Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Phenylephrine 100 micrograms/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains phenylephrine hydrochloride equivalent to 100 micrograms (0.1 mg) phenylephrine.
Each 20 ml vial contains phenylephrine hydrochloride equivalent to 2000 micrograms (2 mg) phenylephrine.

Excipients with known effect:
Each ml of solution for injection contains 3.9 mg equivalent to 0.17 mmol of sodium.
Each 20 ml vial contains 78 mg equivalent to 3.4 mmol of sodium.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion
Clear colourless solution
pH: 4.5 – 5.5
Osmolality: 270 – 330 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of hypotension during spinal, epidural or general anaesthesia.

4.2 Posology and method of administration

Posology

Adults

Intravenous bolus injection:

Normal dose is 50 to 100 micrograms, which can be repeated until the desired effect is obtained. One bolus dose should not exceed 100 micrograms.

Continuous infusion:

Initial dose is 25 to 50 micrograms/min. Doses can be increased up to 100 micrograms/min or reduced in order to maintain systolic blood pressure close to the normal value.
Doses between 25 and 100 micrograms/min have been considered effective.

Renal impairment

Lower doses of phenylephrine may be needed in patients with impaired renal function.

Hepatic Impairment

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

Elderly:

Treatment of the elderly should be carried out with care.

Paediatric population

The safety and efficacy of phenylephrine in children have not been established. No data are available.

Method of administration:

Intravenous bolus injection or intravenous infusion.

This medicine should only be administered by healthcare professionals with appropriate training and relevant experience.

4.3 Contraindications

Phenylephrine should not be used:
- In case of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- in combination with non-selective monoamine oxidase inhibitors (MAOs) (or within 2 weeks of their withdrawal) due to risk of paroxysmal hypertension and possibly fatal hyperthermia (see section 4.5);
- in patients with severe hypertension or peripheral vascular disease due to the risk of ischemic gangrene or vascular thrombosis;
- in patients with severe hyperthyroidism.

4.4 Special warnings and precautions for use

The arterial blood pressure should be monitored during treatment.

Phenylephrine should be administered with care to patients with:
- diabetes mellitus;
- arterial hypertension;
- uncontrolled hyperthyroidism;
- coronary heart disease and chronic heart conditions;
- non-severe peripheral vascular insufficiency;
- bradycardia;
- partial heart block;
- tachycardia;
- arrhythmias;
- angina pectoris (phenylephrine can precipitate or exacerbate angina in patients with coronary artery disease and history of angina);
- aneurysm;
- closed angle glaucoma.

Phenylephrine can induce a reduction in cardiac output. Consequently, it must be administered with extreme caution to patients with arteriosclerosis, to elderly and to patients with impaired cerebral or coronary circulation.

In patients with reduced cardiac output or coronary vascular disease, vital organ functions should be closely monitored and dose reduction should be considered when systemic blood pressure is near the lower end of the target range.
In patients with serious heart failure or cardiogenic shock, phenylephrine may cause deterioration in the heart failure as a consequence of the induced vasoconstriction (increase in afterload).
Particular attention should be paid when administering phenylephrine injection to avoid extravasation, since this may cause tissue necrosis.
This medicinal product contains sodium.

This medicine contains 3.4 mmol (78 mg) sodium per vial, equivalent to 4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interactions

Contraindicated combinations (see section 4.3)

- Non-selective MAO inhibitors
Paroxysmal hypertension, hyperthermia possibly fatal. Due to the long duration of action of MAOIs, this interaction is still possible 15 days after discontinuation of the MAOI.

Inadvisable combinations (see section 4.4)
- Dopaminergic ergot alkaloids (bromocriptine, cabergoline, lisuride, pergolide):
Risk of vasoconstriction and/or hypertensive crisis.

- Vasoconstrictor ergot alkaloids (dihydroergotamine, ergotamine, methylergometrine, methylsergide):
Risk of vasoconstriction and/or hypertensive crisis.

- Tricyclic antidepressants (e.g. imipramine):
Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

- Noradrenergic-serotoninergic antidepressants (milnacipran, venlafaxine):
Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

- Selective type A MAO inhibitors
Risk of vasoconstriction and/or hypertensive crisis.

- Linezolid:
Risk of vasoconstriction and/or hypertensive crisis.

- Guanethidine and related products:
Substantial increase in blood pressure (hyperreactivity linked to the reduction in sympathetic tone and /or to the inhibition of adrenaline or noradrenaline entry in sympathetic fibres). If the combination cannot be avoided, use with caution lower doses of sympathomimetic agents.

- Cardiac glycosides, quinidine:
Increased risk of arrhythmias.

- Sibutramine:
Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

- Halogenated volatile anaesthetics (desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane):
Risk of perioperative hypertensive crisis and arrhythmia.

