PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrCARIPUL®

Epoprostenol for Injection

0.5 or 1.5 mg epoprostenol (as epoprostenol sodium) per vial

Vasodilator

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RECENT MAJOR LABEL CHANGES

Transition from CARIPUL™ to CARIPUL® SEPT 2019

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CARIPUL® (epoprostenol sodium) is indicated for:

- the long-term intravenous treatment of idiopathic pulmonary arterial hypertension (iPAH), heritable pulmonary arterial hypertension (HPAH) and pulmonary arterial hypertension associated with connective tissue disease in NYHA functional Class III and Class IV patients who did not respond adequately to conventional therapy.

Prior to initiation of therapy, the potential benefit of CARIPUL® should be weighed against the risks associated with use of the drug and the presence of an indwelling central venous catheter.

CARIPUL® should be used only by clinicians experienced in the diagnosis and treatment of pulmonary hypertension. The diagnosis of iPAH, HPAH or PAH associated with connective tissue disease (CTD) should be carefully established by standard clinical tests.

1.1 Pediatrics

Pediatrics (**< 18 years of age)**: The safety and effectiveness of epoprostenol in pediatric patients has not been established.

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of epoprostenol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection in the geriatric population should be made carefully, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

2 CONTRAINDICATIONS

CARIPUL® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, structurally-related compounds, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

The chronic use of CARIPUL® (epoprostenol sodium) in patients with congestive heart failure due to severe left ventricular systolic dysfunction is contraindicated. A large study evaluating the effect of epoprostenol on survival in NYHA Class III and IV patients with congestive heart failure due to severe left ventricular systolic dysfunction was terminated after an interim analysis of 471 patients revealed a higher mortality in patients receiving epoprostenol plus conventional therapy than in those receiving conventional therapy alone.

CARIPUL® should not be used chronically in patients who develop pulmonary edema during dose initiation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

CARIPUL® (epoprostenol sodium) must be reconstituted only as directed with Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Reconstituted solutions of CARIPUL® must not be diluted or administered with other parenteral solutions or medications.

CARIPUL® is not to be used for bolus administration.

During dose initiation and dose-finding, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output occurred rarely. In such cases, consider dose reduction, but such an increase does not imply that chronic treatment is contraindicated. However, in the rare occurrence of pulmonary edema, chronic treatment is contraindicated.

During chronic use, CARIPUL® is delivered continuously on an ambulatory basis through a permanent indwelling central venous catheter. Unless contraindicated, anticoagulant therapy should be administered to iPAH patients receiving CARIPUL® to reduce the risk of pulmonary thromboembolism or systemic embolism through a patent foramen ovale. In order to reduce the risk of infection, aseptic technique must be used in the reconstitution and administration of CARIPUL® as well as in routine catheter care. Because CARIPUL® is metabolized rapidly, even brief interruptions in the delivery of CARIPUL® may result in symptoms associated with rebound pulmonary hypertension including dyspnea, dizziness, and asthenia. The decision to initiate therapy with CARIPUL® should be based upon the understanding that there is a high likelihood that intravenous therapy with CARIPUL® will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully considered.

4.2 Recommended Dose and Dosage Adjustment

Dosage

Continuous chronic infusion of CARIPUL® should be prepared as directed (see **DOSAGE AND ADMINISTRATION, Reconstitution**) and administered through a central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Chronic infusion of CARIPUL® should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established or further increases in the infusion rate are not clinically warranted (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Dosage Adjustments**). If dose-limiting pharmacologic effects occur, then the infusion rate should be decreased to the point that the pharmacologic effects of CARIPUL® are tolerated. In clinical trials, the most common dose-limiting adverse events were nausea, vomiting, hypotension, sepsis, headache, abdominal pain, or respiratory disorder (most treatment-limiting adverse events were not serious). If the initial infusion rate of 2 ng/kg/min is not tolerated, use a lower dose.

In the controlled 12-week trial in PAH associated with CTD, for example, the dose increased from a mean starting dose of 2.2 ng/kg/min. During the first 7 days of treatment, the dose was increased daily to a mean dose of 4.1 ng/kg/min on day 7 of treatment. At the end of week 12, the mean dose was 11.2 ng/kg/min. The mean incremental increase was 2 to 3 ng/kg/min every 3 weeks.

Dosage Adjustments

Changes in the chronic infusion rate should be based on persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the occurrence of adverse events due to excessive doses of CARIPUL®. In general, increases in dose from the initial chronic dose should be expected.

Increments in dose should be considered if symptoms of pulmonary hypertension persist or recur after improving. The infusion should be increased by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. In clinical trials, incremental increases in dose occurred at intervals of 24 to 48 hours or longer. Following establishment of a new chronic infusion rate, the patient should be observed, and standing and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During chronic infusion, the occurrence of dose-limiting pharmacological events may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2-ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of CARIPUL® or sudden large reductions in infusion rates should be avoided. Except in life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of CARIPUL® should be adjusted only under the direction of a physician.

In patients receiving lung transplants, doses of epoprostenol were tapered after the initiation of cardiopulmonary bypass.

Pediatrics
Pediatrics (**< 18 years of age)**: The safety and effectiveness of epoprostenol in pediatric patients has not been established.

4.3 Reconstitution

CARIPUL® is stable only when reconstituted as directed using Sterile Water for Injection, or Sodium Chloride 0.9% Injection. CARIPUL® must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration. Each vial is for single use only; discard any unused solution.

