SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Phenylephrine Sintetica 0.1 MG/ML SOLUTION FOR INFUSION

2. Qualitative and quantitative composition

Each 1 ml ampoule contains 0.1 mg phenylephrine hydrochloride
For the full list of excipients, see section 6.1

3. Pharmaceutical form and amount of active substance per unit

Phenylephrine Sintetica 0.1 mg/ml, solution for injection/solution for IV infusion
1 ml contains 0.1 mg Phenylephrine hydrochloride;
Each 5ml ampoule contains 0.5 mg Phenylephrine hydrochloride.
Each 50 ml vial contains 5 mg Phenylephrine hydrochloride

4. Clinical particulars

4.1 Therapeutic indications

Phenylephrine Sintetica 0.1mg/ml is indicated: for the treatment of hypotensive states, e.g. septic shock, circulatory failure, during spinal anaesthesia or drug-induced hypotension

4.2 Posology and method of administration

Phenylephrine Sintetica 0.1 mg/ml should only be administered by physicians with appropriate training and experience.
In case of caesarean section, administration should only be done intravenously
Phenylephrine Sintetica 0.1 mg/ml is also available in the galenic form of already diluted solution (ready to use) for administration by continuous intravenous infusion or bolus injection (Phenylephrine Sintetica 0.1 mg/ml).
For patients with paroxysmal supraventricular tachycardia and if indicated in an emergency, administer Phenylephrine Sintetica 0.1 mg/ml intravenously. The dose should be adjusted to the blood pressure response.

Mild or moderate hypotension
Phenylephrine Sintetica 0.1 mg/ml, solution for injection/solution for infusion (ready to use)
Slow intravenous injection or intravenous infusion:

Calculation of the dose

Dose required	Use of Phenylephrine Sintetica 0.01% (0.1 mg/ml)
50 µg	0.5 ml
75 µg	0.75 ml
100 µg	1 ml

Slow intravenous bolus injection:

The usual dose is 50 µg (0.5 ml Phenylephrine Sintetica 0.1 mg/ml), which can be repeated until the desired effect is achieved. In case of severe hypotension, the doses can be increased without exceeding the bolus dose of 100 µg (1 ml Phenylephrine Sintetica 0.1 mg/ml).

Continuous infusion:

The initial dose is 25-50 µg/min, up to 180 µg/min. The doses can be increased or decreased to keep the systolic blood pressure level near normal. Doses between 25 and 100 µg/min (0.25 ml – 1.0 ml Phenylephrine Sintetica 0.1 mg/ml per minute) have been considered effective.

Significant hypotension and shock, including drug-induced hypotension

Before administration of vasopressors, volume depletion should always be corrected as far as possible. When the intra-aortic pressure must be maintained in an emergency to avoid ischemia of the cerebral or coronary arteries, *Phenylephrine Sintetica 0.1 mg/ml* can be administered before and during volume filling.

Overdose and idiosyncrasy after administration of certain medicinal products, beta-adrenergic and ganglionic blockers, Rauwolfia and veratrum alkaloids and phenothiazine tranquillizers, in particular, can cause hypotension and occasionally severe shock. Patients receiving a phenothiazine derivative before surgery are particularly susceptible to these types of reactions. In the treatment of this type of reaction, *Phenylephrine Sintetica 0.1 mg/ml* is an appropriate adjunctive treatment for restoring blood pressure.

In patients with severe hypotension or prolonged or untreated shock, higher initial and maintenance doses of *Phenylephrine Sintetica 0.1 mg/ml* are required. Intensive treatment may also be necessary for hypotension triggered by strong peripheral beta-adrenergic blockers, by chlorpromazine, or by removal of a pheochromocytoma.

Spinal anaesthesia – hypotension

Phenylephrine Sintetica 0.1 mg/ml

Intravenous route

In an emergency, during episodes of hypotension during spinal anaesthesia, Phenylephrine Sintetica 0.1 mg/ml can be administered intravenously at an initial dose of 0.2 mg (2 ml Phenylephrin Sintetica 0.1 mg/ml).
None of the subsequent doses should be more than 0.1 mg to 0.2 mg higher than the previous dose (1 ml to 2 ml Phenylephrine Sintetica 0.1 mg/ml), and each dose should be lower than 0.5 mg (5 ml Phenylephrin Sintetica 0.1 mg/ml)

Paroxysmal supraventricular tachycardia
Phenylephrine Sintetica 0.1 mg/ml
Rapid intravenous injection
A rapid intravenous injection (in 20-30 seconds) is recommended. The initial dose should not exceed 0.5 mg (5 ml Phenylephrine Sintetica 0.1 mg/ml) and subsequent doses, which depend on the initial blood pressure reaction, should not be more than 0.1 to 0.2 mg higher than the previous dose, and never exceed 1 mg (10 ml Phenylephrine Sintetica 0.1 mg/ml).

