The first and only FDA-approved, ready-to-use formulation of phenylephrine HCl injection.

Indications and Usage
Biorphen is indicated for patients with clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia. Adjust dosage according to the blood pressure goal.

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 Safety Information continued throughout and accompanying full Prescribing Information.
PHENYLEPHRINE USE HAS BEEN ASSOCIATED WITH CERTAIN RISKS

**RISK 1**
DILUTION REQUIRED

- Concentrated phenylephrine
- Maximum diluted phenylephrine dose
- 1 TO 100 DILUTION

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

**RISK 2**
POTENTIAL MEDICATION ERRORS

- Perioperative medication administrations included a medication error
- 1 IN 20
- Medication errors associated with phenylephrine
- 1 IN 10

In a 2016 study:

**RISK 3**
POTENTIAL UNSAFE INJECTION PRACTICE

- Sometimes or routinely use a diluted saline bag for more than one patient (using a clean needle and syringe)
- 89%
- Sometimes or routinely use a medication vial for more than one patient (using a clean needle and syringe)
- 83%
- Sometimes or routinely use phenylephrine for more than one patient
- 83%

* Prospective observational study at 1,046-bed tertiary care academic medical center to identify medication errors and adverse drug events over 8 months. Authors acknowledged that observed subjects might have altered their behavior, suggesting that actual event rate could be higher than reported. Authors also state that observers could have missed events; researchers also performed retrospective chart abstraction to flag events that observers missed.

** Anonymous 17-question online survey sent to Canadian Anesthesiologists’ Society (CAS) members on medication preparation and administration practices. Of 2,656 CAS members, 546 (21%) responded. Authors acknowledge that response rate is a limitation; findings are potentially impacted by the large number of non-responders. There are also differences in survey sample compared with all licensed anesthesiologists across Canada.

In a 2017 survey of Canadian anesthesiologists:

- Sometimes or routinely use a diluted saline bag for more than one patient (using a clean needle and syringe)
- 89%
- Sometimes or routinely use a medication vial for more than one patient (using a clean needle and syringe)
- 83%
- Sometimes or routinely use phenylephrine for more than one patient
- 83%
ACCORDING TO FDA, A READY-TO-USE PHENYLEPHRINE CAN HELP MITIGATE CERTAIN RISKS\(^5\star\)

* Clinical implications for Biophen (phenylephrine HCl) injection, 500 mcg/5mL (100 mcg/mL) have not been determined. No claims are made about safety implications for Biophen.

** Adjust dosage according to the blood pressure goal.\(^1\)

\(\checkmark\) **CALCULATION AND COMPOUNDING ERRORS**

\(\checkmark\) **UNSAFE STERILE TECHNIQUE**

\(\checkmark\) **UNSAFE INJECTION PRACTICES**

BIORPHEN 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 Biophen 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 Biophen blood pressure effect) can occur with \(\alpha\)-adrenergic antagonists, phosphodiesterase Type 5 inhibitors, mixed \(\alpha\)- and \(\beta\)-receptor antagonists, calcium channel blockers, benzodiazepines and ACE inhibitors, centrally acting sympatholytic agents.

Please see additional Important Safety Information continued throughout and accompanying full Prescribing Information.
FDA URGING HOSPITALS TO STOP USING SOME COMPOUNDED DRUGS

The FDA is moving to restrict hospitals’ use of compounded drugs when FDA-approved versions are available, according to a 2018 guidance document. Why? Drugs compounded in hospitals or at 503B outsourcing facilities:

- Have no FDA premarket review for safety, effectiveness, and quality
- Have no FDA premarket review of manufacturing quality
- Can consequently pose higher risks to patients than FDA-approved drugs

503B OUTSOURCING FACILITIES ARE SUBJECT TO FDA ACTIONS THAT CAN INTERRUPT SUPPLY

Between 2013 and 2017, FDA has

- WRITTEN WARNING LETTERS
- RECALLS OF COMPOUNDED DRUGS

* Compounding facilities are inspected by the FDA for Current Good Manufacturing Practices (CGMP) compliance; however, these are not premarket inspections related to the manufacturing process for a particular product.