Use after reconstitution and immediate dilution to final concentration
A concentration for the solution of CARIPUL® should be selected that is compatible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed above. CARIPUL®, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump. Outlined in Table 1 are directions for preparing different concentrations of CARIPUL® for up to a 48-hour period. **Each vial is for single use only; discard any unused solution.**

The vial containing 0.5 mg epoprostenol must be used for the preparation of solutions with final concentrations below 15,000 ng/mL.

Table 1: Reconstitution and Dilution Instructions

To make 100 mL of solution with Final Concentration (ng/mL) of:	Directions:
3,000 ng/mL	Dissolve contents of one **0.5 mg** vial with 5 mL of Sterile Water for Injection or Sodium Chloride 0.9% Injection. Withdraw 3 mL of the vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
5,000 ng/mL	Dissolve contents of one **0.5 mg** vial with 5 mL of Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
10,000 ng/mL	Dissolve contents of two **0.5 mg** vials each with 5 mL of Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
15,000 ng/mL*	Dissolve contents of one **1.5 mg** vial with 5 mL of Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
30,000 ng/mL*	Dissolve contents of two **1.5 mg** vials each with 5 mL of Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.

* Higher concentrations may be prepared for patients who receive CARIPUL® long-term.

Infusion rates may be calculated using the following formula:

$$\textbf{Infusion Rate (mL/hr)} = \frac{\textbf{[Dose (ng/kg/min) x Weight (kg) x 60 min/hr]}}{\textbf{Final Concentration (ng/mL)}}$$

Tables 2 to 6 provide infusion delivery rates for doses up to 16 ng/kg/min based upon patient weight, drug delivery rate, and concentration of the solution of CARIPUL® to be used. These tables may be used to select the most appropriate concentration of CARIPUL® that will result in an infusion rate between the minimum and maximum flow rates of the infusion pump and that will allow the desired duration of infusion from a given reservoir volume. For infusion/dose rates lower than those listed in Tables 2 to 6, it is recommended that the pump rate be set by a healthcare professional such that steady state is achieved in the patient, keeping in mind the half life of epoprostenol is no more than six minutes. Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of CARIPUL®

Table 2: Infusion Rates for CARIPUL® at a Concentration of 3,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)			
	2	3	4	5
	Infusion Delivery Rate (mL/hr)			
20	---	1.2	1.6	2.0
30	1.2	1.8	2.4	3.0
40	1.6	2.4	3.2	4.0
50	2.0	3.0	4.0	
60	2.4	3.6		
70	2.8			
80	3.2			
90	3.6			
100	4.0			

Table 3: Infusion Rates for CARIPUL® at a Concentration of 5,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	2	4	6	8	10	12	14
	Infusion Delivery Rate (mL/hr)						
20	---	1.0	1.4	1.9	2.4	2.9	3.4
30	---	1.4	2.2	2.9	3.6	4.3	5.0
40	1.0	1.9	2.9	3.8	4.8	5.8	6.7
50	1.2	2.4	3.6	4.8	6.0	7.2	8.4
60	1.4	2.9	4.3	5.8	7.2	8.6	10.1
70	1.7	3.4	5.0	6.7	8.4	10.1	11.8
80	1.9	3.8	5.8	7.7	9.6	11.5	13.4
90	2.2	4.3	6.5	8.6	10.8	13.0	15.1
100	2.4	4.8	7.2	9.6	12.0	14.4	16.8

Table 4: Infusion Rates for CARIPUL® at a Concentration of 10,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
20	---	---	1.0	1.2	1.4	1.7	1.9
30	---	1.1	1.4	1.8	2.2	2.5	2.9
40	1.0	1.4	1.9	2.4	2.9	3.4	3.8
50	1.2	1.8	2.4	3.0	3.6	4.2	4.8
60	1.4	2.2	2.9	3.6	4.3	5.0	5.8
70	1.7	2.5	3.4	4.2	5.0	5.9	6.7
80	1.9	2.9	3.8	4.8	5.8	6.7	7.7
90	2.2	3.2	4.3	5.4	6.5	7.6	8.6
100	2.4	3.6	4.8	6.0	7.2	8.4	9.6

Table 5: Infusion Rates for CARIPUL® at a Concentration of 15,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
20	---	---	---	---	1.0	1.1	1.3
30	---	---	1.0	1.2	1.4	1.7	1.9
40	---	1.0	1.3	1.6	1.9	2.2	2.6
50	---	1.2	1.6	2.0	2.4	2.8	3.2
60	1.0	1.4	1.9	2.4	2.9	3.4	3.8
70	1.1	1.7	2.2	2.8	3.4	3.9	4.5
80	1.3	1.9	2.6	3.2	3.8	4.5	5.1
90	1.4	2.2	2.9	3.6	4.3	5.0	5.8
100	1.6	2.4	3.2	4.0	4.8	5.6	6.4

Table 6: Infusion Rates for CARIPUL® at a Concentration of 30,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)					
	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)					
30	---	---	---	---	---	1.0
40	---	---	---	1.0	1.1	1.3
50	---	---	1.0	1.2	1.4	1.6
60	---	1.0	1.2	1.4	1.7	1.9
70	---	1.1	1.4	1.7	2.0	2.2
80	1.0	1.3	1.6	1.9	2.2	2.6
90	1.1	1.4	1.8	2.2	2.5	2.9
100	1.2	1.6	2.0	2.4	2.8	3.2

Use at room temperature (25°C): CARIPUL® solution reconstituted with 5 mL of Sterile Water for Injection or Sodium Chloride 0.9% Injection**,** and immediately diluted to the final concentration in the drug delivery reservoir can be administered at room temperature per the conditions of use as outlined in Table 7.

