106566

EPHEDRINE AGUETTANT
SOLUTION FOR INJECTION
IN PRE-FILLED SYRINGE 30 MG/ 10 ML

1. NAME OF THE MEDICINAL PRODUCT

EPHEDRINE AGUETTANT solution for injection in pre-filled syringe 30 mg/ 10 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ephedrine hydrochloride..... 30 mg/ 10 ml
A 10 ml pre-filled syringe contains 30 mg of ephedrine hydrochloride.
Excipient with known effect: sodium
Each ml of solution for injection contains 3.39 mg sodium, equivalent to 0.15 mmol.
Each 10 ml pre-filled syringe contains 33.9 mg sodium, equivalent to 1.5 mmol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Clear, colourless, liquid.
pH = 4.5 to 5.5
Osmolality: between 270 – 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Reversal of anaesthesia induced hypotension during spinal and epidural anaesthesia

4.2. Dosage and method of administration

Adults and the elderly
Up to 30 mg in increments of 3 - 7.5 mg.
After the development of hypotension, by slow intravenous administration.
Paediatric Population
0.5 - 0.75 mg/kg body weight or 17 - 25 mg/m^2 body surface.
After the development of hypotension, by slow intravenous administration.

Compatibilities
Ephedrine is reported to be compatible with 0.9% sodium chloride.

4.3. Contraindications

This medicinal product must never be used in the following cases:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- in combination with other indirect sympathomimetic agents such as pseudoephedrine, methylphenidate, bupropion, cafedrine, and theodrenaline.
- in combination with alpha sympathomimetic agents.
- in combination with irreversible monoamine oxidase inhibitors (MAOI).

4.4. Special warnings and precautions for use

Special warnings
Ephedrine should be used with caution in patients who may be particularly susceptible to their effects, particularly those with hyperthyroidism.
Great care is also needed in patients with cardiovascular disease such as:
- ischaemic heart disease,
- arrhythmia or tachycardia,
- occlusive vascular disorders including arteriolosclerosis,
- hypertension,
- aneurysms.

Anginal pain may be precipitated in patients with angina pectoris.
Care is also required when Ephedrine is given to patients with diabetes mellitus, closed-angle glaucoma or prostatic hypertrophy.
Ephedrine should be avoided or used with caution in patients undergoing anaesthesia with cyclopropane, halothane, or other halogenated anaesthetics, as they may induce ventricular fibrillation.
An increased risk of arrhythmias may also occur if Ephedrine is given to patients receiving cardiac glycosides, quinidine, or tricyclic antidepressants.
Ephedrine increases blood pressure and therefore special care is advisable in patients receiving antihypertensive therapy.
Interactions of Ephedrine with alpha- and beta-blocking drugs may be complex. Propranolol and other beta- adrenoceptor blocking agents antagonise the effects of beta2 adrenoceptor stimulants (beta2 agonists) such as salbutamol. Adverse metabolic effects of high doses of beta2 agonists may be exacerbated by concomitant administration of high doses of corticosteroids; patients should therefore be monitored carefully when the 2 forms of therapy are used together although this precaution is not so applicable to inhaled corticotherapy.
Hypokalaemia associated with high doses of beta2 agonists may result in increased susceptibility to digitalis-induced cardiac arrhythmias. Hypokalaemia may be enhanced by concomitant administration of aminophylline or other xanthines, corticosteroids, or by diuretic therapy.

Precautions for use
Ephedrine should be used with caution in patients with a history of cardiac disease.
Athletes: warning, this medicinal product contains an active substance which might give a positive reaction in anti-doping tests.
This medicinal product contains 33.9 mg sodium per 10 ml pre-filled syringe, equivalent to 1.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5. Interactions with other medicinal products and other forms of interaction

Contraindicated combinations
- Other indirect sympathomimetic agents (bupropion, cafedrine, methylphenidate, pseudoephedrine, and theodrenaline).

Risks of vasoconstriction and/or acute episodes of hypertension.
- Alphasympathomimetics (oral and/or nasal route of administration).

