

**INDOCO REMEDIES LTD. Packaging Development Department**

Item:	Leaflet (Booklet)
Item Code:	P2PZ00008
Open Size:	200 x 350 mm
Folding Size:	W:Unfolded: 200 mm    Folded: 25 mm H:Unfolded:350 mm    Folded: 58 mm
GSM/ Paper:	41 gsm Bible Paper
Colour:	Black
Pharmacode:	1274 std.

**Reason for Preparation/ Revision:**  
1) New Development




Prepared by	Checked by	Approved by

Path .....

**R1**

Date: 29.10.2021

**PRINTED PACKAGING MATERIAL MASTER**

Product Code: P2PZ00008	Product Description: Phenylephrine HCl Injection USP LEAFLET
Dimensions/Dieline#: unfolded : 200 x 350 mm folded: 25 x 58 mm	Pantone Colour s 1 COLOUR
MFG/Vendor: INDOCO	 BLACK  LINEWORK
 Helvetica Neue Minimum front size: 8 pt	

**Signature means verified and approved as compliant with local regulatory and distribution requirements**

PAGE 1 OF 2

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## PRINTED PACKAGING MATERIAL MASTER

Product Code: P2PZ00008	Product Description: Phenylephrine HCl Injection USP LEAFLET
Dimensions/Dieline#: unfolded : 200 x 350 mm folded: 25 x 58 mm	Pantone Colour s 1 COLOUR
MFG/Vendor: INDOCO	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  BLACK         </div> <div style="text-align: center;">  LINE WORK         </div> </div>
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Signature means verified and approved as compliant with local regulatory and distribution requirements

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- Benzodiazepines
- ACE inhibitors
- Centrally acting sympatholytic agents, such as reserpine guanfacine.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### 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 24% 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 sternalbra).

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).

#### 8.2 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 phenylephrine hydrochloride injection and any potential adverse effects on the breastfed infant from phenylephrine hydrochloride injection or from the underlying maternal condition.

#### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### 8.5 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.

#### 8.6 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 consider that you may need to give more phenylephrine in this population.

#### 8.7 Renal Impairment

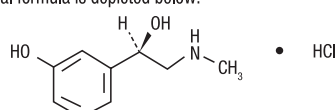
In patients with end stage renal disease (ESRD), dose-response data indicate increased responsiveness to phenylephrine. Consider starting at the lower end of the recommended dose range, and adjusting dose based on the target blood pressure goal.

### 10 OVERDOSAGE

Overdose of Phenylephrine hydrochloride injection 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.

### 11 DESCRIPTION

Phenylephrine is an alpha-1 adrenergic receptor agonist. Phenylephrine hydrochloride injection, 10 mg/mL is a clear, colorless, sterile, nonpyrogenic solution for intravenous use. It must be diluted before administration as an intravenous bolus or continuous intravenous infusion. The chemical name of phenylephrine hydrochloride is (-)-m-hydroxy- $\alpha$ -([methylamino)methyl]benzyl alcohol hydrochloride and is chemically designated as C<sub>9</sub>H<sub>11</sub>ClNO<sub>2</sub> with a molecular weight of 203.66 g/mol. Its structural formula is depicted below:



Phenylephrine hydrochloride is soluble in water and ethanol, and insoluble in chloroform and ethyl ether. Phenylephrine hydrochloride Injection, 10 mg/mL is sensitive to light. Each mL contains: phenylephrine hydrochloride 10 mg, sodium chloride 3.5 mg, sodium citrate dihydrate 4 mg, citric acid monohydrate 1 mg, and sodium metabisulfite 2 mg in water for injection. The pH is adjusted with sodium hydroxide and/or hydrochloric acid if necessary. The pH range is 3.5-5.5.

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Phenylephrine hydrochloride is a  $\alpha$ -1 adrenergic receptor agonist.

#### 12.2 Pharmacodynamics

Interaction of phenylephrine with  $\alpha$ -1-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.

#### 12.3 Pharmacokinetics

Following an intravenous infusion of phenylephrine hydrochloride, the observed effective half-life was approximately 5 minutes. The steady-state volume of distribution of approximately 340 L 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.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 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).

### 14 CLINICAL STUDIES

The evidence for the efficacy of Phenylephrine hydrochloride injection is derived from studies of phenylephrine hydrochloride in the published literature. The literature support includes 16 studies evaluating the use of intravenous phenylephrine to treat hypotension during anesthesia. The 16 studies include 9 studies where phenylephrine was used in low-risk (ASA 1 and 2) pregnant women undergoing neuraxial anesthesia during Cesarean delivery, 6 studies in non-obstetric surgery under general anesthesia, and 1 study in non-obstetric surgery under combined general and neuraxial anesthesia. Phenylephrine has been shown to raise systolic and mean blood pressure when administered either as a bolus dose or by continuous infusion following the development of hypotension during anesthesia.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Phenylephrine hydrochloride Injection, 10 mg/mL is supplied as clear and colorless sterile solution for injection, as follows:

NDC No.	Strength	How Supplied
81284-211-25	10 mg/mL	1 mL vial; for single use (supplied in packages of 25)
81284-212-01	10 mg/mL	5 mL vial; Pharmacy Bulk Package
81284-212-10	10 mg/mL	Outer carton for 5mL carton (supplied in packages of 10)
81284-213-01	10 mg/mL	10 mL vial; Pharmacy Bulk Package (supplied as a single unit)

Vial stopper is not made with natural rubber latex. Store Phenylephrine Hydrochloride Injection, 10 mg/mL at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light. Store in carton until time of use. The 1 mL vials are for single use only; the 5 and 10 mL vials are pharmacy bulk packages. 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.

### 17 PATIENT COUNSELING INFORMATION

If applicable, inform patients, family member, or caregiver that certain medical conditions and medications might influence how Phenylephrine hydrochloride Injection works.

Distributed by:  
 Provepharm, Inc.  
 100 Springhouse Drive  
 Suite 105  
 Collegeville, PA 19426  
 Made in India

**Provepharm**<sup>\*</sup>  
 Life Solutions

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