SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efedrin Aguettant 3 mg/ml, Solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution for injection contains 3 mg ephedrine hydrochloride.
Each 10 ml pre-filled syringe contains 30 mg ephedrine hydrochloride.

Excipients with known effect:
This medicinal product contains sodium.
One ml contains 3.32 mg equivalent to 0.144 mmol of sodium.
Each 10 ml pre-filled syringe contains 33.2 mg equivalent to 1.44 mmol of sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe
Clear, colourless solution
pH = 4.5 to 5.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypotension, associated with spinal, epidural or general anaesthesia.

4.2 Posology and method of administration

Ephedrine must be used solely by or under the supervision of the anaesthesiologist/anaesthetist.

Posology

Adults and children over 12 years
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 total dose administered over 24 hours must not exceed 150 mg.

Paediatric population
Children under 12 years
The paediatric dose is 0.5 to 0.75 mg/kg or 17-25 mg/m^2 every 3-4 minutes according to response.

Elderly
As for adults.

Method of Administration
For intravenous use.
For instruction for use of the medicinal product see section 6.6.

4.3 Contraindications

- Hypersensitivity to ephedrine or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Ephedrine should be used with caution in patients with:
- Hyperthyroidism,
- Hypertension,
- Cardiovascular disease,
- Diabetes mellitus,
- Narrow-angle glaucoma,
- Prostatic hypertrophy

Great care is 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.

Ephedrine should be used with caution in patients undergoing anaesthesia with cyclopropane, halothane, or other halogenated anaesthetics, as they may induce ventricular fibrillation. An increased risk of vasoconstriction and/or of acute episodes of hypertension should be considered when ephedrine is administered concomitantly with indirect sympathomimetic agent (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate).

Ephedrine interacts 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 ephedrine and other sympathomimetics when taking reversible MAOIs (see section 4.5).

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.

Adverse metabolic effects of high doses of ephedrine may be exacerbated by concomitant administration of high doses of corticosteroids; patients should therefore be monitored carefully when the two forms of therapy are used together although this precaution is not so applicable to inhaled corticotheraphy. Hypokalaemia associated with high doses of ephedrine 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
This medicinal product contains 3.32 mg (0.144 mmol) of sodium per ml of injection (a total of 33.2 mg or 1.44 mmol sodium in 10 ml syringe). This amount must be taken into consideration by patients on a salt-restricted diet.

4.5 Interactions with other medicinal products and other forms of interaction

Combinations not recommended:
Indirect sympathomimetic agents (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate)
Risk of vasoconstriction and /or acute episodes of hypertension (see section 4.4).

Volatile halogen anaesthetics
Serious ventricular arrhythmias (increase in cardiac excitability) (see section 4.4).

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

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

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.

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

Combinations requiring precautions for use:
Nonselective MAO inhibitors:
Increase in the pressor action of adrenaline and noradrenaline which is usually moderate. Should be used only under strict medical supervision (see section 4.4).

Selective MAO-A inhibitors (moclobemide, toloxatone:)
By extrapolation from nonselective MAO inhibitors. Risk of increase in the pressor action. Should be used only under strict medical supervision (see section 4.4).

Linezolide: By extrapolation from non-selective MAO inhibitors. Risk of increase in the pressor action. Should be used only under strict medical supervision.

Theophylline: Concomitant administration of ephedrine and theophylline may result in insomnia, nervousness and gastrointestinal complaints.

Clonidine: Augmented pressure response to ephedrine in patients pre –treated with clonidine.

Corticosteroids: Ephedrine has been shown to increase the clearance of dexamethasone. The potential impact on dexamethasone efficacy should be monitored, and dose should be adjusted when appropriate.

Antihypertensives: Ephedrine may antagonize the effects of alpha blockers and possibly other antihypertensive drugs in lowering blood pressure.

Oxytocin: Hypertension with vasoconstrictor sympathomimetics.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Ephedrine in pregnant women.