Risk of vasoconstriction and/or episode of hypertension.
- Irreversible MAOIs

Paroxysmal hypertension, hyperthermia possibly fatal. Due to the duration of action of MAOIs, this interaction is still possible 15 days after stopping the MAOI.

Combinations not recommended
- Dopaminergic ergot alkaloids

Risk of vasoconstriction and/or episode of hypertension.
- Vasoconstrictor ergot alkaloids

Risk of vasoconstriction and/or episode of hypertension.
- Reversible MAO-A inhibitors (administered concomitantly or within the last 2 weeks), including linezolid and methylene blue

Risk of vasoconstriction and/or episode of hypertension.
- Guanethidine and related products

Substantial increase in blood pressure (hyper reactivity 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.
- Tricyclic antidepressants (e.g. imipramine)

Paroxysmal hypertension with possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibre).
- Noradrenergic-serotoninergic antidepressants (minalcipran, sibutramine, venlafaxine)

Paroxysmal hypertension with possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibre).
- Halogenated volatile anaesthetics

Serious ventricular arrhythmias due to increased cardiac excitability.

Combinations requiring precautions for use
- Theophylline

Concomitant administration of ephedrine and theophylline may result in insomnia, nervousness and gastrointestinal complaints.
- Corticosteroids

Ephedrine has been shown to increase the clearance of dexamethasone.
- Antiepileptics

Increased plasma concentration of phenytoin and possibly of phenobarbitone and primidone.
- Doxapram

Risk of hypertension.
- Oxytocin

Hypertension with vasoconstrictor sympathomimetics.
- Hypotensive agents

Reserpine and methyldopa may reduce the vasopressor action of ephedrine.

4.6. Fertility, pregnancy and lactation

Pregnancy
Studies in animals have shown teratogenic effects.
Clinical data from epidemiological studies on a limited number of women appear to indicate no particular effects of ephedrine with respect to malformation.
Isolated cases of maternal hypertension have been described after abuse or prolonged use of vasoconstrictor amines.
However, there is currently insufficient data to confirm the actual foetotoxicity of ephedrine when administered during pregnancy.

Due to its sympathomimetic effect, an increase in foetal heart rate and variability can be observed.
Therefore, ephedrine should be used during pregnancy only if necessary.

Breast-feeding

Ephedrine is excreted in breast milk. Irritability and disturbed sleep patterns have been reported in breast-fed infants. There is evidence that ephedrine is eliminated within 21 to 42 hours after administration, therefore a decision needs to be made on whether to avoid ephedrine therapy or lactation should be suspended for 2 days following its administration taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

The adverse effects are classified by organ system and by frequency according to the following rule:
Very common: > 1/10; common: (≥1/100 to <1/10); uncommon: (≥1/1000 to <1/100); rare: (≥1/10000 to <1/1000); very rare: (<1/10000); frequency not known: (cannot be estimated based on currently available data).

• Blood and lymphatic system disorders
Not known: primary haemostasis modifications.

• Immune system disorders
Not known: hypersensitivity.

• Psychiatric disorders
Common: confusion, anxiety, depression.
Not known: psychotic states, fear

• Nervous system disorders
Common: nervousness, irritability, insomnia, restlessness, weakness, headache, sweating,
Not known: tremors, hypersalivation

• Eye disorders
Not known: episodes of angle-closure glaucoma.

• Cardiac disorders
Common: palpitations, hypertension tachycardia, ,
Rare: cardiac arrhythmia
Not known: anginal pain, reflex bradycardia cardiac arrest. A Takotsubo syndrome (stress cardiomyopathy) might occur.

• Vascular disorders
Not known: cerebral haemorrhage.

• Respiratory, thoracic and mediastinal disorders
Common: dyspnoea
Not known: pulmonary oedema

• Renal and urinary disorders
Rare: acute urinary retention

• Investigations:
Not known: hypokalaemia, changes in blood glucose levels

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.

4.9. Overdose

In the event of overdose, the occurrence of nausea, vomiting, fever, paranoid psychosis, ventricular and supraventricular arrhythmia, hypertension, respiratory depression, convulsions and coma is observed.
The lethal dose in humans is approximately 2 g corresponding to blood concentrations of approximately 3.5 to 20 mg/ml.