Table 7: Maximum duration of administration (hours) at room temperature (25°C) of fully diluted solutions in the drug delivery reservoir

Final concentration range	**Immediate administration ***	**If stored for up to 8 days at 2° to 8°C ***
≥3,000 ng/mL and <15,000 ng/mL	48 hours	24 hours
≥15,000 ng/mL	48 hours	48 hours

⁎Short excursions at 40°C are permitted for up to:
2 hours for concentrations below 15,000 ng/mL,
4 hours for concentrations between 15,000 ng/mL and 60,000 ng/mL
8 hours for concentrations above 60,000 ng/mL

A single reservoir of fully diluted solution of CARIPUL® prepared as directed above can also be administrated as outlined in Table 8.

Table 8: Maximum duration of administration (hours) at higher temperatures (>25°C up to 30°C) of fully diluted solutions in the drug delivery reservoir

Final concentration range	Immediate administration *	If stored for up to 8 days at 2° to 8°C *
All concentrations	24 hours	24 hours

**Short excursions at 40°C are permitted for up to:*
2 hours for concentrations below 15,000 ng/mL,
4 hours for concentrations between 15,000 ng/mL and 60,000ng/mL,
8 hours for concentrations above 60,000 ng/mL.

Do not expose the reconstituted or diluted solutions to direct sunlight.

4.4 Administration

CARIPUL®, once prepared as directed (see **DOSAGE AND ADMINISTRATION, Reconstitution**), is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. During initiation of treatment, CARIPUL® may be administered peripherally.

Infusion sets with an in-line 0.22 micron filter should be used.

The ambulatory infusion pump used to administer CARIPUL® should: (1) be small and lightweight, (2) be able to adjust infusion rates in 2-ng/kg/min increments, (3) have occlusion, end-of-infusion, and low-battery alarms, (4) be accurate to ±6% of the programmed rate, and (5) be positive pressure-driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver CARIPUL®. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. The infusion pump used in the most recent clinical trials was the CADD-1 HFX 5100 (SIMS Deltec). A 60-inch microbore non-DEHP extension set with proximal antisyphon valve, low priming volume (0.9 mL), and in-line 0.22 micron filter was used during clinical trials.

Suitable ambulatory pumps to be used for the administration of CARIPUL® include:
- CADD-Solis VIP

Manufactured by Smiths Medical.

Pump accessories found compatible with the administration of CARIPUL® include:
- CADD disposable Medication Cassette Reservoir 100 mL from Smiths Medical.
- CADD extension set with in-line 0.2 micron filter (CADD extension set with male luer, 0.2-micron air- eliminating filter, clamp, and integral anti-siphon valve with male luer) from Smiths Medical.

To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets. A multi-lumen catheter should be considered if other intravenous therapies are routinely administered.

5 OVERDOSAGE

Signs and symptoms of excessive doses of epoprostenol are the expected dose-limiting pharmacologic effects of epoprostenol, including flushing, headache, hypotension and complications of hypotension (e.g., tachycardia, nausea, vomiting, and diarrhea). Treatment will ordinarily require dose reduction of epoprostenol sodium or discontinue the infusion and initiate appropriate supportive measures as necessary; for example, plasma volume expansion and/or adjustment to pump flow.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unspecified concentration of epoprostenol. The patient vomited and became unconscious with an initially unobtainable blood pressure. Epoprostenol was discontinued and the patient regained consciousness within seconds.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 9: Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
injectable/ intravenous (I.V.)	Sterile powder for solution for injection - epoprostenol sodium equivalent to 0.5 mg (500,000 ng) epoprostenol - epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng) epoprostenol	L-Arginine Sodium hydroxide (for pH adjustment) Sucrose

Dosage Forms and Packaging

CARIPUL® (epoprostenol for injection) is a sterile lyophilized product for intravenous (IV) administration. CARIPUL® contains epoprostenol sodium equivalent to 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol in a 10 mL vial, individually package in a carton.

Composition

Each 10 mL vial of CARIPUL® contains epoprostenol sodium equivalent to 0.5 mg (500,000 ng) epoprostenol.

Each 10 mL vial of CARIPUL® contains epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng) epoprostenol.

7 WARNINGS AND PRECAUTIONS

General

Reconstitute CARIPUL® only as directed using Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Do not mix CARIPUL® with any other parenteral medications or solutions prior to or during administration.

CARIPUL® is not to be used for bolus administration (see **ADVERSE REACTIONS, Adverse Events During Dose Escalation, Tables 10 and 11**).

Epoprostenol is a potent inhibitor of platelet aggregation, therefore, an increased risk for hemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding (see **WARNINGS AND PRECAUTIONS, Risk of Bleeding and DRUG INTERACTIONS**).

Because of the high pH of the final infusion solutions, care should be taken to avoid extravasation during their administration and consequent risk of tissue damage.

During the early phase of chronic administration, intense patient education is required.

Due to the potential for problems associated with the drug delivery system, immediate access to medical care should be available during chronic treatment.

Elevated serum glucose levels have been reported during infusion of epoprostenol in man but these are not inevitable.

Hypotension may occur during infusions of CARIPUL®. If excessive hypotension occurs during administration of CARIPUL®, the dose should be reduced or the infusion discontinued. Hypotension may be profound in overdose and may result in loss of consciousness (see **OVERDOSAGE**).

Epoprostenol use has been associated with an increased incidence of bradycardia in patients with pulmonary hypertension and with episodes of severe hypotension, including fatalities.

