	
Breathing,		Dyspnoea*	Hyperventilation	Hypoxia

chest and mediastinal disorders				
Disorders of the skin and of subcutaneous tissue			Rash	
Gastrointestinal disorders	Nausea, vomiting, abdominal pain			
Musculoskeletal and conjunctive tissue disorders				Myasthenia, Muscle cramps
General disorders and alterations at the place of administration			Weakness	Excessive sweating, loss of consciousness*

* They may particularly appear in treatments repeated during several days and as a result of the toxicity of their metabolites, cyanide and thiocyanate.
In some cases, particularly in infusions which are too rapid, there may be hypotensive crises caused by a too sharp a fall in blood pressure which could be manifested in the form of nausea and vomiting, excessive sweating, headaches, nervousness, agitation, muscle cramps, precordial pain, palpitations, dizziness, weakness, rash, abdominal pain, confusion and sleepiness. These symptoms rapidly disappear by reducing the infusion rate or suspending temporarily the administration of sodium nitroprusside and they do not reappear if a slower rate of administration is maintained (see section 4.4. Special warnings and precautions for use).

Sodium nitroprusside is rapidly transformed into cyanide and then into thiocyanate (see section 5.2, *Pharmacokinetic properties*). During prolonged treatments, with high dosages, or when there is an endogenous thiosulfate depletion which transforms cyanide into thiocyanate, an accumulation of cyanide in plasma may be produced which may be manifested in the form of tachycardia, excessive sweating, metabolic acidosis, hyperventilation and arrhythmias. Methemoglobinemia and hypothyroidism can also be observed. The secondary effects attributed to intoxication by thiocyanate include tinnitus, myosis and hyperreflexia.

Notification of suspected adverse reactions:
It is important to notify any suspected adverse reactions to the drug after its authorisation. This allows continuous supervision of the risk-benefit ratio of the drug. Health professionals are invited to report any suspected adverse reactions through the Spanish Drug Pharmacovigilance System for Drugs for Human Use https://www.notificaram.es

4.9. Overdoses
Signs of overdosage may be manifested in the form of excessive hypotension or of signs of intoxication by cyanide or thiocyanate (see section 4.8. *Adverse reactions*).
A massive overdose may produce a comatose symptoms with an imperceptible pulse, no reflexes, mydriasis, flushing, hypotension and shallow breathing which may lead to the death of the patient. To treat intoxication by cyanide, the following measures shall be taken:

- Suspend the infusion of sodium nitroprusside immediately.

- If the patient is conscious, immediately administrate amyl nitrite by inhalation at the rate of one ampoule for 30 seconds every 2 minutes, unless blood pressure is less than 80 mm Hg.
- Immediately afterwards (but not together with the amyl nitrite), give 10 ml of sodium nitrite at 3% slowly and intravenously for 3 minutes. It is possible that during the administration of the amyl nitrite, noradrenaline must be administered in an intravenous infusion to maintain the blood pressure levels.
- Then, give 50 ml of sodium thiosulfate 25% in intravenous infusion for 10 minutes.
- Introduce support measures as quickly as possible (e.g. assisted breathing with 100% oxygen).
- If the symptoms reappear, the administration of sodium nitrite and sodium thiosulfate shall be repeated, but the dosages must be reduced by 50%.
- Peritoneal dialysis may be useful to reduce the thiocyanate levels.
- The levels of cyanide and thiocyanate in the blood shall be constantly monitored.
- If there is serious, prolonged hypoxemia secondary to excessive methaemoglobinaemia, it may be necessary to administrate pure oxygen via inhalation or carry out a blood transfusion.

It has been demonstrated that the possible undesirable effects of cyanide may be minimise by administering hydroxocobalamin (vitamin B_{12}) together with Nitroprussiat Fides. Vitamin B_{12} reacts with cyanide to form cyanocobalamin, thereby preventing the passage of cyanide into the tissues. Vitamin B_{12} may be administered by intravenous infusion in an approximate dosage of 12.5 mg for 30 minutes, preparing the solution for infusion, for example, dissolving 100 mg of hydroxocobalamin in 100 ml of dextrose solution 5%. Both the infusion of the hypotensive drug and of the vitamin may start and end simultaneously.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensive drugs: Nitroferricyanide, derivatives. ATC Code: C02DD.

