INDICATIONS AND USAGE

Biorphen is indicated for patients with clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia. New Biorphen can be conveniently administered without compounding, unlike concentrated phenylephrine that must be diluted before use. Adjust dosage according to the blood pressure goal. Please see Important Safety Information below.

BENEFITS OF BIORPHEN

- No compounding
- 3-year shelf life
- Standardized across hospitals
- Administered by any trained staff without compounding
- Sulfite and preservative free

STANDARDIZED ACROSS YOUR HOSPITAL

With a 3-year shelf life and $10 list price, Biorphen can be standardized throughout your hospital without frequent restocking.

Operating Room (OR)  Intensive Care Unit (ICU)  Emergency Department (ED)  Ambulatory Surgery Center (ASC)  Crash Carts

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Biorphen® can precipitate angina in patients with severe arteriosclerosis or history of angina, exacerbate underlying heart failure, and increase pulmonary arterial pressure. Can also cause excessive peripheral and visceral vasoconstriction and ischemia to vital organs. Extravasation during intravenous administration may cause necrosis or sloughing of tissue. Can cause severe bradycardia and decreased cardiac output, renal toxicity, augmented pressor effect in patients with autonomic dysfunction, and pressor effect with concomitant oxytocic drugs.

Please see additional Important Information on reverse and accompanying full Prescribing Information.

For more information, please visit www.biorphen.com
ADVERSE REACTIONS

SUSPECTED ADVERSE REACTIONS, contact Eton Pharmaceuticals, Inc. at 1-888-450-0568 or FDA at 1-800-FDA-1088.

DRUG INTERACTIONS

- MAOI, oxytocin and oxytocic drugs, tricyclic antidepressants, angiotensin and aldosterone, atropine, steroids, norepinephrine transporter inhibitors, ergot alkaloids.
- α-adrenergic antagonists, phosphodiesterase Type 5 inhibitors, mixed α- and β-receptor antagonists, calcium channel blockers, benzodiazepines and ACE inhibitors, centrally acting sympatholytic agents.

WARNINGS AND PRECAUTIONS

Overdose of Biorphen (phenylephrine hydrochloride) 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.

For more information, please see Biorphen Full Prescribing Information.

REFERENCES


ORDERING INFORMATION

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IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS

Most common adverse reactions during treatment: nausea, vomiting, and headache. To report SUSPECTED ADVERSE REACTIONS, contact Eton Pharmaceuticals, Inc. at 1-888-450-0568 or FDA at 1-800-FDA-1088.

DRUG INTERACTIONS

- Agonistic Effects (increase in Biorphen blood pressure effect) can occur with monoamine oxidase inhibitors (MAOI), oxytocin and oxytocic drugs, tricyclic antidepressants, angiotensin and aldosterone, atropine, steroids, norepinephrine transporter inhibitors, ergot alkaloids.
- Antagonistic Effects (decrease in Biorphen blood pressure effect) can occur with α-adrenergic antagonists, phosphodiesterase Type 5 inhibitors, mixed α- and β-receptor antagonists, calcium channel blockers, benzodiazepines and ACE inhibitors, centrally acting sympatholytic agents.

WARNINGS AND PRECAUTIONS

For more information, please see Biorphen Full Prescribing Information.

REFERENCES

BIORPHEN (phenylephrine hydrochloride) injection, for intravenous use

Initial U.S. Approval: 1954

INDICATIONS AND USAGE

BIORPHEN injection is injected intravenously as a bolus.

DOSEAGE AND ADMINISTRATION

BIORPHEN is injected intravenously as a bolus.

• DO NOT DILUTE before administration.

• BIORPHEN is supplied as a READY-TO-USE formulation.

• Bolus intravenous injection: 40 mcg to 100 mcg every 1-2 minutes as needed, to not exceed a total dosage of 200 mcg.

• Adjust the dose according to the pressor response (i.e., titrate to effect).