Children and adolescents:
The use and safety of Phenylephrine have not been studied to date in children and adolescents. For this reason, use in children and adolescents is not recommended.

4.3 Contraindications

Phenylephrine Sintetica 0.1 mg/ml should not be used in patients with severe hypertension, ventricular tachycardia, angle-closure glaucoma or hypersensitivity to the active substance or to one of the excipients depending on the composition.

4.4 Special Warnings and precautions for use

Blood pressure should be monitored during treatment.
Phenylephrine Sintetica 0.1 mg/ml should be administered with caution in patients with:

- diabetes
- arterial hypertension
- aneurism
- uncontrolled hyperthyroidism
- myocardial pathology
- coronary disease and chronic heart disease
- bradycardia
- partial heart block
- tachycardia
- arrhythmia
- angina pectoris, (phenylephrine may precipitate or worsen angina in patients with coronary artery disease and a history of angina pectoris)

- non-severe peripheral vascular insufficiency
- serious arteriosclerosis

Phenylephrine Sintetica 0.1 mg/ml can induce decreased cardiac output. Therefore, it should be administered with extreme caution in patients with atherosclerosis, in the elderly and in patients with cerebral or coronary circulation dysfunction.

In patients with acute heart failure or cardiogenic shock, *Phenylephrine Sintetica 0.1 mg/ml* can aggravate the heart failure as a result of the induced vasoconstriction (increased afterload).

Frequent monitoring of vital body functions of patients with conditions such as decreased cardiac output or peripheral arterial disease should take place, and the systolic blood pressure lower limit should be considered as a criterion for dose reduction or discontinuation of *Phenylephrine Sintetica 0.1 mg/ml*.

Particular attention should be given to the injection of phenylephrine in order to avoid extravasation, as this could cause tissue necrosis.

Lower doses may be required in patients with renal failure.

Higher doses may be required in patients with cirrhosis of the liver.

Concomitant administration of *Phenylephrine Sintetica 0.1 mg/ml* and the following medicinal products is not recommended due to the risk of vasoconstriction and/or hypertensive crisis associated with its indirect sympathomimetic effect:

- ergot alkaloid dopamine agonists (bromocriptine, cabergoline, lisuride, pergolide) or vasoconstrictors (dihydroergotamine, ergotamine or methysergide, methylergometrine)
- in combination with linezolid

To be taken into consideration in patients following a strict sodium diet.

In case of concomitant administration of *Phenylephrine Sintetica 0.1 mg/ml* and oxytocic drugs (oxytocin, neurohypophyseal extracts, rye ergot alkaloids, etc.), the effect of sympathomimetics is enhanced.

Phenylephrine Sintetica 0.1 mg/ml. contains less than 1 mmol (23 mg) of sodium per 5 ml ampoule, i.e., it is essentially “sodium free”.

Phenylephrine Sintetica 0.1 mg/ml contains 35.4 mg sodium per 10 ml ampoule, equivalent to 1.8% of the WHO recommended maximum daily dietary intake of 2 g of sodium per adult.

Phenylephrine Sintetica 0.1 mg/ml contains 177 mg sodium per 50 ml vial, equivalent to 8.9% of the WHO recommended maximum daily dietary intake of 2 g of sodium per adult.

4.5 Interaction with other medicinal products and other forms of interaction

Oxytocin, MAO inhibitors and tricyclic antidepressants enhance the effect of *Phenylephrine Sintetica 0.1 mg/ml*.

Vasopressors, in particular metaraminol, can cause severe cardiac arrhythmias during halothane narcosis and therefore should only be used with great caution.

4.6 Pregnancy and Breastfeeding

Pregnancy
No experimental animal studies are available regarding the effect on pregnancy, embryonic development, foetal development and/or postnatal development. The potential risk for humans is unknown.
Phenylephrine Sintetica 0.1 mg/ml should not be used during pregnancy unless the treatment is absolutely necessary.

Breastfeeding
It is not known if Phenylephrine is passed into breast milk. *Phenylephrine Sintetica 0.1 mg/ml* should therefore not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

No relevant study has been performed. When using Phenylephrine, adverse reactions such as nausea and headaches have been reported occasionally. If a patient is affected by these reactions, they should not drive any vehicle or use machines.

4.8 Adverse reactions

"Very common" (≥1/10), "common" (<1/10 and ≥1/100), "uncommon" (<1/100 and ≥1/1000), "rare" (<1/1000 and ≥1/10,000), "very rare" (<1/10,000).
Most of the adverse reactions caused by phenylephrine are dose-dependent and as a consequence of the expected pharmacodynamic profile.
The most common adverse reactions are bradycardia, episodes of hypertension, nausea and vomiting. Hypertension is more common with high doses.
The following side effects may occur:
Immune system disorders
Hypersensitivity.
Metabolism and nutrition disorders
Abnormal glucose metabolism.
Psychiatric disorders
Euphoria, agitation, anxiety, psychotic states, mental confusion.
Nervous system disorders
Uncommon: Headaches, stinging sensation, heaviness in the head, nervousness, insomnia, paresthesia, shaking.
Eye disorders
Mydriasis, worsening of pre-existing angle-closure glaucoma.
Cardiac disorders
Uncommon: Reflex bradycardia, arrhythmia, tachycardia, cardiac arrest, angina pain, palpitations, myocardial ischemia.