Abrupt Withdrawal
Abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in dosage of CARIPUL® may result in symptoms associated with rebound pulmonary hypertension, including dyspnea, dizziness, and asthenia and may lead to death. In clinical trials, there were rare reports of deaths considered attributable to the interruption of epoprostenol. Abrupt withdrawal should be avoided, except in life-threatening situations (e.g., unconsciousness, collapse, etc.).

Carcinogenesis and Mutagenesis
Studies have not been performed to evaluate the carcinogenic potential of epoprostenol sodium. Preliminary studies revealed no evidence of mutagenicity in the Ames test. Micronucleus test and DNA elution tests were also negative.

Chronic Use and Dose Adjustment
CARIPUL® is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with CARIPUL® requires commitment by the patient to drug reconstitution, drug administration, care of the permanent central venous catheter, and access to intense and ongoing patient education. Sterile technique must be adhered to in preparing the drug and in the care of the catheter, and even brief interruptions in the delivery of CARIPUL® may result in rapid symptomatic deterioration. The decision to receive CARIPUL® for pulmonary hypertension should be based upon the understanding that there is a high likelihood that therapy with CARIPUL® will be needed for prolonged periods, possibly

years, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully considered.

Based on clinical trials, the acute hemodynamic response to epoprostenol did not correlate well with survival during chronic use of epoprostenol. Dosage of CARIPUL® during chronic use should be adjusted at the first sign of recurrence or worsening of symptoms attributable to pulmonary hypertension or the occurrence of adverse events associated with CARIPUL® (see **DOSAGE AND ADMINISTRATION**). During administration and following dosage adjustments, standing and supine blood pressure and heart rate should be monitored closely for several hours.

During ongoing treatment, patients should avoid situations which promote vasodilation such as saunas, hot baths and sunbathing. Severe hypotension has been seen in patients treated with chronic epoprostenol infusions under such circumstances.

Dose Initiation
CARIPUL® is a potent pulmonary and systemic vasodilator. The cardiovascular effects during infusion disappear within 30 minutes of the end of administration. Acute dose initiation with CARIPUL® must be performed in a hospital setting with adequate personnel and equipment for physiologic monitoring and emergency care.

Driving and Operating Machinery
Pulmonary hypertension and its therapeutic management may affect the ability to drive and operate machinery.

Pulmonary Edema
A minority of patients have pulmonary hypertension associated with pulmonary veno-occlusive disease. Some of these patients develop pulmonary edema during dose initiation. Where pulmonary edema arises within hours to days of starting CARIPUL® infusion, a diagnosis of veno-occlusive disease should be considered. In such cases consideration should be given to discontinuation of CARIPUL®. The CARIPUL® should be discontinued after dose tapering.

CARIPUL® should not be used chronically in patients who develop pulmonary edema during dose initiation.

Reproductive Health: Female and Male Potential
Animal studies did not indicate harmful effects with respect to fertility. However, the relevance of these findings in humans is unknown (see **TOXICOLOGY**).

Risks of Bleeding
Prothrombin times should be monitored because anticoagulant therapy is generally recommended in these patients. Platelet counts should also be monitored.

Sepsis
Sepsis/septicemia is a known risk associated with the presence of an indwelling central venous catheter and requires immediate access to expert medical care (see **ADVERSE REACTIONS, Adverse Events Attributable to the Drug Delivery System**).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Animal studies did not indicate harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. However, the relevance of these findings in humans is unknown (see **TOXICOLOGY**).

Labour and Delivery
The use of epoprostenol during labor, vaginal delivery, or caesarean section has not been studied in humans.

7.1.2 Breast-Feeding

It is not known whether epoprostenol or its metabolites are excreted in human milk. A risk to the nursing child cannot be excluded. Because many drugs are excreted in human milk, consideration should be given to discontinuation of breast feeding when CARIPUL® is to be administered to a nursing woman or to discontinue/abstain from CARIPUL® therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and effectiveness of epoprostenol in children has not been established.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Clinical studies of epoprostenol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

During clinical trials, adverse events were classified as follows: (1) adverse events during dose escalation, (2) adverse events during chronic dosing, and (3) adverse events associated with the drug delivery system.

Adverse Events During Dose Escalation

In early clinical trials, epoprostenol was increased in 2 ng/kg/min increments until such time as the patients developed symptomatic intolerance. The most common adverse events and those that limited further increases in dose were generally related to vasodilation, the major pharmacologic effect of epoprostenol. The most common dose-limiting adverse events (occurring in ≥1% of patients) were nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, and musculoskeletal pain. Table 10 lists the adverse events reported during dose escalation in decreasing order of frequency as well as the percent of cases where the event was dose limiting. Age related differences (< 16 vs ≥16 years) in the incidence of adverse events are shown in Table 11.

Table 10: Adverse Events During Dose Escalation

Adverse Events Occurring in ≥ 1% of patients	epoprostenol **(n=391) % of patients where event was reported**	epoprostenol **(n=391) % of patients where event was dose-limiting**
Flushing	58	14
Headache	49	18
Nausea/Vomiting	32	19
Hypotension	16	15
Anxiety, nervousness, agitation	11	7
Chest pain	11	7
Dizziness	8	4
Bradycardia	5	4
Abdominal pain	5	2
Musculoskeletal pain	3	2
Dyspnea	2	2
Back pain	2	-
Sweating	1	≤ 1
Dyspepsia	1	≤ 1
Hypesthesia/Paresthesia	1	≤ 1
Tachycardia	1	≤ 1

Table 11: Age Related Adverse Events During Dose Escalation

Adverse Events	< 16 y.o. (n=63) % of patients reporting event	≥ 16 y.o. (n=328) % of patients reporting event
Flushing	14	66
Headache	8	57
Nausea/Vomiting	40	30
Hypotension	14	16
Anxiety, nervousness, agitation	21	9
Chest pain	0	13
Dizziness	2	9
Bradycardia	6	5
Abdominal pain	6	5

Adverse Events During Chronic Administration

Interpretation of adverse events is complicated by the clinical features of PAH (pulmonary arterial hypertension), which may be similar to some of the pharmacologic effects of epoprostenol (e.g., dizziness, syncope). Adverse events which may be related to the underlying disease include dyspnea, fatigue, chest pain, edema, hypoxia, right ventricular failure, and pallor. Several adverse events, on the other hand, can clearly be attributed to epoprostenol. These include jaw pain, flushing, headache, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness.