1. INDICATIONS AND USAGE

BIORPHEN is indicated for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.

2. DOSAGE AND ADMINISTRATION

BIORPHEN injection in the alpha-1 adrenergic receptor agonist indicated for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia. (1)

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BIORPHEN injection in the alpha-1 adrenergic receptor agonist indicated for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia. (1)
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) coincided 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 rabbits 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 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).

8.3 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 based on age-related changes in renal function and body weight.

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 more phenylephrine may be needed 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.

9.2 Overdose
Overtreatment with BIOPHREN (phenylephrine hydrochloride) can cause a rapid rise in blood pressure. Symptoms of overdose include headache, vertigo, 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. BIOPHREN (phenylephrine hydrochloride) injection, 0.1 mg/mL, is a sterile, nonpyrogenic, aqueous solution for intravenous infusion. IT MUST NOT BE DILUTED before administration as an intravenous bolus. The chemical name of phenylephrine hydrochloride is (1S,2R)-1-(3,4-dimethoxyphenyl) 2-hydroxypropan-2-amine hydrochloride, its molecular formula is C14H23NO.HCl (Molecular Weight: 230.67) and its structural formula is depicted below:

\[
\text{HO} \quad \text{N} \quad \text{CH} \quad \text{CH}_{3} \quad \text{H} \quad \text{Cl}
\]

Phenylephrine hydrochloride is soluble in water and ethanol, and insoluble in chloroform and ether.

Each mL contains: phenylephrine hydrochloride 0.1 mg (equivalent to 0.08 mg of phenylephrine base), sodium chloride 9.0 mg, in water for injection, pH is adjusted with hydrochloric acid if necessary. The pH range is 3.0 - 5.0.

12.1 Clinical Pharmacology
Phenylephrine hydrochloride is an 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 increases following intravenous bolus phenylephrine hydrochloride administration is rapid, typically within minutes. As blood pressure increases following intravenous administration, vasoconstriction 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 of 56 minutes. Phenylephrine is metabolized primarily by monooamine oxidase and sulfotransferase. After intravenous administration of radioiodinated phenylephrine, approximately 80% of the total dose was eliminated within 12 hours; and approximately 86% of the total dose was recovered in the urine within 48 hours.

The excreted unchanged parent drug was 16% of the total dose in the urine at 48 hours post-intravenous administration. There are two major metabolites, with approximately 57 and 8% of the total dose excreted as -hydroxymandelic acid and sulfate conjugates, respectively. The metabolites are not considered 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 based on body surface area) or rats administered approximately 50 mg/kg/day (48 times the HDD).

Mutagenesis: Phenylephrine hydrochloride tested negative in the in vitro bacterial reverse mutation assay (E. coli strain TA98, TA100, TA1535 and TA1537), in the in vitro chromosomal aberrations assay, in the in vivo sister chromatid exchange assay, and in 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 dose 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 BIOPHREN, 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 general 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
BIOPHREN (phenylephrine hydrochloride) injection USP, 0.1 mg/mL, for intravenous use, is a clear and colorless solution supplied as follows:

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<th>Strength</th>
<th>Each</th>
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<td>NDC No. 71863-202-06</td>
<td>0.1 mg/mL</td>
<td>5 mL ampule for single use</td>
</tr>
<tr>
<td>NDC No. 71863-202-05</td>
<td>0.1 mg/mL</td>
<td>1-ml prefilled syringe</td>
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Store BIOPHREN (phenylephrine hydrochloride) injection USP, 0.1 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]. The 5 mL ampule is for single use only. Discard any unused portion.

17. PATIENT COUNSELING INFORMATION
If applicable, inform patient, family member, or caregiver that certain medical conditions and medications might influence how BIOPHREN injection works.

Manufactured for: Eton Pharmaceuticals, Inc.
Deer Park, IL 60010 USA
Rev. 10/19
PI-202_001-rev_10/19