SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenylephrine 0.08 mg/ml, solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection/infusion contains 0.1 mg of phenylephrine hydrochloride equivalent to 0.08 mg of phenylephrine base.

Each bag of 100 ml contains 10 mg phenylephrine hydrochloride equivalent to 8 mg phenylephrine base.

Excipients with known effect:

This medicinal product contains sodium.

Each bag of 100 ml of solution for injection/infusion contains 366.2 mg equivalent to 15.9 mmol of sodium.

For the 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 and general anesthesia.

4.2 Posology and method of administration

Posology

1.Intravenous bolus injection:

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

2. Continuous infusion:

Initial dose is 25 to 50 micrograms/min. The doses may be increased or decreased to maintain the systolic blood pressure close to the normal value. Doses between 25 and 100 micrograms/min have been assessed to be 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.

Older people:

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:

Parenteral administration, by intravenous infusion. Phenylephrine should only be administered by healthcare professionals with appropriate training and relevant experience.

4.3 Contraindications

- 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);

- hyperthyroidism.

4.4 Special warnings and precautions for use

Caution is required when administering phenylephrine in patients with:

- pre-existing cardiovascular disease
- diabetes mellitus
- arterial hypertension
- ischemic heart disease
- arrhythmia
- bradycardia
- incomplete heart block
- tachycardia
- occlusive peripheral vascular disease including arteriosclerosis
- aneurysm
- in patients with angina pectoris, phenylephrine may precipitate or exacerbate angina.
- angle closure glaucoma

Phenylephrine may induce a reduction in cardiac output. Therefore, caution is required when administering to patients with atherosclerosis, the elderly, and patients with compromised cerebral or coronary circulation.

In patients with severe heart failure or cardiogenic shock, phenylephrine may cause worsening of heart failure as a consequence of the induced vasoconstriction and increased afterload.

Special attention should be given to the injection of phenylephrine to prevent extravasation, as this may cause tissue necrosis (see section 4.8).

This medicinal product contains 366.2 mg sodium per 100 ml, equivalent to 18.3% 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 interaction

Contraindicated combinations (see section 4.3)

Non-selective monoamine oxidase inhibitors (MAOs) (fenelzine, tranylcyprominet)

Paroxysmal hypertension, possibly fatal hyperthermia. Due to the long duration of MAO inhibitory action, this interaction is still possible 15 days after the MAO inhibitor is discontinued.

Combinations not advisable

Dopaminerge ergot alkaloids (bromocriptine, cabergoline, lisuride, pergolide):

Risk of vasoconstriction and/or hypertensive crisis.

Vasoconstrictor ergot alkaloids (dihydroergotamine, ergotamine, methylergometrine, methysergide):

Risk of vasoconstriction and/or hypertensive crisis.

Tricyclic antidepressants (for example, imipramine):

Paroxysmal hypertension with the possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry into sympathetic fibers).

Noradrenergic-serotonergic antidepressants (minalcipran, venlafaxine):

Paroxysmal hypertension with the possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry into sympathetic fibers).

Selective monoamine oxidase inhibitors (MAOs) type A (moclobemide, toloxatone)

Risk of vasoconstriction and/or episodes of hypertension.

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 fibers). 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 fibers).

Halogenated volatile anesthetics (desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane):

Risk of hypertensive crisis and perioperative arrhythmia.

Combinations requiring precautions for use:

Antihypertensives including α and β receptor blockers

Phenylephrine can raise blood pressure and therefore reverse the action of many agents antihypertensives. The interaction between phenylephrine and α and β receptor blockers can be complex. Medicinal products that act on the alpha-1 adrenoreceptors can potentiate the action of phenylephrine (like granisetron) or diminish (like doxazosine or buspiron).

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

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of phenylephrine in pregnant women.

Animal studies are insufficient to determine reproductive toxicity and teratogenicity (see section 5.3). The administration of phenylephrine at the end of pregnancy or at delivery can potentially cause fetal hypoxia and bradycardia. It is possible to use injectable phenylephrine during pregnancy according to the indications. The combination with some oxytocic agents can cause severe hypertension (see section 4.5).

Breast-feeding

Small amounts of phenylephrine are excreted in human breast milk and oral bioavailability may be low. The administration of vasoconstrictors to the mother exposes the baby to a theoretical risk of cardiovascular and neurological effects.

Fertility

No data on fertility are available after exposure to phenylephrine (see section 5.3).

4.7 Effects on ability to drive and use machines

No adverse effects on the ability to drive or use machines are known.

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

The following adverse reactions have been reported during the use of phenylephrine, although their frequency has not been clearly established:

Immune system disorders:

Not Known: hypersensitivity

Psychiatric disorders:

Not Known: Anxiety, excitability, agitation, psychotic states, confusion.

Nervous system disorders:

Not Known: Headache, brain haemorrhage, vertigo, fainting, torpor, insomnia, paresthesia, tremor.

Eye disorders:

Not Known: Mydriasis, aggravation of pre-existing closed angle glaucoma.

Cardiac disorders:

Not Known: Reflex bradycardia, reflex tachycardia, cardiac arrhythmia, anginal pain, palpitations, cardiac arrest.

Vascular disorders:

Not Known: Hypertension, hypotension, flushing, hypertensive crisis

Respiratory, thoracic and mediastinal disorders:

Not Known: Dyspnea, pulmonary oedema.

Gastrointestinal disorders:

Not Known: Nausea, Vomiting, hypersalivation.

Skin and subcutaneous tissue disorders:

Not Known: Sweating, temporary tingling, coolness of the skin, pallor or skin blanching, piloerection

Renal and urinary disorders:

Not Known: Difficulty urinating, urinary retention.

Metabolism and nutrition disorders:

Not Known: Alterations to glucose metabolism.

General disorders and administration site conditions:

Not Known: Extravasation of phenylephrine may cause tissue necrosis.

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 national reporting system Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

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: Cardiac stimulants, excluding cardiac glycosides, 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 and

water for injections.

6.2 Incompatibilities

Phenylephrine 0.08 mg/ml, solution for injection/infusion is incompatible with bases, iron (III) salts, phenytoin sodium and oxidising agents.

6.3 Shelf life

27 months for Polypropylene bags.

18 months for PVC-free polyolefin bags

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25ºC for the product without the external pouch and exposed to daylight.

From a microbiological point of view, the product should be used immediately after first opening. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions for Polypropylene bags.

Do not store above 30ºC for PVC-free polyolefin bags.

Store in the original package (bag overwrapped in outer pouch) in order to protect from light.

Do not freeze.

6.5 Nature and contents of container

Phenylephrine 0.08 mg/ml, solution for injection/infusion is available in the following presentation:

- 100 ml solution in a 100 ml flexible Polypropylene bag with an aluminium overpouch

- 100 ml solution in a 100 ml PVC-free polyolefin bag with an aluminium overpouch

Each Polypropylene or PVC-free polyolefin bag contains one non PVC point for filling and closure of the bag port and one non PVC administration port.

Pack sizes: 10 bags of 100 ml

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or material that has been in contact with it should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited,
2nd Floor, Connect 38, 1 Dover Place,
Ashford, Kent, England, TN23 1FB

8 MARKETING AUTHORISATION NUMBER(S)

PL 51463/0203

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