Action mechanism

The active ingredient of Nitroprussiat Fides is sodium nitroprusside, a powerful hypotensive agent which is fast-acting and fleeting which, administrated intravenously, produces a reduction in peripheral vascular resistance and a marked drop in blood pressure. Its action is exerted directly on the walls of the vessels and it is independent of the vegetative innervation.

Pharmacodynamic effects

Sodium nitroprusside dilates the arterioles and venules. Its haemodynamic response is owing to the combination of an increase in venous capacitance and a reduction in arterial impedance. When it is given in an intravenous infusion, both in hypertensive and in normotensive patients, a considerable decrease is observed in the mean blood pressure, an effect which, although more moderate, is also observed at venous levels and it leads to a reduction in peripheral resistances.

Clinical efficacy and safety

The hypotensive activity of sodium nitroprusside is the result of its relaxing action on the smooth vascular muscle. Its effects on the working and output of the heart seem to depend on the pre-existing cardiac efficiency; hence, changes observed in the heart function are preferably attributed to a reduction in the left ventricular afterload (owing to a reduction in arteriolar resistance and an increase in the *compliance* of the ventricle/aorta) and a reduction in the preload owing to a lower venous return at the auricle.

The intravenous infusion of Nitroprussiat Fides produces an immediate, powerful and short-lasting response; a few minutes (1-10) after having interrupted the infusion, the blood pressure of the patient returns to the initial levels.

5.2. Pharmacokinetic properties

Absorption
Given intravenously, the hypotensive activity of the sodium nitroprusside starts to be observed in less than 2 minutes.

Biotransformation
The sodium nitroprusside is metabolized by the erythrocytes and body tissues, bringing about cyanide which is also metabolized in the liver, giving rise to the formation of thiocyanates which are eliminated in the urine.

Elimination
The elimination half-life of thiocyanate is 2.7 to 7 days, although it may attain 9 days with kidney failure. The elimination half-life may also increase in the event of hyponatremia. Thiocyanate can be eliminated by means of haemodialysis or peritoneal dialysis.

5.3. Preclinical safety data

The DL_{50} of the sodium nitroprusside administered intravenously is 2.8 mg/kg in rabbits, 5.0 mg/kg in dogs, 8.4 mg/kg in mice and 11.2 mg/kg in rats.

There are no data in the literature indicating any potential carcinogenic effect of sodium nitroprusside.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Sodium citrate, anhydrous glucose, water for injections.

6.2. Incompatibilities

Nitroprussiat Fides is totally incompatible with other drugs and it must also be administered by itself. It should not be given directly, but rather in the form of an intravenous infusion diluted with an isotonic dextrose solution (a sterile solution of glucose in water 4.7-5%).

6.3. Expiry period

5 years.

Once the infusion solution has been prepared, the latter must be used within a maximum period of 4 hours, protected from the light by wrapping the phial in tinfoil which is attached in the box.

6.4. Special storage precautions

Keep in the original packaging.
For the storage conditions after the reconstitution/dilution of the drug, see section 6.3.

6.5. Nature and content of the packaging

Boxes containing 1 lyophilised phial, 1 ampoule of solvent and tinfoil to protect the infusion solution from the light once prepared.

6.6. Special precautions for disposal and other handling

The disposal of the unused drug and of all the materials which have been in contact with it shall be carried out in accordance with local regulations.

Preparation of the infusion solution and precautions:

The content of the phial is dissolved in the solvent ampoule carrier **(no other solvent must be used).**
This stock solution is diluted in 500-1000 ml of isotonic dextrose solution (a sterile solution of glucose in water 4.7-5%), taking the precaution to keep the solution, as from this time, protected from the light (wrapping the phial in tinfoil which is attached in the box). Once
prepared, the solution must be used within a maximum time of 4 hours (see sections 4.2 Dosage and form of administration and 6.3 Expiry period).

7. MARKETING AUTHORISATION HOLDER

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Avda. de Castilla 2, Edificio Berlín (2ª planta)
28830 San Fernando de Henares (Madrid)

8. MARKETING AUTHORISATION NUMBER (S)

Registration no.: 54,575.

9. DATE OF THE FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

July 1979 / July 2009

10. TEXT REVISION DATE

May 2017

Detailed information about this drug is available at the website of the Spanish Agency of Medicines and Medical Devices (AEMPS) http://www.aemps.gob.es/