ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ephedrine hydrochloride.....3 mg

For 1 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 prefilled 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.

pH = 4.5 to 5.5

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of hypotension during general anaesthesia and locoregional anaesthesia, whether spinal or epidural, and whether for surgical or obstetric procedures.
- Preventive treatment of hypotension during spinal anaesthesia for surgical or obstetric procedures.

4.2. Dosage and method of administration

Dosage

Adults

The dose is from 3 to 6 mg, repeated as needed every 5 to 10 min.

The dose for 24 hours must be less than 150 mg.

A lack of efficacy should lead to reconsideration of the choice of the therapeutic agent.

Paediatric population

The administration route is intravenous.

The dose is from 0.1 to 0.2 mg/kg every 4 to 6 hours.

Method of administration

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

For intravenous use.

Intravenous infusion or IV bolus. The administration route varies depending on the patient's condition, weight and additional therapies.

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 MAOIs

4.4. Special warnings and precautions for use

Special warnings

Ephedrine should be used with caution in patients who may be particularly susceptible to theirs 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.

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 prefilled 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, including linezolid and methylene blue

Risk of vasoconstriction and/or episode of hypertension.

- 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.

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

There is no data on the excretion of ephedrine into human milk. However, based on the method of administration of this medicinal product, breast-feeding is permitted.

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

Not known: confusion, anxiety, depression.

- Nervous system disorders

Not known: nervousness, irritability, insomnia, tremors.

- Eye disorders

Not known: episodes of angle-closure glaucoma.

- Cardiac disorders

Not known: palpitations, hypertension, tachycardia, cardiac arrhythmia, anginal pain, reflex bradycardia, cardiac arrest.

- Vascular disorders

Not known: cerebral haemorrhage.

- Respiratory, thoracic and mediastinal disorders

Not known: dyspnoea, pulmonary oedema

- Renal and urinary disorders

Not known: urinary retention

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: Agence nationale de sécurité du médicament et des produits de santé [National Agency for the Safety of Medicines and Health Products] (ANSM) and the network of French Regional Pharmacovigilance Centres – Website:www.signalement-sante.gouv.fr.

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.

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

Check for any change in colour and/or formation of a precipitate, insoluble compound or crystals.

6.3. Shelf life

3 years.

After opening the blister: 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 in pre-filled syringe (polypropylene); box of 1, 5, 10, 12, 20, 50 and 100.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

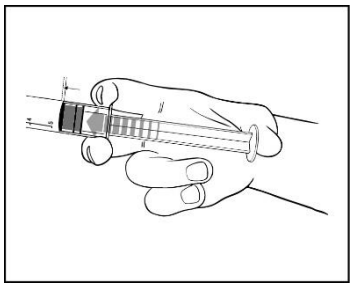
Be careful to strictly respect the instructions for use of the syringe.

The pre-filled syringe is for single patient only. After first use, the remaining product should be discarded.

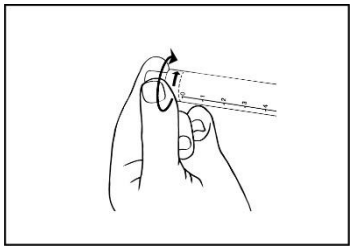
The content of un-opened and un-damaged blister is sterile, and must not be opened until use.

When handled using an aseptic method, EPHEDRINE AGUETTANT 3 mg/mL, solution for injection in pre-filled syringe can be placed on a sterile field.

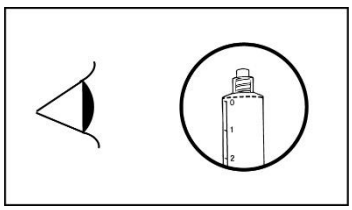
1) Withdraw the pre-filled syringe from the sterile blister.



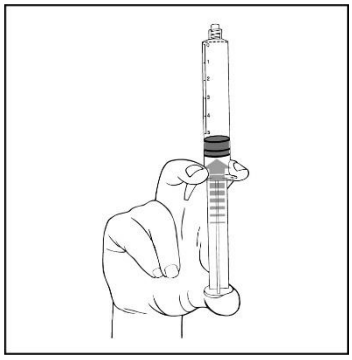
2) Push on the plunger to free the bung. The sterilisation process may have caused adhesion of the bung to the body of the syringe.



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. MARKETING AUTHORISATION HOLDER

Laboratoire AGUETTANT
1 rue Alexander Fleming
69007 LYON Cedex
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT