PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Synephrine Injection (Phenylephrine Hydrochloride Injection USP 10mg/ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Phenylephrine HCl 10mg/ml

Excipients: Refer to Section 7.1

3. PHARMACEUTICAL FORM

Intramuscular/Intravenous Infusion Solution. Clear, colorless solution free from foreign particles. For intravenously, must be diluted before administration to achieve the desired concentration.

After Dilution: Clear and colorless solution. Do not use if the solution is colored or cloudy, or if it contains particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Synephrine (Phenylephrine Hydrochloride) Injection 10mg/ml, is an alpha-1 adrenergic receptor agonist indicated for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.

Posology

General Dosage and Administrative instructions

Synephrine (Phenylephrine Hydrochloride) Injection 10mg/ml must be diluted before administration as an intravenous bolus or continuous intravenous infusion to achieve the desired concentration:

• Bolus: Dilute with normal saline or 5% dextrose in water.
• Continuous infusion: Dilute with normal saline or 5% dextrose in water.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the solution is colored or cloudy, or if it contains particulate matter. The diluted solution should not be held for more than 4 hours at room temperature or for more than 24 hours under refrigerated conditions. Discard any unused portion.

During Synephrine administration:

• Correct intravascular volume depletion.
• Correct acidosis. Acidosis may reduce the effectiveness of phenylephrine.

Dosing for Treatment of Hypotension during Anesthesia

The following are the recommended dosages for the treatment of hypotension during anesthesia.

- The recommended initial dose is 40 to 100 mcg administered by intravenous bolus.
- May administer additional boluses every 1-2 minutes as needed; not to exceed a total dosage of 200 mcg.
- If blood pressure is below the target goal, start a continuous intravenous infusion with an infusion rate of 10 to 35 mcg/minute; not to exceed 200 mcg/minute.
- Adjust dosage according to the blood pressure goal

Prepare a 100mcg/ml Solution for Bolus Intravenous Administration

For bolus intravenous administration, prepare a solution containing a final concentration of 100 mcg/mL of Synephrine:

- Withdraw 10 mg (1 mL of 10 mg/mL) of Phenylephrine Hydrochloride Injection USP, 10 mg/mL and dilute with 99 mL of 5% Dextrose Injection, USP or 0.9%Sodium Chloride Injection, USP.
- Withdraw an appropriate dose from the 100 mcg/mL solution prior to bolus intravenous administration.

Prepare a Solution for Continuous Intravenous Administration

For continuous intravenous infusion, prepare a solution containing a final concentration of 20 mcg/mL of 100 mcg/mL of Synephrine in 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP:

- Withdraw 10 mg (1 mL of 10 mg/mL) of Phenylephrine Hydrochloride Injection USP, 10 mg/mL and dilute with 500 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP.

4.3 Contraindications

None

4.4 Special warnings and precautions for use

Exacerbation of Angina, Heart Failure, or Pulmonary Arterial Hypertension

Because of its increasing blood pressure effects, SYNEPHRINE can precipitate angina in patients with severe arteriosclerosis or history of angina, exacerbate underlying heart failure, and increase pulmonary arterial pressure.

Peripheral and Visceral Ischemia

Synephrine can cause excessive peripheral and visceral vasoconstriction and ischemia to vital organs, particularly in patients with extensive peripheral vascular disease.

Skin and Subcutaneous Necrosis

Extravasation of Synephrine can cause necrosis or sloughing of tissue. The infusion site should be checked for free flow. Care should be taken to avoid extravasation of SYNEPHRINE.

Bradycardia

Synephrine can cause severe bradycardia and decreased cardiac output. Allergic

Reactions

Synephrine contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Renal Toxicity

Synephrine can increase the need for renal replacement therapy in patients with septic shock. Monitor renal function.

Risk of Augmented Pressor Affect in Patients with Autonomic Dysfunction

The increasing blood pressure response to adrenergic drugs, including Synephrine, can be increased in patients with autonomic dysfunction, as may occur with spinal cord injuries.

Pressor Effect with Concomitant Oxytocic Drugs

Oxytocic drugs potentiate the increasing blood pressure effect of sympathomimetic pressor amines including Synephrine, with the potential for hemorrhagic stroke.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions that Augment Pressor Effect

The increasing blood pressure effect of SYNEPHRINE is increased in patients receiving:

- Monoamine oxidase inhibitors (MAOI)
- Oxytocin and oxytocic drugs

- Tricyclic antidepressants
- Angiotensin, aldosterone
- Atropine
- Steroids, such as hydrocortisone
- Norepinephrine transporter inhibitors, such as atomoxetine
- Ergot alkaloids, such as methylergonovine maleate

Interactions that Antagonize the Pressor Effect

The increasing blood pressure effect of SYNEPHRINE is decreased in patients receiving:

- α-adrenergic antagonists
- Phosphodiesterase Type 5 inhibitors
- Mixed α- and β-receptor antagonists
- Calcium channel blockers, such as nifedipine
- Benzodiazepines
- ACE inhibitors
- Centrally acting sympatholytic agents, such as reserpine, guanfacine.

4.6 Fertility, pregnancy and lactation

Risk Summary
Data from randomized controlled trials and meta-analyses with phenylephrine hydrochloride injection use in pregnant women during Cesarean section have not established a drug-associated risk of major birth defects and miscarriage. These studies have not identified an adverse effect on maternal outcomes or infant Apgar scores [see Data]. There are no data on the use of phenylephrine during the first or second trimester. In animal reproduction and development studies in normotensive animals, evidence of fetal malformations was noted when phenylephrine was administered during organogenesis via a 1-hour infusion at 1.2 times the human daily dose (HDD) of 10 mg/60 kg/day. Decreased pup weights were noted in offspring of pregnant rats treated with 2.9 times the HDD [See Data]. The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 4% and 15-20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryofetal Risk
Untreated hypotension associated with spinal anesthesia for Cesarean section is associated with an increase in maternal nausea and vomiting. A sustained decrease in uterine blood flow due to maternal hypotension may result in fetal bradycardia and acidosis.

Data
Human Data
Published randomized controlled trials over several decades, which compared the use of phenylephrine injection to other similar agents in pregnant women during Cesarean section, have not identified adverse maternal or infant outcomes. At recommended doses, phenylephrine does not appear to affect fetal heart rate or fetal heart rate variability to a significant degree. There are no studies on the safety of phenylephrine injection exposure during the period of organogenesis, and therefore, it is not possible to draw any conclusions on the risk of birth defects following exposure to phenylephrine injection during pregnancy. In addition, there are no data on the risk of miscarriage following fetal exposure to phenylephrine injection.

Animal Data
No clear malformations or fetal toxicity were reported when normotensive pregnant rabbits were treated with phenylephrine via continuous intravenous infusion over 1 hour (0.5 mg/kg/day; approximately equivalent to a HDD based on body surface area) from Gestation Day 7 to 19. At this dose, which demonstrated no maternal toxicity, there was evidence of developmental delay (altered ossification of sternebra). In a non-GLP dose range-finding study in normotensive pregnant rabbits, fetal lethality and cranial, paw, and limb malformations were noted following treatment with 1.2 mg/kg/day of phenylephrine via continuous intravenous infusion over 1 hour (2.3-times the HDD). This dose was clearly maternally

toxic (increased mortality and significant body weight loss). An increase in the incidence of limb malformation (hyperextension of the forepaw) coincident with high fetal mortality was noted in a single litter at 0.6 mg/kg/day (1.2-times the HDD) in the absence of maternal toxicity. No malformations or embryo-fetal toxicity were reported when normotensive pregnant rats were treated with up to 3 mg/kg/day phenylephrine via continuous intravenous infusion over 1 hour.

(2.9-times the HDD) from Gestation Day 6 to 17. This dose was associated with some maternal toxicity (decreased food consumption and body weights). Decreased pup weights were reported in a pre- and postnatal development toxicity study in which normotensive pregnant rats were administered phenylephrine via continuous intravenous infusion over 1 hour (0.3, 1.0, or 3.0 mg/kg/day; 0.29, 1, or 2.9 times the HDD) from Gestation Day 6 through Lactation Day 21). No adverse effects on growth and development (learning and memory, sexual development, and fertility) were noted in the offspring of pregnant rats at any dose tested. Maternal toxicities (mortality late in gestation and during lactation period, decreased food consumption and body weight) occurred at 1 and 3 mg/kg/day of phenylephrine (equivalent to and 2.9 times the HDD, respectively).

Lactation
Risk Summary
There are no data on the presence of phenylephrine hydrochloride injection or its metabolite in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Synephrine injection and any potential adverse effects on the breastfed infant from Synephrine injection or from the underlying maternal condition.

4.7 Special populations

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of phenylephrine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

Hepatic Impairment

In patients with liver cirrhosis [Child Pugh Class B and Class C], dose-response data indicate decreased responsiveness to phenylephrine. Start dosing in the recommended dose range, but more phenylephrine may be needed in this population.

Renal Impairment

In patients with end stage renal disease (ESRD), dose-response data indicate increased responsiveness to phenylephrine. Consider starting at the lower end of the recommended dose range, and adjusting dose based on the target blood pressure goal.

4.8 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.9 Undesirable effects

Adverse reactions are primarily attributable to excessive pharmacologic activity. Adverse reactions reported in published clinical studies, observational trials, and case reports of Synephrine are listed below by body system. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

- Cardiac disorders: Reflex bradycardia, lowered cardiac output, ischemia, hypertension, arrhythmias
- Gastrointestinal disorders: Epigastric pain, vomiting, nausea
- Nervous system disorders: Headache, blurred vision, neck pain, tremors
- Vascular disorders: Hypertensive crisis
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea
- Skin and subcutaneous tissue disorders: Pruritis.

