Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Phenylephrine 50 micrograms/ml, solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains phenylephrine hydrochloride equivalent to 50 micrograms (0.05 mg) phenylephrine.
Each 10 ml pre-filled syringe contains phenylephrine hydrochloride equivalent to 500 micrograms (0.5 mg) phenylephrine.

Excipients with known effect:
This medicinal product contains sodium.
Each ml of solution for injection contains 3.72 mg equivalent to 0.162 mmol of sodium.
Each 10 ml pre-filled syringe contains 37.2 mg equivalent to 1.62 mmol of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe. (Injection)
Clear colourless solution.
pH: 4.7 – 5.3
Osmolality: 270-300 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
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.

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.
Phenylephrine, 50 micrograms/ml, solution for injection should only be administered by healthcare professionals with appropriate training and relevant experience.
The pre-filled syringe is not suitable for use in a syringe driver.

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 patients with severe hypertension or peripheral vascular disease due to the risk of ischemic gangrene or vascular thrombosis;
- 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 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. Therefore, care should be exercised in administering to patients with arteriosclerosis, the 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 37.2 mg sodium per pre-filled syringe, equivalent to 1.9 % 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 monoamine oxidase inhibitors (MAOs) (iproniazid, nialamide)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

- 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 (minalcipram, venlafaxine): Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).
- Selective type A monoamine oxidase inhibitors (MAOs) (moclobemide, toloxatone)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 infant 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
Website: www.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

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 volume of distribution after single dose is 340 litres.

Phenylephrine is metabolised in the liver by monoamine oxidase.

Phenylephrine is mainly excreted via the kidneys as m-hydroxymandelic acid and phenol conjugates.

The duration of effect is 20 minutes after intravenous administration.
The terminal half life of injectable phenyleprine is about 3 hours.

The plasma protein binding is unknown.

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,
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 syringe in its unopened blister until use. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

10 ml solution for injection in a pre-filled syringe (polypropylene) with plunger stopper (chlorobutyl), without a needle, with a graduated self- adhesive label from 0 until 10 ml. The polypropylene pre-filled syringe is individually packed in a transparent blister. The pre-filled syringes are available in box of 1 and 10 syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Instructions for use:

Please prepare the syringe carefully as follows

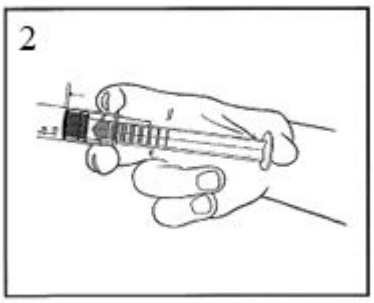
The pre-filled syringe is for single patient only. Discard syringe after use. DO NOT REUSE.

The content of un-opened and un-damaged blister is sterile, and must not be opened until use.
The product should be inspected visually for particles and discoloration prior to administration. Only clear colourless solution free from particles or precipitates should be used.
The product should not be used if the tamper evident seal on the syringe is broken.

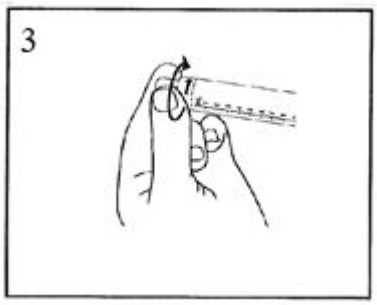
The external surface of the syringe is sterile until the blister is opened.

When handled using an aseptic method, Phenylephrine 50 micrograms/ml, solution for injection in pre-filled syringe can be placed on a sterile field.

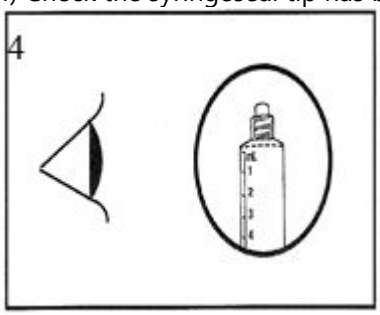
1) Withdraw the pre-filled syringe from the sterile blister.
2) Push on theplunger to free the bung. The sterilisation process may have caused adhesion ofthe bung to the body of the syringe.



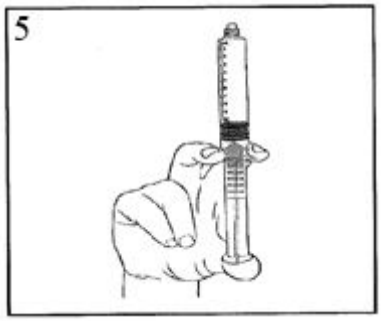
3) Twist off the end cap to break the seal. Inorder to avoid contamination, do not touch the exposed luer connection.



4) Check the syringeseal tip has been completely removed. If not, replace the cap and twist again



5) Expel the air bygently pushing the plunger.



6) Connect the syringe to the IV access. Push the plunger slowly to inject the required volume.

7 MARKETING AUTHORISATION HOLDER

Laboratoire AGUETTANT
1 Rue Alexander Fleming
69007 LYON
France

8 MARKETING AUTHORISATION NUMBER

PA1968/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th Novemeber 2015
Date of last renewal: 28th September 2020

10 DATE OF REVISION OF THE TEXT

September 2020