Ephedrine should not be used during pregnancy unless the clinical condition of the woman requires treatment with it as ephedrine crossed the placenta and this has been associated with an increase in foetal heart rate and beat-to-beat variability.

In caesarean section, ephedrine can be used to prevent hypotension caused by spinal anaesthesia. Foetal acidosis has been observed with ephedrine use; however, this did not translate into deleterious effects on neonatal outcome as reflected by Apgar score.

Since parenteral administration of ephedrine can cause acceleration of foetal heart rate, it should not be used when maternal blood pressure exceeds 130/80 mmHg.

Breastfeeding
Ephedrine is excreted in breast milk and therefore lactation should be suspended for the 2 days following its administration. Irritability and disturbed sleep patterns have been reported in breast fed infants.

Fertility
Animal studies are insufficient with respect to effects on fertility (see section 5.3).

4.7 Effects on the ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The evaluation of adverse reactions is based on the following definition of frequency:
Very common: ≥1/10; **Common:** ≥1/100, <1/10 ; **Uncommon:** ≥1/1,000, <1/100 ; **Rare:** ≥1/10,000, <1/1,000; **Very rare:** <1/10,000; **Not known:** cannot be estimated from the available data

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 arrhythmias
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, the occurrence of nausea, vomiting, fever, paranoid psychosis, ventricular and supraventricular arrhythmias, 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.

Treatment
The treatment 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 (<2.8mmol/L) 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Adrenergic and Dopaminergic Agent
ATC Code : C01CA

Mechanism of action
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.

5.2 Pharmacokinetic properties

A small quantities of ephedrine are metabolised, but the majority of ephedrine is excreted unchanged into urine. The plasma half life of ephedrine is 3-6 h depending on urinary pH; occasionally longer half-lives up to about 9 h have been reported. Elimination of ephedrine is increased (and hence the half life is decreased) with decreasing pH of the urine.

5.3 Preclinical safety data

No studies to current standards on fertility have been conducted. However, anti-estrogenic effects of ephedrine have been found in immature rats given ephedrine at a dose of 5 mg/kg orally, indicating the potential for effects on female fertility.

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 storage conditions

Store the blister in the outer carton in order to protect from light.

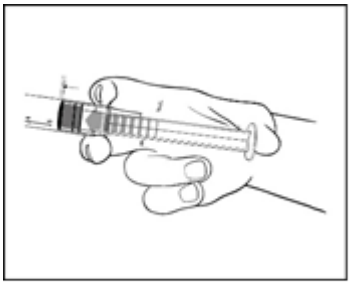
6.5 Nature and content of the container

10 ml polypropylene pre-filled syringe with a polypropylene tip cap and tamper proof seal; individually packaged in a transparent blister pack; in box of 10 or 12.

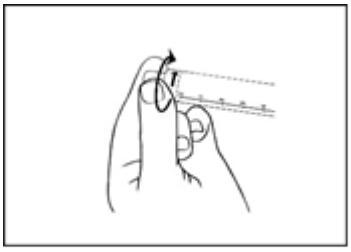
6.6 Special precautions for disposal and other handling

Instructions for use:
Be careful to strictly respect the protocol for the use of the syringe.
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.

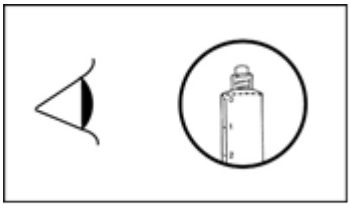
Using aseptic techniques, Efedrin Aguettant can be used on a sterile field.



1. Before opening the syringe, push firmly the piston rod in order to break loose the syringe plunger.



2. Twist off the tip cap to break the frangible obturator.



3. Check that the sealing cap has been completely removed.

4. Purge the air of the syringe by pushing the piston slightly.

5. Connect the syringe to the intravenous access. Push the piston carefully to inject the required volume.

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

7. MARKETING AUTHORIZATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORIZATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

Date of first authorisation: <[To be completed nationally]>
Date of of latest renewal: <[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

15 February 2021