** Warning letters and recalls for all compounded drugs
The first and only FDA-approved, ready-to-use (RTU) formulation of Phenylephrine HCl injection.

### BIORPHEM VS COMPOUNDED PHENYLEPHRINE

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>BIORPHEN</th>
<th>COMPOUNDED PHENYLEPHRINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved drug</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>No compounding or dilution*</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>3-year shelf life⁹</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>Standardized RTU concentration</td>
<td>✔️</td>
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</table>

* Adjust dosage according to the blood pressure goal.¹

**IMPORTANT SAFETY INFORMATION (CONTINUED)**

**Overdosage**

Overdose of Biorphen (phenylephrine hydrochloride) can cause a rapid rise in blood pressure.

Please see additional Important Safety Information continued throughout and accompanying full Prescribing Information.
With a 3-year shelf life\(^9\) and $10 list price, Biorphen can be standardized throughout your hospital without frequent restocking.

### ASHP Guidelines

Biorphen meets certain risk-reduction strategies outlined in American Society of Health-System Pharmacists (ASHP) Guidelines for Preventing Medication Errors in Hospitals,\(^{10}\) including:

- ✔️ Standardizing concentration
- ✔️ Using commercially available products instead of compounding

### Important Safety Information (Continued)

**Overdosage (Continued)**

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.

Please see additional Important Safety Information continued throughout and accompanying full Prescribing Information.
BIORPHEN CAN BE CONVENIENTLY ADMINISTERED WITHOUT COMPOUNDING

BIORPHEN is supplied as a READY-TO-USE formulation.
Recommended dosing for treatment of hypotension during anesthesia:

- INITIAL BOLUS DOSE IS 40 TO 100 MCG
- ADMINISTER AS INTRAVENOUS BOLUS,
  Additional boluses may be administered every 1-2 minutes as needed; not to exceed a total dosage of 200mcg
- ADJUST DOSAGE ACCORDING TO THE BLOOD PRESSURE GOAL

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.

Please see additional Important Safety Information continued throughout and accompanying full Prescribing Information.
REFERENCES
BIORPHEN (phenylephrine hydrochloride) injection, for intravenous use

[Brief information]

Initial U.S. Approval: 1954

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**DOSAGE AND ADMINISTRATION**

BIORPHEN is indicated as a bolus. Do NOT DELAY before administration.

**CONTRAINDICATIONS**

None (4)

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**INDICATIONS AND USAGE**

BIORPHEN injection is an alpha-1 adrenergic receptor agonist indicated for the treatment of clinically important hypotension resulting primarily from a vasodilatory state of anesthesia. (1)

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**DOSE FORMS AND STRENGTHS**

BIORPHEN injection is an alpha-1 adrenergic receptor agonist. BIORPHEN injection is supplied as an intravenous bolus. It is supplied as a ready-to-use formulation.

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**WARNINGS AND PRECAUTIONS**

Exacerbation of Angina, Heart Failure, or Pulmonary Arterial Hypertension

BIORPHEN can precipitate angina in patients with severe arteriosclerosis or history of angina, exacerbate underlying hypertension, and increase pulmonary arterial pressure. (5.1)

Peripheral and Visceral Ischemia

BIORPHEN can cause excessive peripheral and visceral vasoconstriction and ischemia to vital organs.

Skin and Subcutaneous Necrosis

Extravasation during intravenous administration may cause necrosis or sloughing of tissue. (5.3)

Bradycardia

BIORPHEN can cause severe bradycardia and decreased cardiac output. (5.4)

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**ADVERSE REACTIONS**

Most common adverse reactions during treatment: nausea, vomiting, and headache. (6)

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**DRUG INTERACTIONS**

Antagonistic Effects (increase in BIORPHEN blood pressure effect)

An antagonistic effect on BIORPHEN blood pressure effect can occur with monoamine oxidase inhibitors (MAO), oxytocin and oxytocin agonists, ergot alkaloids, atropine, strophanthidin, phenylephrine, and adrenaline antagonists, and aldososterone, atropine, strophanthidin, and dopamine transporters, ergot alkaloids, and adrenergic antagonists. (7.1)