Treatment

The treatment of ephedrine overdose with this product may require intensive supportive treatment. Slow intravenous injection of labetalol 50-200 mg may be given with electrocardiograph monitoring for the treatment of supraventricular tachycardia. Marked hypokalaemia (<2.8mmol.l-1) due to compartmental shift of potassium predisposes to cardiac arrhythmias and may be corrected by infusing potassium chloride in addition to propranolol and correcting respiratory alkalosis, when present.
A benzodiazepine and/or a neuroleptic agent may be required to control CNS stimulant effects.
For severe hypertension, parenteral antihypertensive options include intravenous nitrates, calcium channel blockers, sodium nitroprusside, labetalol or phentolamine. The choice of antihypertensive drug is dependent on availability, concomitant conditions and the clinical status of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ADRENERGIC AND DOPAMINERGIC, ATC code: C01CA26.

Ephedrine is a sympathomimetic amine acting directly on alpha and beta receptors and indirectly by increasing the release of noradrenaline by the sympathetic nerve endings. As with any sympathomimetic agent, ephedrine stimulates the central nervous system, the cardiovascular system, the respiratory system, and the sphincters of the digestive and urinary systems. Ephedrine is also a monoamine oxidase inhibitor (MAOI).

5.2. Pharmacokinetic properties

Excretion depends on urine pH:
• From 73 to 99% (mean: 88%) in acid urine,
• From 22 to 35% (mean: 27%) in alkaline urine.
After oral or parenteral administration, 77% of ephedrine is excreted in unchanged form in the urine
The half-life depends on urine pH, When the urine is acidified at pH = 5, the half-life is 3 hours; when the urine is rendered alkaline at pH = 6.3, the half-life is approximately 6 hours.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride, citric acid monohydrate, sodium citrate, hydrochloric acid or sodium hydroxide, water for injections.

6.2. Incompatibilities

Ephedrine is reported to be physically incompatible with the phenobarbitone sodium, pentobarbitone sodium, quinalbarbitone sodium and thiopentone sodium, and with hydrocortisone sodium succinate in some infusion solutions.

6.3. Shelf life

3 years.
After opening the blister: the product must be used immediately

6.4. Special precautions for storage

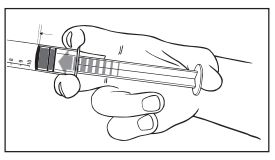
Store below 30°C. Store the blister in the outer carton in order to protect from light.

6.5. Nature and contents of container

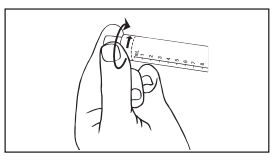
10 ml polypropylene pre-filled syringe; box of 10.

6.6. Special precautions for disposal and other handling

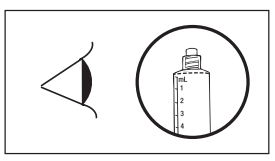
Be careful to strictly respect the instructions for use of the syringe.
The pre-filled syringe is for single patient only. After first use, the remaining product should be discarded.
The content of un-opened and un-damaged blister is sterile, and must not be opened until use.
When handled using an aseptic method, EPHEDRINE AGUETTANT solution for injection in pre-filled syringe 30 mg/ 10 ml can be placed on a sterile field.
1) Withdraw the pre-filled syringe from the sterile blister.



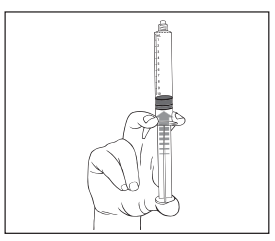
2) Push on the plunger to free the bung. The sterilisation process may have caused adhesion of the bung to the body of the syringe.



3) Twist off the end cap. Do not touch the exposed luer connection in order to avoid contamination.



4) Check the syringe seal tip has been completely removed.



5) Expel the air by gently pushing the plunger.

6) Connect the syringe to the IV access. Push the plunger slowly to inject the required volume.
7) After use, discard the syringe in accordance with local requirements in your facility.

7. PRODUCT OWNER

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8. DATE OF REVISION OF THE TEXT

April 2023