4.10 Overdose

Overdose of Synephrine can cause a rapid rise in blood pressure. Symptoms of overdose include headache, vomiting, hypertension, reflex bradycardia, a sensation of fullness in the head, tingling of the extremities, and cardiac arrhythmias including ventricular extrasystoles and ventricular tachycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action: Phenylephrine hydrochloride is an α-1 adrenergic receptor agonist. Interaction of phenylephrine with α1-adrenergic receptors on vascular smooth muscle cells causes activation of the cells and results in vasoconstriction. Following phenylephrine hydrochloride intravenous administration, increases in systolic and diastolic blood pressures, mean arterial blood pressure, and total peripheral vascular resistance are observed. The onset of blood pressure increase following an intravenous bolus phenylephrine hydrochloride administration is rapid, typically within minutes. As blood pressure increases following intravenous administration, vagal activity also increases, resulting in reflex bradycardia. Phenylephrine has activity on most vascular beds, including renal, pulmonary, and splanchnic arteries.

5.2 Pharmacokinetic properties

Following an intravenous infusion of phenylephrine hydrochloride, the observed effective half- life was approximately 5 minutes. The steady-state volume of distribution of approximately 340L suggests a high distribution into organs and peripheral tissues. The average total serum clearance is approximately 2100 mL/min. The observed phenylephrine plasma terminal elimination half- life was 2.5 hours.

Phenylephrine is metabolized primarily by monoamine oxidase and sulfotransferase. After intravenous administration of radiolabeled phenylephrine, approximately 80% of the total dose was eliminated within first 12 h; and approximately 86% of the total dose was recovered in the urine within 48 h. The excreted unchanged parent drug was 16% of the total dose in the urine at 48 h post intravenous administration. There are two major metabolites, with approximately 57 and 8% of the total dose excreted as m-hydroxymandelic acid and sulfate conjugates, respectively. The metabolites are considered not pharmacologically active.

6. PRE-CLINICAL SAFETY DATA

6.1 Non-clinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies that evaluated the carcinogenic potential of orally administered phenylephrine hydrochloride in F344/N rats and B6C3F1 mice were completed by the National Toxicology Program using the dietary route of administration. There was no evidence of carcinogenicity in mice administered approximately 270 mg/kg/day (131 times the human daily dose (HDD) of 10 mg/60 kg/day based on body surface area) or rats administered approximately 50 mg/kg/day (48 times HDD) based on body surface area comparisons.

Mutagenesis

Phenylephrine hydrochloride tested negative in the in vitro bacterial reverse mutation assay (S. typhimurium strains TA98, TA100, TA1535 and TA1537), the in vitro chromosomal aberrations assay, the in vitro sister chromatid exchange assay, and the in vivo rat micronucleus assay. Positive results were reported in only one of two replicates of the in vitro mouse lymphoma assay.

Impairment of Fertility

Phenylephrine did not impair mating, fertility, or reproductive outcome in normotensive male rats treated with 3 mg/kg/day phenylephrine via continuous intravenous infusion over 1 hour (2.9 times the HDD) for 28 days prior to mating and for a minimum of 63 days prior to sacrifice and female rats treated with the same dosing regimen for 14 days prior to mating and through Gestation Day 6. This dose was associated with increased mortality in both male and female rats and decreased body weight gain in treated males. There were decreased caudal sperm density and increased abnormal sperm reported in males treated with 3 mg/kg/day phenylephrine (2.9 times the HDD).

7. PHARMACEUTICAL PARTICULARS

7.1 List of excipients

List of Excipients

- Citric Acid
- Sodium Citrate
- Sodium Chloride
- Sodium Metabisulphite
- Water for Injection

7.2 Incompatibilities

Synephrine Injection has been stated to be incompatible with alkalis, ferric salts, phenytoin sodium and oxidising agents.

7.3 Shelf life

For unopened vial:
Do not store above 30°C. Protect from light. Store in carton until time of use. The 1 mL vials are for single use only.

After Dilution:
The diluted solution should not be held for more than 4 hours at room temperature or for more than 24 hours under refrigerated conditions (2-8°C). Discard any unused portion.

7.4 Special precautions for storage

- Do not store & transport above 30ºC.
- Protect from light.

7.5 Nature and contents of container

1ml x 5's ampoules of Synephrine Injection containing 10mg/ml of Phenylephrine hydrochloride are supplied in a box.

7.6 Special precautions for disposal and other handling

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the solution is colored or cloudy, or if it contains particulate matter. Discard unused portion. Keep out of the reach of children. Use as directed by the physician.

8 PRODUCT REGISTRATION HOLDER & IMPORTED BY :

Zulat Pharmacy Sdn Bhd
No 23 & 23A, Jln Bandar 3,
Tmn Melawati, 53100 Kuala Lumpur.

9 MANUFACTURER

ATCO Laboratories Limited
B-18, S.I.T.E., Karachi-75700, Pakistan

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