SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efedrin Unimedic 5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 5 mg ephedrine hydrochloride.

10 ml solution for injection contains 50 mg ephedrine hydrochloride.

Excipient(s) with known effect
This medicinal product contains sodium. One ml contains 3,20 mg equivalent to 0,139 mmol sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution of injection.
Clear colourless solution.
pH 4,0-6,5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypotension associated with spinal, epidural, or general anaesthesia.

4.2 Posology and method of administration

Ephedrine may only be used by or under the supervision of an anesthesiologist.

Posology
Adults:
Slow intravenous injection of 5 to 10 mg repeated as needed every 3-4 minutes. In the absence of effect after 30 mg the choice of drug shall be reconsidered.

Paediatric population
Adolescents 12-17 years of age:
Slow intravenous injection of 3-7.5 mg repeated as needed every 3-4 minutes (max. 9 mg per dose), adjusted according to response, maximum 30 mg per course.

Children 1-11 years of age:
Slow intravenous injection of 0,5 to 0,75 mg/kg or 17-25 mg/m^2 every 3-4 minutes adjusted according to response, maximum 30 mg per course.

Children under 1 year:
A safe and efficacious dose in children aged 0-1 years has not been established.

Special populations
Elderly, in the very elderly population ≥ 85 years of age, there may be an increased need for ephedrine to adjust hypotension following anaesthesia, due to a decrease in systematic vascular resistance. When administering ephedrine in patients with severe renal impairment it should be taken into consideration that the majority of ephedrine is excreted unchanged in urine, see section 4.4 and 5.2.

Method of administration
For intravenous use.

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:
- Hypertension
- Cardiovascular disease
- Diabetes Mellitus
- Hyperthyreosis
- Narrow angle glaucoma
- Prostate hypertrophy
- Severe renal impairment

Great care is required in patients with cardiovascular disease such as eg ischemic heart disease, arrhythmia or tachycardia, occlusive vascular diseases including arteriosclerosis, hypertension or aneurysms. Anginous pain can be expected in patients with angina pectoris.

Ephedrine should be used with caution in patients undergoing anaesthesia with cyclopropane, halothane or other halogenated anaesthetics since they may cause ventricular arrythmias.

An increased risk of vasoconstriction and/or acute hypertensive periods shall be taken under consideration when ephedrine is administered together with indirect sympathomimetic drugs (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate).

Ephedrine interacts with monoaminooxidase inhibitors (MAOI) and shall not be given to patients who receives this treatment or within 14 days after the treatment is terminated. It is adviseable to avoid ephedrine and other sympathomimetics when reversible MAOI´s are used (see section 4.5).

An increased risk for arrhythmias may occur if ephedrine is provided to patients receiving cardiac glycosides, quinidine or tricyclic antidepressants.

Ephedrine increases the blood pressure and particular caution should be exercised in patients receiving antihypertensive treatment. Interactions between ephedrine and alpha- and betablocking medicinal products can be complicated.

Negative metabolic effects of high ephedrine doses may be aggravated by concomitant high doses of corticosteroids. The patients shall be monitored thoroughly when the two drug treatments are used concomitantly, even if this precaution is not as applicable on inhaled corticosteroid treatment.

Hypokalemia in connection with high ephedrine doses may lead to increased sensitivity for digitalis induced cardiac arrhythmias. Hypokalemia may be aggravated by concomittant administration of aminophylline or other xanthines, corticosteroids or by diuretic treatment.

Precautions for use

This medicinal product contains 32 mg sodium per 10 ml injection vial, equivalent to 1,6% 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

Indirect sympatomimetic drugs (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate).
There is an increased risk of vasoconstriction and/or acute hypertension episodes if ephedrine is combined with indirect symathomimetics (see Section 4.4).

Volatile halogenic anaesthetics
There is a risk of serious ventricular arrythmias (increase in cardiac excitability) if ephedrine is combined with volatile halogenic anaesthetics (see Section 4.4).

Antidepressants, cardiac glycosides and quinidine
When ephedrine is administered together with tricyclic antidepressants (clomipramine, amitriptyline, nortriptyline) and SNRIs (venlafaxine, reboxetine, duloxetine) there is a risk for paroxysmal hypertension with possible arrhythmias (inhibition of adrenaline or noradrenaline entrance into sympatic fibres). Similarly, the risk of arrhythmias is present upon co-administration with cardiac glycosides and quinidine.

Guanetidine and related products
There is a risk of significant increase in bloodpressure (hyperreactivity connected with decreased sympathic tonus and/or inhibition of adrenaline or noradrenaline entrance in sympatic fibers).

Selective reversible MAO-A-inhibitors (moclobemid)
There is a risk for increased hypertensive effect and concomitant administration should be avoided. Treatment with ephedrine can be started earlier than 14 days following discontinuation of moclobemide, given the relatively short half-life of moclobemide (see Section 4.4).

Non-selective reversible MAO-A-inhibitors (linezolid)
Upon combination with the antibiotic linezolid (a weak and non-selective reversible MAO-inhibitor), there is a risk of increased hypertensive effect. Concomitant administration should be avoided.

Selective irreversible MAO-B inhibitors (rasagilin and safinamide)
There is a risk of increased hypertensive effect with the concomittant administration.

Levodopa and bromocriptine
There is a risk for additive cardiovascular toxicity with the concomittant administration.