Adverse Events During Chronic Administration for iPAH (**idiopathic pulmonary arterial hypertension**): In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 12 lists adverse events that occurred at a rate at least 10% different in the two groups in controlled trials for iPAH.

Table 12: Adverse Events Regardless of Attribution Occurring in Patients with iPAH During Chronic Administration in Controlled Trials with ≥ 10% Difference between epoprostenol and Conventional Therapy Alone

Adverse Event	epoprostenol (n=52) % of patients	Conventional Therapy (n=54) % of patients
Occurrence More Common With epoprostenol		
General		
Chills/fever/sepsis/flu-like symptoms	25	11
Cardiovascular		
Tachycardia	35	24
Flushing	42	2
Gastrointestinal		
Diarrhea	37	6
Nausea/vomiting	67	48

Musculoskeletal		
Jaw Pain	54	0
Myalgia	44	31
Nonspecific musculoskeletal pain	35	15
Neurological		
Anxiety/nervousness/tremor	21	9
Dizziness	83	70
Headache	83	33
Hypesthesia, Hyperesthesia, Paresthesia	12	2
Occurrence More Common With Conventional Therapy		
Cardiovascular		
Heart failure	31	52
Syncope	13	24
Shock	0	13
Respiratory		
Hypoxia	25	37

Thrombocytopenia, dry mouth, lassitude, chest tightness, reddening over the infusion site, occlusion of the long i.v. catheter and bleeding at various sites (e.g., pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal) have been reported during uncontrolled clinical trials and post marketing clinical use in patients receiving epoprostenol.

Table 13 lists those additional adverse events reported in iPAH patients receiving epoprostenol plus conventional therapy versus conventional therapy alone during controlled clinical trials where the difference in incidence of the event between treatment groups was < 10%.

Table 13: Adverse Events Regardless of Attribution Occurring During Chronic Administration in Controlled Trials with < 10% Difference between epoprostenol and Conventional Therapy Alone

Adverse Event	epoprostenol (n=52) % of patients	Conventional Therapy (n=54) % of patients
GENERAL		
Asthenia	87	81
CARDIOVASCULAR		
Angina Pectoris	19	20
Arrhythmia	27	20
Bradycardia	15	9
Supraventricular tachycardia	8	0
Pallor	21	30
Cyanosis	31	39
Palpitation	63	61
Cerebrovascular accident	4	0
Hypotension	27	31
Myocardial ischemia	2	6
GASTROINTESTINAL		
Abdominal pain	27	31

Adverse Event	epoprostenol (n=52) % of patients	Conventional Therapy (n=54) % of patients
Anorexia	25	30
Ascites	12	17
Constipation	6	2
METABOLIC		
Edema	60	63
Hypokalemia	6	4
Weight reduction	27	24
Weight gain	6	4
MUSCULOSKELETAL		
Arthralgia	6	0
Bone pain	0	4
Chest pain	67	65
NEUROLOGICAL		
Confusion	6	11
Convulsion	4	0
Depression	37	44
Insomnia	4	4
RESPIRATORY		
Cough increase	38	46
Dyspnea	90	85
Epistaxis	4	2
Pleural effusion	4	2
SKIN AND APPENDAGES		
Pruritus	4	0
Rash	10	13
Sweating	15	20
SPECIAL SENSES		
Amblyopia	8	4
Vision abnormality	4	0
OTHER		
Hemorrhage	19	11

Although the number of patients was small, in controlled trials there was a trend towards increased incidence of bradycardia associated with chronic treatment in patients < 16 vs those ≥ 16 years of age. Bradycardia, sometimes accompanied by orthostatic hypotension, has occurred in healthy volunteers at doses of epoprostenol greater than 5 ng/kg/min. Bradycardia associated with a considerable fall in systolic and diastolic blood pressure has followed i.v. administration of a dose of epoprostenol equivalent to 30 ng/kg/min in healthy conscious volunteers.

Adverse Events During Chronic Administration for PAH (pulmonary arterial hypertension) associated with CTD (connective tissue disease): In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 14 lists adverse events that occurred at a rate at least 10% different between the two groups in the controlled trial for patients with PAH.

Table 14: Adverse Events Regardless of Attribution Occurring in Patients with PAH associated with CTD with ≥ 10% Difference between epoprostenol and Conventional Therapy Alone

Adverse Event	epoprostenol (n=56) % of patients	Conventional Therapy (n=55) % of patients
Occurrence More Common With **epoprostenol**		
CARDIOVASCULAR		
Flushing	23	0
Hypotension	13	0
GASTROINTESTINAL		
Anorexia	66	47
Nausea/vomiting	41	16
Diarrhea	50	5
MUSCULOSKELETAL		
Jaw pain	75	0
Pain/neck pain/arthralgia	84	65
NEUROLOGICAL		
Headache	46	5
SKIN AND APPENDAGES		
Skin ulcer	39	24
Eczema/rash/urticaria	25	4
Occurrence More Common With **Conventional** Therapy		
CARDIOVASCULAR		
Cyanosis	54	80
Pallor	32	53
Syncope	7	20
GASTROINTESTINAL		
Ascites	23	33
Esophageal reflux/gastritis	61	73
METABOLIC		
Weight decrease	45	56
NEUROLOGICAL		
Dizziness	59	76
RESPIRATORY		
Hypoxia	55	65

Table 15 lists additional adverse events reported in PAH associated with CTD patients receiving epoprostenol plus conventional therapy or conventional therapy alone during controlled clinical trials.