Vascular disorders

Cerebral haemorrhage, hypertension, hypotension with sensation of dizziness, fainting, flushing, coldness of the skin, pallor.

Respiratory, thoracic and mediastinal disorders

Dyspnoea, pulmonary oedema.

Gastrointestinal disorders

Uncommon: Nausea, hypersalivation and vomiting.

Skin and subcutaneous tissue disorders

Diaphoresis, piloerection, secretion of sweat, paling of the skin.

Renal and urinary tract disorders

Difficulty urinating, urinary retention.

General disorders and administration site conditions

Extravasation necrosis at the injection site.

Reporting suspected adverse reactions after authorization 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 overdose, mainly by direct IV administration, ventricular extrasystoles and even brief episodes of ventricular tachycardia may be observed.

Treatment

In case of excessive increase in blood pressure, it can be immediately reduced by an alpha-adrenergic blocker, e.g. phentolamine.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: C01CA06

Mechanism of action

Vasoconstriction caused by phenylephrine lasts 20 minutes after intravenous injection and up to 50 minutes after subcutaneous injection. Phenylephrine slows the heart rate and increases systolic volume without affecting the heart rate.

Phenylephrine is a postsynaptic alpha-adrenergic receptor agonist with limited effect on beta receptors in the heart. In therapeutic doses, it does not induce either stimulation of the spinal cord or brain, or a moderate stimulation. Repeated injections may enable comparable effects to be obtained. Phenylephrine acts mainly on the cardiovascular system. Parenteral administration causes an increase in systolic and diastolic blood pressure in humans and in other species. The pressor response to phenylephrine is accompanied by marked reflex bradycardia which can be inhibited by atropine; after administration of atropine, high doses of the medicinal product increase the heart rate only to a limited extent. In humans, the minute volume of the heart is slightly reduced and the peripheral resistance is considerably increased. The circulation time is slightly prolonged and the venous pressure slightly increased; there is no marked venous constriction. Most of the vascular beds are narrowed; renal, splanchnic, cutaneous and limb blood supply is reduced; coronary circulation is increased. The pulmonary vessels are narrowed and the pulmonary arterial pressure increases.

Clinical efficacy

No data available.

5.2 Pharmacokinetic properties

Absorption

In case of oral absorption, the bioavailability is 38%.

Distribution

The distribution half-life is 5 minutes and the distribution volume is greater than 40 liters. After IV administration, the volume of distribution of the central compartment is comparable to the extracellular volume (approx. 40 liters), while the volume of distribution at steady state is 340 liters.

Metabolism

Phenylephrine is metabolized to m-hydroxymandelic acid and phenolic conjugates. Degradation to phenolic conjugates is increased with oral administration and reduced with intravenous administration. Metabolisation takes place in the liver and intestinal wall.

Elimination

In case of IV administration, the elimination half-life is 2-3 hours, renal excretion is 80-86%, and 16% of the active substance is excreted in the urine unchanged. The elimination half-life is 2-3 hours.

Kinetics of special patient groups

No data available.

5.3 Preclinical safety data

No experimental animal studies are available on the toxicity of phenylephrine for reproduction and development

Experimental data obtained with rats and mice do not indicate any carcinogenic or genotoxic potential.

6. Special notes

6.1 List of excipients

Sodium Chloride
Hydrochloric acid concentrated
Water for injection

6.2 Incompatibilities

Phenylephrine Sintetica is incompatible with alkaline solutions, ferric and other metal salts, phenytoin sodium and oxidising agents.

6.3 shelf life

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

Shelf life after first opening:

Phenylephrine Sintetica 0.1 mg/ml, solution for injection/solution for IV infusion:
The preparation does not contain a preservative. For microbiological reasons, the ready to use preparation should be used immediately after opening.

Discard the leftover solution.

6.4 Special notes on storage

For 5ml ampoule:

- Store below 30°C
- Store in the original package in order to Protected from light
- Keep out of the reach of children.

For 50ml Vial:

- Store below 25°C
- Do not refrigerate or freeze
- Store in the original package in order to Protected from light
- Keep out of the reach of children

6.5 Nature and contents of container

- Type I clear one point cut clear glass 5ml ampoule
- Type I clear colorless glass 50ml vial

7. **Marketing Authorization holder**

   CTS LTD
   4 HAHARASH ST.,HOD-HASHARON
   4524075

8. **Authorization number**

   177-43-37116-99.

9. **Manufacturer**

   Sintetica SA
   Via Penate 5, CH-6850 Mendrisio,
   Switzerland

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