Selegiline
Severe hypertension may occur and concomitant administration should be avoided.

COMT-inhibitor (entacapone, tolcapone)
Severe hypertension has been reported (likely due to inhibited metabolism of noradrenaline) and concomitant administration should be avoided. A similar interaction can be expected with tolcapone.

Theophylline
Concomittant administration of ephedrine and theophylline may result in insomnia, nervousness and gastrointestinal problems.

Clonidine
There is an enhanced blood pressure response to ephedrine in patients pre-treated with clonidine.

Corticosteroids

Ephedrine has shown to increase clearance of dexamethasone. The potential effect on the dexamethasone efficiency should be monitored and the dose adjusted when suitable.

Antihypertensive medicinal products
Ephedrine can counteract the effects of alphablockers and betablocking medicinal products.

Oxytocin
May cause hypertension by enhancing the pressor effect of sympathomimetic vasoconstrictor, such as ephedrine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data from use of ephedrine in pregnant women.
Ephedrine shall not be used during pregnancy unless the clinical condition of the mother requires treatment. Ephedrine passes the placenta and this has been connected with an increase in the fetal heart rate and heart frequency variability.
During a Cesarean section ephedrine can be used to prevent hypotension caused by spinal anaesthesia. Fetal acidosis has been observed with the use of ephedrine; however this was not translated into any harmful neonatal effects on the Apgar scores. Since parenteral administration of ephedrine can cause the fetal heart rate to accelerate it should not be used when the maternal blood pressure exceeds 130/80 mmHg.

Breastfeeding
Ephedrine is excreted in breast milk and breast-feeding shall therefore be discontinued for 2 days after administration. Irritability and disrupted sleeping pattern have been reported in breast-feeding infants.

Fertility
Animal studies on the effect on fertility are incomplete (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The adverse reactions are classified according to frequency of occurrence as follows:

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).

Tabulated list of adverse reactions known to be associated with ephedrine:

System Organ Class	**Adverse reactions**	**Frequency**
Immune system disorders	hypersensitivity	*Not known*
Psychiatric disorders	confusion, anxiety, depression	*Common*
	psychotic states, fear	*Not known*
Nervous system disorders	nervousness, irritability, restlessness, weakness, insomnia, headache, sweating	*Common*
	tremor, hypersalivation	*Not known*
Eye disorders	episodes of narrow angle glaucoma	*Not known*
Cardiac disorders	palpitation, hypertension, tachycardia	*Common*
	cardiac arrhythmias	*Rare*

	angina pain, reflex bradycardia, cardiac arrest, hypotension	*Not known*
Vascular disorders	cerebral haemorrhage	*Not known*
Respiratory, thoracic and mediastinal disorders	dyspnoea	*Common*
	pulmonary oedema	*Not known*
Gastrointestinal disorders	nausea, vomiting	*Common*
	reduced appetite	*Not known*
Renal and urinary disorders	acute urinary retention	*Rare*
Investigations	hypokalemia, altered blood glucose levels	*Not known*

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

Symtoms of overdose may include nausea, vomiting, fever, paranoid psychosis, cardiac arrhythmias such as ventricular and supraventricular tachycardia, hypertension, respiratory depression, convulsions and coma.
The lethal dose in human is approximately 2 g equivalent to blood concentration of approximately 3,5 to 20 mg/l.

Treatment
Treatment of ephedrine overdose may require intensive supportive treatment. Slow intravenous injection of labetalol 50-200 mg may be given under ECG surveillance to treat supraventricular tachycardia. Severe hypokalaemia (<2,8 mmol/l) due to compartmental switch of potassium predisposes to cardiac arrythmias and may be corrected by infusion of potassium chloride in addition to propranolol. Potassium chloride may also be used to correct respiratory alkalosis, when this is present.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic drugs, ATC code: C01C A26

Mechanism of action
Ephedrine is a sympathomimetic amine with a direct effect on alpha- and beta receptors and an indirect effect by increasing the release of norepinephrine in the sympathetic nerve endings. Like all sympathomimetic agents ephedrine stimulates the central nevous system, the cardiovascular system, the respiratory system and the sfincters of the gastrointestinal and urinary systems.

5.2 Pharmacokinetic properties

Biotransformation and Elimination
A small amount of ephedrine is metabolised to norephedrine, but the majority of ephedrine is excreted unchanged in urine. The plasma half-life of ephedrine is 3-6 hours depending on the pH of the urine. In rare instances, longer half-lives of up to 9 hours have been reported. Elimination of ephedrine increases (and half-life is consequently lowered) with a decreasing pH in urine.

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 citrate
Anhydrous citric acid
Sodium chloride
Hydrochloric acid (pH adjustment)
Sodium hydroxide (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

2 years

After opening the product should be used immediately.

6.4 Special precautions for storage

No special precautions.

6.5 Nature and contents of container

10x10 ml one-point cut ampoules of clear Type I glass, in a cardboard box.

6.6 Special precautions for disposal and other handling

The ampoules are intended for single use only. To open, break the ampoule at the narrow section below the white dot.

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

7. MARKETING AUTHORISATION HOLDER

Unimedic Pharma AB
Box 6216
102 34 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2018-03-22

Detailed information on this medicinal product is available on the website of {name of MS Agency (link)}