

**1.4.1. PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)**

**1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT**

EPHEVER ((Ephedrine Hydrochloride Injection BP 50mg/ml, 1ml)

**2. Qualitative and Quantitative composition**

**2.1 Qualitative composition**

Each ml contains

Ephedrine Hydrochloride BP

Water for Injection BP

**2.2 Quantitative composition**

Each ml contains

Ephedrine Hydrochloride BP      50mg

Water for Injection BP              q.s

**2.3 Salts and hydrates**

Ephedrine is equivalent to 50mg of Ephedrine Hydrochloride.

**2.4 Esters and pro-drugs**

Not Applicable

**2.5 Oral powders for solution or suspension**

Not Applicable

**2.6 Parenterals excluding powders for reconstitution**

Each ml contains

Ephedrine BP 50mg

**2.7 Powders for reconstitution prior to parenteral administration**

Not Applicable

**2.8 Concentrates**

Not Applicable

**2.9 Transdermal patches**

Not Applicable

**2.10 Multi dose solid or semi-solid products**

Not Applicable

**2.11 Biological medicinal products**

**2.11.1 Expression of strength**

Not Applicable

**2.11.2 The biological origin of the active substance**

Not Applicable

**2.11.3 Special provisions for normal immunoglobulins**

Not Applicable

**2.11.4 Herbal pharmaceutical products**

Not Applicable

**3. Pharmaceutical form**

Solution for Injection

Clear, colourless to slightly pale yellowish, solution.

PH = 4.5 – 7.

**4. Clinical particulars**

**4.1 Therapeutic indications**

Reversal of hypotension from spinal or epidural anaesthesia.

**4.2 Posology and method of administration**

Posology

*Adults and the elderly*

Up to 30 mg in increments of 3 - 7.5 mg.

After the development of hypotension, by slow intravenous injection.

*Paediatric population*

Ephedrine Hydrochloride 30 mg/ml Solution for Injection 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.

#### **4.3 Method of administration**

Intravenous use.

For instructions on dilution of the medicinal product before administration, see section 6.6.

#### **4.4 Contraindications**

Ephedrine Hydrochloride 50 mg/ml Solution for Injection 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 Monoamine Oxidase Inhibitors (MAOI) or within 14 days of their withdrawal.

#### **4.5 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. Angina 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 arrhythmias 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 betaadrenoceptor 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 arrhythmias. 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 administration.

#### **4.6 Paediatric population**

Ephedrine Hydrochloride 30 mg/ml Solution for Injection is generally not recommended for use in children due to insufficient data on efficacy, safety and dosage recommendations.

#### **4.7 Interaction 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 arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

*Noradrenergic-serotonergic antidepressants (minalcipran, venlafaxine)*

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

*Guanethidine and related products*

Substantial increase in blood pressure (hyper reactivity 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.

**4.8 Additional information on special populations**

**4.9 Paediatric population**

Ephedrine Hydrochloride 30 mg/ml Solution for Injection is generally not recommended for use in children due to insufficient data on efficacy, safety and dosage recommendations.

**4.10 Fertility, pregnancy and lactation**

**4.10.1 General principles**

**4.10.2 Women of childbearing potential / Contraception in males and females**

**4.10.3 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 fetal heart rate and beat-to-beat variability.

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

#### **4.10.4 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.

#### **4.10.5 Fertility**

No data available.

#### **4.11 Effects on ability to drive and use machines**

Not relevant.

#### **4.12 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 hemostasis 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 arrhythmias

Not known: angina 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

#### **4.13 Overdose**

Symptoms

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 50-200 mg may be given with electrocardiograph monitoring for the treatment of supraventricular tachycardia. Marked hypokalaemia (<2.8 mmol/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 agents, 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.

### **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 SmPC.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Sodium Metabisulphite

Di sodium E.D.T.A

Sodium Chloride

Tri sodium Citrate Dihydrate

Citric Acid (Anhydrous)

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**

*Unopened:* 24 months

*Diluted solution:*

Chemical and physical in-use stability has been demonstrated for 72 hours at 25°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 temperature storage conditions.

Keep the container in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

## **6.5 Nature and contents of container**

### **1ml**

10 x 1 ml amber USP Type-1 glass ampoules loaded on a plastic tray.

10 x 1 ml tray loaded clear USP Type-1 glass ampoules in an inner printed carton.

10 x 10 x 1 ml clear USP Type-1 glass ampoules in an outer printed carton.

**6.6 Special precautions for disposal and other handling**

For single use only.

Ephedrine hydrochloride is compatible with sodium chloride 9 mg/ml (0.9%), Ringer's lactate solution and glucose 50 mg/ml (5%).

The drug product should be examined visually and should not be used if particulate matter or discolouration are present.

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

**7. MARKETING AUTHORISATION HOLDER**

Verve Human Care Laboratories

15-A, Pharmacy,

Selaqui, Dehradun-248011

India

**8. MARKETING AUTHORISATION NUMBER**

Not Applicable

**9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION**

Not Applicable

**10. DATE OF REVISION OF THE TEXT**

**11. DOSIMETRY (IF APPLICABLE)**

Not Applicable

**12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

Not Applicable