Table 15: Adverse Events Regardless of Attribution Occurring in Patients with PAH associated with CTD with < 10% Difference Between epoprostenol and Conventional Therapy Alone

Adverse Event*	epoprostenol (n=56) % of patients	Conventional Therapy (n=55) % of patients
GENERAL		
Asthenia	100	98
Hemorrhage/hemorrhage injection	11	2
Site/hemorrhage rectal		
Infection/rhinitis	21	20
Chills/fever/sepsis/flu-like symptoms	13	11
CARDIOVASCULAR		
Heart failure/heart failure right	11	13
Myocardial Infarction	4	0
Palpitation	63	71
Shock	5	5
Tachycardia	43	42
Thrombocytopenia	4	0
Vascular disorder peripheral	96	100
Vascular disorder	95	89
GASTROINTESTINAL		
Abdominal enlargement	4	0
Abdominal pain	14	7
Constipation	4	2
Flatulence	5	4
METABOLIC		
Edema/edema peripheral/edema	79	87
genital	48	51
Hypercalcemia	4	0
Hyperkalemia	0	4
Thirst		
MUSCULOSKELETAL		
Arthritis	52	45
Back pain	13	5
Chest pain	52	45
Cramps leg	5	7
RESPIRATORY		
Cough increase	82	82
Dyspnea	100	100
Epistaxis	9	7
Pharyngitis	5	2
Pleural effusion	7	0
Pneumonia	5	0
Pneumothorax	4	0
Pulmonary edema	4	2
Respiratory disorder	7	4
Sinusitis	4	4

Adverse Event*	epoprostenol (n=56) % of patients	Conventional Therapy (n=55) % of patients
NEUROLOGICAL		
Anxiety/hyperkinesia/nervousness/tremor	7	5
Depression/depression psychotic	13	4
Hyperesthesia/hypesthesia/paresthesia	5	0
Insomnia	9	0
Somnolence	4	2
SKIN AND APPENDAGES		
Collagen disease	82	84
Pruritus	4	2
Sweat	41	36
UROGENITAL		
Hematuria	5	0
Urinary tract infection	7	0

* Table lists adverse events which occurred in at least 2 patients in either group.

Adverse Events Attributable to the Drug Delivery System

Chronic infusions of epoprostenol are delivered using a small, portable infusion pump through an indwelling central venous catheter. During controlled iPAH trials of up to 12 weeks duration, up to 21% of patients reported a local infection and up to 13% of patients reported pain at the venous catheter insertion site. During a 12 week controlled trial of PAH associated with CTD, 14% of patients reported a local infection and 9% of patients reported pain at the venous catheter insertion site. During subsequent long-term follow-up in clinical trials of iPAH, sepsis/septicemia (mostly related to delivery system for epoprostenol) was reported at least once in 14% of patients and occurred at a rate of 0.32 infections per patient per year in patients treated with epoprostenol. When suspected, sepsis should be diagnosed and treated quickly. It is therefore important that these patients have immediate access to expert medical care. Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported. Malfunctions in the delivery system resulting in an inadvertent bolus of, or a reduction in, epoprostenol were associated with symptoms related to excess or insufficient epoprostenol respectively, that may lead to serious consequences including death (see **WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS, Adverse Events During Chronic Administration; and OVERDOSAGE**).

8.5 Post-Market Adverse Reactions

In addition to adverse reactions reported from clinical trials, the following adverse reactions were reported spontaneously to various surveillance systems during post-approval use of epoprostenol:

Blood and Lymphatic: Hypersplenism, splenomegaly.
Cardiac Disorders: High output cardiac failure
Endocrine Disorders: Hyperthyroidism

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Additional reductions in blood pressure may occur when CARIPUL® is administered with diuretics, antihypertensive agents, or other vasodilators. When NSAIDS or other drugs affecting platelet aggregation are used concomitantly, there is the potential for CARIPUL® to increase the risk of bleeding. In clinical trials, epoprostenol was used with digoxin, diuretics, anticoagulants, oral vasodilators and supplemental oxygen.

The vasodilator effects of CARIPUL® may augment or be augmented by concomitant use of other vasodilators.

In a pharmacokinetic substudy in patients with congestive heart failure receiving furosemide or digoxin in whom epoprostenol therapy was initiated, apparent oral clearance values for furosemide (n=23) and digoxin (n=30) were decreased by 13% and 15%, respectively, on the second day of therapy and returned to baseline values by day 87. The change in furosemide clearance value is not likely to be clinically significant. However, patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with epoprostenol, which may be clinically significant in patients prone to digoxin toxicity.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

CARIPUL® (epoprostenol sodium), also known as prostacyclin, PGI_2 or PGX, a metabolite of arachidonic acid, is a naturally occurring prostaglandin. Epoprostenol has two major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation.