Combinations requiring precautions for use:

- *Oxytocic agents:*
The effect of presso-active sympathomimetic amines is potentiated. Thus, some oxytocic agents may cause severe persistent hypertension and strokes can occur during post-partum period.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies are insufficient with respect to reproductive toxicity and teratogenicity (see section 5.3).
Administration of phenylephrine in late pregnancy or labour may potentially cause foetal hypoxia and bradycardia. Use of injectable phenylephrine is possible during pregnancy in accordance with the indications.
The combination with some oxytocic agents can cause severe hypertension (see section 4.5).

Breast-feeding
Small quantities of phenylephrine are excreted in human breast milk and oral bioavailability may be low.
Administering vasoconstrictors to the mother exposes the neonate to a theoretical risk of cardiovascular and neurological effects. However, in the event of a single bolus administration during childbirth, breast-feeding is possible.

Fertility
There is no available data concerning fertility after exposure to phenylephrine (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse events of phenylephrine are bradycardia, hypertensive episodes, nausea and vomiting. Hypertension is more frequent with high doses.
The most commonly reported cardiovascular adverse event appears to be bradycardia, likely due to baroreceptor-mediated vagal stimulation and consistent with the pharmacological effect of phenylephrine.

List of adverse reactions

Frequency: Not known (cannot be estimated from available data)

Immune system disorders:
Not known: hypersensitivity.

Psychiatric disorders:
Not known: Anxiety, excitability, agitation, psychotic states, confusion.

Nervous system disorders
Not known: Headache, nervousness, insomnia, paresthesia, tremor.
Eye disorders:
Not known: Mydriasis, aggravation of pre-existing angle-closure glaucoma.

Cardiac disorders:
Not known: Reflex bradycardia, tachycardia, palpitations, hypertension, arrhythmia, angina pectoris, myocardial ischemia.

Vascular disorders:
Not known: Cerebral haemorrhage, hypertensive crisis.

Respiratory, thoracic and mediastinal disorders:
Not known: Dyspnoea, pulmonary oedema.

Gastrointestinal disorders:
Not known: Nausea, vomiting.

Skin and subcutaneous tissue disorders:
Not known: Sweating, pallor or skin blanching, piloerection, skin necrosis with extravasation.

Musculoskeletal and connective tissue disorders:
Not known: muscular weakness.

Renal and urinary disorders:
Not known: Difficulty in micturition and urinary retention.

Description of selected adverse reactions
As phenylephrine has been frequently used in the critical care setting in patients with hypotension and shock, some of the reported serious adverse events and deaths are probably related to the underlying disease and not related to the use of phenylephrine.

Other special population(s)
Elderly: risk for phenylephrine toxicity is increased in elderly patients (see section 4.4).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of overdose include headache, nausea, vomiting, paranoid psychosis, hallucinations, hypertension and reflex bradycardia. Cardiac arrhythmia such as ventricular extrasystoles and short paroxysmal episodes of ventricular tachycardia may occur.

Treatment should consist of symptomatic and supportive measures. The hypertensive effects may be treated with an alpha-adrenoceptor blocking drug, such as phentolamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents, ATC Code: C01CA06

Mechanism of action

Phenylephrine is a potent vasoconstrictor that acts almost exclusively by stimulating alpha-1-adrenergic receptors. Such arterial vasoconstriction is also accompanied by venous vasoconstriction. This gives an increase in blood pressure and reflex bradycardia. The potent arterial vasoconstriction gives an increase in the systemic vascular resistance (increase in afterload). The overall result is a reduction in the cardiac output. This is less pronounced in healthy people but it may worsen in cases of previous heart failure. As phenylephrine effects are linked to its pharmacological properties, they can be controlled by known antidotes.

5.2 Pharmacokinetic properties

The duration of effect is 20 minutes after intravenous administration.

Distribution

The volume of distribution after single dose is 340 litres.
The plasma protein binding is unknown.

Biotransformation

Phenylephrine is metabolised in the liver by monoamine oxidase.

Elimination

Phenylephrine is mainly excreted via the kidneys as m-hydroxymandelic acid and phenol conjugates.
The terminal half life of injectable phenylephrine is about 3 hours.

Special patient populations

There is no data available on the pharmacokinetics in special patient groups.

5.3 Preclinical safety data

There is no evidence of genotoxicity or carcinogenicity of phenylephrine.

Animal studies are insufficient to evaluate effects on fertility and reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium citrate
Citric acid monohydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

20 ml clear type II glass vial closed with a chlorobutyl rubber stopper and an aluminium cap.
The vials are available in box of 1 or 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicine should be inspected for particles or discoloration prior to administration. This medicine should not be used if the solution is colored or contains particles.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoire AGUETTANT
1 Rue Alexander Fleming
69007 LYON
France

8 MARKETING AUTHORISATION NUMBER

PA1968/007/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th February 2020

10 DATE OF REVISION OF THE TEXT

January 2022