

1. NAME OF THE MEDICINAL PRODUCT

AGUETTANT Ephedrine 3 mg/ml, solution for injection in prefilled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Solution for Injection contains 3 mg ephedrine hydrochloride, corresponding to 2.46 mg ephedrine.

Each 10 ml pre-filled syringe contains 30 mg ephedrine hydrochloride, corresponding to 24.6 mg ephedrine.

Excipient with known effect:

This medicinal product contains sodium.

Each ml of Solution for Injection contains 3.39 mg equivalent to 0.15 mmol of sodium. Each 10 ml pre-filled syringe contains 33.9 mg equivalent to 1.5 mmol of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (Injection).

Clear, colourless liquid pH = 4.5 to 5.5

Osmolality: between 270 – 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypotension from spinal, epidural, and general anaesthesia.

4.2 Posology and method of administration

Posology

Adults

Slow intravenous injection of 3 to 6 mg (maximum 9 mg), repeated as needed every 3- 4 min to a maximum of 30 mg. A lack of efficacy after 30 mg should lead to reconsideration of the choice of the therapeutic agent.

The dose administered for 24 hours must not exceed 150 mg.

Paediatric population

AGUETTANT Ephedrine 3 mg/ml, solution for injection in prefilled syringe is generally not recommended for use in children due to insufficient data on efficacy, safety and dosage recommendations.

- Children under 12 years

The safety and efficacy of ephedrine in paediatric patients under 12 years have not been established. No data are available.

- Children over 12 years

The posology and method of administration is the same as for adults.

Patients with renal or hepatic impairment

There are no dose adjustment recommended for patients with renal or hepatic impairment.

Eldery

As for adults.

Method of administration

Ephedrine must be used solely by or under the supervision of the anaesthetist as an injection via intravenous route.

For intravenous use.

4.3 Contraindications

Ephedrine 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 other indirect sympathomimetic agents such as phenylpropanolamine, phenylephrine, pseudoephedrine and methylphenidate.
- In combination with alpha sympathomimetic agents.
- In combination with non-selective MAO inhibitors or within 14 days of their withdrawal.

4.4 Special warnings and precautions for use

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 arteriosclerosis, hypertension, or 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 arrhythmia may also occur if ephedrine is given to patients receiving cardiac glycosides, quinidine, or tricyclic antidepressants.

Many sympathomimetics interact with monoamine oxidase inhibitors, and should not be given to patients receiving such treatment or within 14 days of its termination. It is advisable to avoid sympathomimetics when taking selective MAO inhibitors.

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 arrhythmia. 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 should be informed that this preparation contains an active substance which might give a positive reaction in anti-doping tests.

Check that the solution is clear and contains no visible particles before infusion. This medicinal product contains sodium:

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:

Indirect sympathomimetic agents (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate)

Risk of vasoconstriction and/or of acute episodes of hypertension.

Alpha sympathomimetics (oral and/or nasal route of administration)

Risk of vasoconstriction and/or episodes of hypertension.

Non-selective MAO inhibitors

Paroxysmal hypertension, hyperthermia possibly fatal.

Combinations not recommended:

Ergot alkaloids (dopaminergic action)

Risk of vasoconstriction and/or episodes of hypertension.

Ergot alkaloids (vasoconstrictors)

Risk of vasoconstriction and/or episodes of hypertension.

Selective MAO-A inhibitors (administered concomitantly or within the last 2 weeks): Risk of vasoconstriction and/or episodes of hypertension.

Linezolid

Risk of vasoconstriction and/or episodes of hypertension

Tricyclic antidepressants (e.g. imipramine)

Paroxysmal hypertension with possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

Noradrenergic-serotonergic antidepressants (minalcipran, venlafaxine)

Paroxysmal hypertension with possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

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.

Sibutramine

Paroxysmal hypertension with possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

Halogenated volatile anaesthetics

Risk of perioperative hypertensive crisis and serious ventricular arrhythmias.

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 a teratogenic effect.

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.

Ephedrine crosses the placenta and this has been associated with an increase in foetal heart rate and beat-to-beat variability.

Therefore, ephedrine should be avoided or used with caution, and only if necessary, during pregnancy.

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.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Very common: $\geq 1/10$; **Common:** $\geq 1/100$, $< 1/10$; **Uncommon:** $\geq 1/1,000$, $< 1/100$; **Rare:** $\geq 1/10,000$, $< 1/1,000$; **Very rare:** $< 1/10,000$; **Not known:** cannot be estimated from the 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, restlessness, weakness, insomnia, headache, sweating

Not known: tremor, 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, hypotension

Vascular disorders:

Not known: cerebral haemorrhage

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea

Not known: pulmonary oedema

Gastrointestinal disorders:

Common: nausea, vomiting

Not known: reduced appetite

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/l.

Management

The management of ephedrine overdose with this product may require intensive supportive treatment. Slow intravenous injection of labetalol 50-200mg may be given with electrocardiograph monitoring for the treatment of supraventricular tachycardia. Marked hypokalaemia ($<2.8\text{mmol.l}^{-1}$) due to compartmental shift of potassium predisposes to cardiac arrhythmia 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 Agent. ATC Code: C01CA26

Ephedrine is a sympathomimetic amine acting directly on the 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 (MAO) inhibitor.

5.2 Pharmacokinetic properties

After intravenous administration, ephedrine is completely biologically available, and after oral administration, the bioavailability of ephedrine has been reported to be above 90%.

Excretion depends on urine pH:

From 73 to 99% (mean: 88%) in acidic 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

There is no pre-clinical data of relevance to the prescriber which is additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Citric acid monohydrate

Sodium citrate

Hydrochloric acid (for pH adjustment)

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.

After opening: the product must be used immediately.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

10 ml polypropylene pre-filled syringe with a polypropylene tip cap and tamper proof seal, individually packaged in a transparent blister pack. The prefilled syringes are available in box of 10.

6.6 Special precautions for disposal and other handling

Instructions for use:

Please prepare the syringe carefully as follows

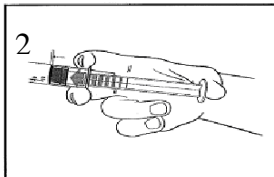
The pre-filled syringe is for single patient only. Discard syringe after use. **DO NOT REUSE.**

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.

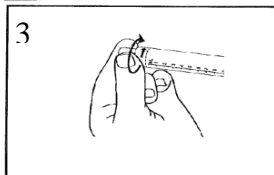
The product should not be used if the tamper evident seal on syringe is broken.

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



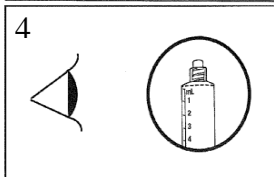
1) Withdraw the pre-filled syringe from the sterile blister.

2) Push on the plunger to free the bung.

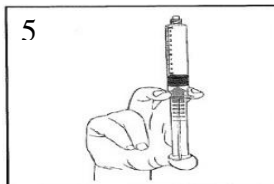


3) Twist off the end cap to break the seals

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



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.

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

7. MANUFACTURER AND PRODUCT REGISTRATION HOLDER

Manufacturer:

Laboratoire AGUETTANT
Lieu-dit Chantecaille
07340 Champagne
France

Product Registration Holder:

FIRST PHARMACEUTICAL SDN BHD
20, Jalan SS 19/5
47500 Subang Jaya
Selangor
Malaysia

8. MARKETING AUTHORISATION NUMBER(S)

MALxxxxxxxAZ

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

July 2024