10.2 Pharmacodynamics

In animals, the vasodilatory effects of epoprostenol reduce right and left ventricular afterload and increase cardiac output and stroke volume. The effect of epoprostenol on heart rate in animals varies with dose. At low doses, there is vagally mediated bradycardia, but at higher doses, epoprostenol causes reflex tachycardia in response to direct vasodilation and hypotension. No major effects on cardiac conduction have been observed. Additional pharmacologic effects of epoprostenol in animals include bronchodilation, inhibition of gastric acid secretion, and decreased gastric emptying.

Cardiovascular Pharmacology: Epoprostenol sodium produces vascular relaxation *in vitro*, and systemic, pulmonary, and coronary vasodilation *in vivo* without significant electrocardiographic effects.

In anesthetized rats, epoprostenol sodium (0.125-64 µg/kg I.V.) caused dose-dependent decreases in systolic and diastolic blood pressures (up to 100 mm Hg) along with tachycardia (up to 66 beats/min) which was reflex in origin. Dose-dependent reductions in mean arterial blood pressure (up to 40 mm Hg) accompanied by tachycardia (up to 80 beats/min) was observed in conscious rats receiving 0.1-1 µg/kg/min I.V.

In anesthetized dogs, epoprostenol sodium (0.01-0.3 µg/kg/min I.V.) produced dose dependent decreases in total peripheral resistance (27-61%), mean arterial blood pressure (15-61%), and pulmonary vascular resistance (32-44%), and increases in cardiac output which were a function of dose-dependent increases in stroke volume (+40% at 0.3 µg/kg/min).

In conscious dogs, intra-arterial administration of epoprostenol sodium (0.1-1 µg/kg/min) effected dose-dependent decreases in left ventricular work (-39% at 1 µg/kg/min) and mean arterial blood pressure (-28% at 1 µg/kg/min). Pulmonary artery and renal artery blood flows were increased by 45% and 43% respectively at the highest dose, while most other organs showed dose-dependent decreases in blood flow.

The hypoxia-induced increases in pulmonary arterial blood pressure and pulmonary vascular resistance in anesthetized cats were respectively reduced (by 70%) and abolished by epoprostenol sodium (0.3 µg/kg/min I.V.).

The effects of epoprostenol sodium are mediated through a specific membrane receptor, with signal transduction through the adenylate cyclase/cAMP secondary messenger system.

Endocrine Effects: The effects of epoprostenol sodium on the circulating levels of anterior pituitary hormones was studied in rats. Although 1 mg/kg epoprostenol sodium given subcutaneously for seven consecutive days was a no-effect dose, 60 mg/kg/day produced decreased plasma luteinizing hormone but had no effect on follicle stimulating hormone. There were no significant differences in pituitary weights and no drug-related lesions were found by light-microscopy. In a primate luteolysis screening bioassay, 11.5 mg/kg epoprostenol sodium given by intramuscular injection did not produce signs of luteolysis (decreased levels of progesterone).

Subcutaneous injection of 30 mg/kg epoprostenol sodium in two male patas monkeys produced a prominent and persistent increase in plasma cortisol but did not affect either thyroid hormone T3 or T4.

Gastrointestinal Effects: Epoprostenol sodium produces dose-dependent *in vivo* and *in vitro* inhibition of gastric acid secretion induced by histamine and pentagastrin in rats and rat isolated tissue. Dose-dependent inhibition of ethanol-induced gastric lesions in rats has been observed. Gastric emptying may be decreased.

Neuropharmacological Effects: Epoprostenol sodium administered as a single intravenous bolus to conscious mice (1-10 mg/kg) and rats (0.1 µg/kg-100 mg/kg) exerts relatively minor behavioural effects until high doses are achieved. Decreases in body temperature and peripheral flushing are commonly observed secondary to the vasodilation caused by this agent.

Platelet Aggregation: Epoprostenol sodium is the most potent inhibitor of platelet aggregation known, with profound inhibition of aggregation observed in virtually all species, both *in vivo* and *ex vivo*. Increased bleeding times were observed in rats and dogs.

Renal Effects: Under basal conditions, epoprostenol sodium causes equivocal changes in urine output and ion excretion. Renal function following ischemia is preserved by treatment with epoprostenol sodium. In rabbits, epoprostenol caused a dose dependent reduction in glomerular filtration rate.

Respiratory Effects: Epoprostenol sodium has bronchodilator effects in guinea pigs and dogs exposed to the bronchoconstriction induced by histamine, acetylcholine and $PGF_{2\alpha}$.

10.3 Pharmacokinetics

Epoprostenol is rapidly hydrolyzed at neutral pH in blood and is also subject to enzymatic degradation. Animal studies using tritium-labeled epoprostenol have indicated a high clearance (93 mL/kg/min), small volume of distribution (357 mL/kg), and a short half-life (2.7 minutes). During infusions in animals, steady-state plasma concentrations of tritium-labeled epoprostenol were reached within 15 minutes and were proportional to infusion rates.

No available chemical assay is sufficiently sensitive and specific to assess the *in vivo* human pharmacokinetics of epoprostenol. The *in vitro* half-life of epoprostenol in human blood at 37°C and pH 7.4 is approximately 6 minutes; therefore, the *in vivo* half-life of epoprostenol in humans is expected to be no greater than 6 minutes. The *in vitro* pharmacologic half-life of epoprostenol in human plasma, based on inhibition of platelet aggregation, is 10.6 minutes in males (n = 954) and 10.8 minutes in females (n = 1024).

