Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ephedrine Kabi 30 mg/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution for injection contains 30 mg ephedrine hydrochloride.
Each 1 ml glass ampoule contains 30 mg ephedrine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to pale yellow solution for injection
pH 30 mg/ml: 5.4-7.0
Osmolality: 270 – 330 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypotension from spinal, epidural and general anaesthesia in adults and children (over 12 years).

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 total dose administered over 24 hours must not exceed 150 mg.

Paediatric population
Ephedrine Kabi 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.

Elderly
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.
The medicinal product should be diluted before use as applicable (see section 6.6).
For intravenous use.

4.3 Contraindications

Ephedrine Kabi 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 (see section 4.5).
- In combination with alpha sympathomimetic agents (see section 4.5).
- In combination with non-selective MAO inhibitors or within 14 days of their withdrawal (see section 4.5).

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 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 (see section 4.5).

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 reversible MAOIs (see section 4.5).

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 (see section 4.5).

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 two 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 (see section 4.5).

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.

Excipients:

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations:

Indirect sympathomimetic agents (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate)
Risk of vasoconstriction and /or acute episodes of hypertension (see section 4.3)

Alpha sympathomimetics (oral and/or nasal route of administration)
Risk of vasoconstriction and/or episodes of hypertension (see section 4.3).

Non-selective MAO inhibitors
Paroxysmal hypertension, hyperthermia possibly fatal (see section 4.3).

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-serotoninergic antidepressants (milnacipran, 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.

Breastfeeding
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: ≥1/10; **Common:** ≥1/100 to <1/10 ; **Uncommon:** ≥1/1,000 to <1/100 ; **Rare:** ≥1/10,000 to <1/1,000; Very rare: <1/10,000; **Not known:** cannot be estimated from the available data

System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders					primary haemostasis modifications
Imune system disorders					hypersensitivity
Psychiatric disorders		confusion, anxiety, depression			psychotic states, fear
Nervous system disorders		nervousness, irritability, restlessness, weakness, insomnia, headache, sweating			tremor, hypersalivation
Eye disorders					episodes of angle-closure glaucoma
Cardiac disorders		palpitations, hypertension, tachycardia		cardiac arrhythmias	anginal pain, reflex bradycardia, cardiac arrest, hypotension
Vascular disorders					cerebral haemorrhage
Respiratory, thoracic and mediastinal disorders		dyspnoea			pulmonary oedema

Gastrointestinal disorders		nausea, vomiting			reduced appetite
Renal and urinary disorders:				acute urinary retention	
Investigations					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 HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

In the event of overdose, the occurrence of nausea, vomiting, fever, paranoid psychosis, ventricularand 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.

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 (<2.8mmol/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.

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

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

Biotransformation and elimination
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 Hydroxide (for pH adjustment)
Hydrochloric Acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

30 months

Shelf life after opening the ampoule:
The product must be used immediately.

Shelf-life for non-diluted solution when stored in syringe:
Chemical and physical in-use stability has been demonstrated for 72 hours at 25 °C and for 72 hours at 2 to 8 °C.

Shelf life after dilution for 10mg/ml and 30 mg/ml:
Chemical and physical in-use stability has been demonstrated for 72 hours at 25 °C and for 72 hours at 2 to 8 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 ml type I clear glass ampoules
Pack of 5, 10 and 50 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

The solution is to be visually inspected prior to use. The solution should not be used if it contains any visible particles.

Dilute the solution for injection to final concentration of 3mg/ml or 5 mg/ml as appropriate (see section 4.2).

Ephedrine Kabi is compatible with:

- sodium chloride 9 mg/ml (0.9% w/v)
- glucose 50 mg/ml (5% w/v) infusion
- Ringer Lactate infusion

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

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

PA2059/086/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 2nd August 2024

10 DATE OF REVISION OF THE TEXT