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**CONTRAINDICATIONS**

None (4)

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**SPECIAL POPULATIONS**

Hypertension

The recommended initial dose is 40 to 100 mcg administered by intravenous bolus. Additional boluses may be administered every 1-2 minutes as needed, not to exceed 100 mcg. (5.5)

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**ADVERSE REACTIONS**

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

- Monoamine oxidase inhibitors (MAO)
- Certain and anticoagulants
- Tricyclic antidepressants
- Angiotensin, aldososterone
- Analgesics, such as hydrocodone
- Norepinephrine transporter inhibitors, such as atomoxetine
- Certain sympathomimetic agents, such as ephedrine, guanfacine

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**SPECIAL POPULATIONS**

8.1 Pregnancy

Risk Summary

Data from randomized controlled trials and meta-analyses with phenylephrine hydrochloride injection use in pregnant women during caesarean 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 not observed in offspring of pregnant rats treated with 2.9 times the 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 is 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

Unreconciled hypertension associated with spinal anesthesia for cesarean delivery is associated with an increase in maternal hypotension and an increased rate of maternal hypotension associated with spinal anesthesia for cesarean delivery. A sustained decrease in uterine blood flow due to maternal hypertension may result in fetal bradycardia and acidosis.

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use BIORPHEN® safely and effectively. See full prescribing information for BIORPHEN®.
In patients with end stage renal disease (ESRD), dose-response more phenylephrine may be needed in this population. C], dose-response data indicate decreased responsiveness to 8.6 Hepatic Impairment has not identified differences in responses between the elderly and differently from younger subjects. Other reported clinical experience of subjects aged 65 and over to determine whether they respond established. Safety and effectiveness in pediatric patients have not been 8.4 Pediatric Use breastfed infant from phenylephrine hydrochloride injection or from considerations along with the mother's clinical need for phenylephrine developmental and health benefits of breastfeeding should be considered in addition to any contraindications or drug interactions. Ther Lactation 8.2 Lactation Risk Summary There are no data on the presence of Phenylephrine Hydrochloride in breast milk. In a human lactation study that included 3 nursing women, the amount of phenylephrine excreted in human milk was not quantified. The milk concentration was less than 0.08 mg/L at 0.5 hours post-dose. It is not known whether this drug is distributed in human milk, and therefore, nursing mothers should be advised not to breastfeed if they require therapy with phenylephrine. Animal Data 11 DESCRIPTION Phenylephrine is an alpha-1 adrenergic receptor agonist. BIORPHEN (phenylephrine hydrochloride) injection, 0.1 mg/mL, is a sterile, nonpyrogenic clear and colorless solution for injection. The pH is adjusted with hydrochloric acid if necessary. No more than 5 mL should be drawn into a syringe or added to 0.9% sodium chloride injection USP to dilute to 20 mL. The pH range is 3.0 -5.0. 12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Phenylephrine hydrochloride is an alpha-1 adrenergic receptor agonist. 12.2 Pharmacodynamics Phenylephrine hydrochloride 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 systemic 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 of phenylephrine hydrochloride administration is rapid, typically within minutes. As blood pressure increases following intravenous administration, vasoconstriction 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 monooamine oxidase and sulfotransferase. After intravenous administration of radiolabeled phenylephrine, approximately 80% of the total dose was eliminated within first 12h; and approximately 86% of the total dose was recovered in the urine within 48h. 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/90 kg/day based on body surface area) or rats administered approximately 50 mg/kg/day (48 times the HDD). Mutagenesis: Phenylephrine hydrochloride injection tested negative in the in vitro bacterial reverse mutation assays (S. typhimurium strains TA98, TA100, TA1535 and TA1537), the in vitro chromosomal aberration assay, and the in vitro mouse micronutrient 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 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, 1.0, or 2.9 times the HDD) from Gestation Day 6 through Day 21. No adverse effects on growth and development (learning and memory, sexual development, and fertility) were noted in the offspring of pregnant rats. 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. The pH is adjusted with hydrochloric acid if necessary. The pH range is 3.0 -5.0. NDC No. 71863-202-05 5 mL ampule; for single use.