Tritium-labelled epoprostenol has been administered to humans in order to identify the metabolic products of epoprostenol. Epoprostenol is metabolized to 2 primary metabolites: 6-keto-PGF1α (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-PGF1α (enzymatically formed), both of which have pharmacological activity at orders of magnitude less than epoprostenol in animal test systems. The recovery of radioactivity in urine and feces over a one-week period was 82% and 4% of the administered dose, respectively. Fourteen additional minor metabolites have been isolated from urine, indicating that epoprostenol is extensively metabolized in humans.

Absorption and Disposition: Epoprostenol is rapidly hydrolyzed at neutral pH in blood and is also subject to enzymatic degradation. In one study in rabbits, after a 107 mg/kg bolus I.V. dose of ^{3}H-epoprostenol sodium, clearance was 93 mL/min/kg, volume of distribution was 357 mL/kg, and the terminal half-life was 2.7 min.

In a separate study in rabbits, after an 85 mg/kg dose of ^{3}H-epoprostenol sodium, clearance was 256 mL/min/kg, volume of distribution was 1015 mL/kg, and the terminal half-life was 2.9 min. When rabbits were given intravenous infusions of tritiated epoprostenol sodium (ranging from 4.2 to 604 ng/kg/min), plasma steady-state concentrations were achieved within 15 minutes of initiation of the infusions, and steady-state concentrations increased linearly with increasing infusion rate. A study performed in cats (100 ng/kg/min of ^{3}H-epoprostenol sodium) using the same analytical methodology, indicated that steady state was achieved by 60 minutes after initiation of the infusion.

Elimination and Metabolism: Epoprostenol undergoes rapid chemical hydrolysis under physiological conditions to yield 6-keto-$PGF_{1\alpha}$. In addition, the metabolism of epoprostenol involves dehydrogenation of the C-15 hydroxyl group, reduction of the 13,14-trans double bond, β-oxidation, ω or ω-1 oxidation. Metabolites consistent with all these metabolic reactions were observed in *in vitro* and *in vivo* studies in rats, dogs and monkeys. In addition, glucuronide-conjugated metabolites have been isolated from rat bile after epoprostenol sodium administration. Cytochrome P-450-dependent epoxidation of epoprostenol has been described *in vitro*. All of the metabolites reported in animal studies are essentially inactive, with the exception of 6-keto-PGE_1, that has been detected in dogs but not in any other species. Liver and kidney may be the most important organs with respect to metabolism.

Epoprostenol-derived material is rapidly excreted into urine and feces after dosing with epoprostenol sodium. Dogs excrete nearly 90% of the administered dose in the urine, while in rats there was a more balanced distribution into urine and feces. Monkeys excreted 45.2% of the dose into urine, but fecal recovery was not determined.

Tissue Distribution: Tissue distribution studies have been performed in rats given either intravenous or subcutaneous doses of tritiated epoprostenol sodium. Tritium concentrations declined rapidly after either route of administration. The highest levels of radioactivity were observed in the kidney, liver, and small intestine and the lowest levels were observed in brain and adipose tissue. After an I.V. dose, approximately one-third of the radioactivity was detected in the liver 15 minutes after dosing.

Pharmacokinetic/Pharmacodynamic Relationship(s)
In a study carried out in twenty healthy male subjects, CARIPUL® and FLOLAN were administered in a cross-over design in sequential infusions of 2, 4, 6, and 8 ng/kg/min for 2 h each. Due to the very short half-life of epoprostenol, the pharmacokinetic profiles of CARIPUL® and FLOLAN were characterized via analysis of the concentration-time profiles of 2 primary metabolites, 6-keto-prostacyclin F1α (spontaneously formed by hydration) and 6,15-diketo-13,14-dihydro-prostacyclin F1α (formed by enzymatic degradation). Overall, the pharmacokinetic profiles of CARIPUL® and FLOLAN were comparable. This resulted into comparable area under the curve (AUC0) values with 90% CIs of the geometric mean ratios contained within the 0.8–1.25 equivalence range. In addition, both formulations showed comparable hemodynamic (mainly cardiac output and heart rate), safety, and tolerability characteristics.

11 STORAGE, STABILITY AND DISPOSAL

Powder for solution for infusion
Store the vials CARIPUL® between 15-30°C. Protect from freezing.

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

12 SPECIAL HANDLING INSTRUCTIONS

Unopened vials of CARIPUL® are stable until the date indicated on the package when stored between 15-30°C. Protect from freezing.

Do not expose the reconstituted or diluted solution to direct sunlight.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, CARIPUL® should not be administered.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

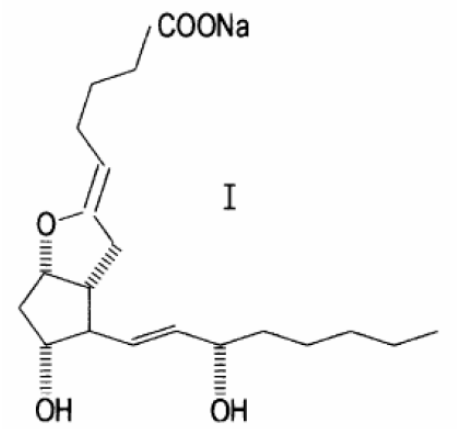
Proper name: Epoprostenol sodium

Chemical name [USAN]: Prosta-5,13-dien-1-oic acid, 6,9-epoxy- 11,15-dihydroxy-, sodium salt, (5*Z*, 9α, 11α, 13*E*, 15S)

Chemical name [Chem. Abstr.]: (5Z,9α,11α,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-l-oic acid. It is used as sodium salt.

Molecular formula and molecular mass: $C_{20}H_{31}NaO_5$ and 374.45

Structural formula [USAN]:



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Physicochemical properties: Epoprostenol sodium is a white to off-white solid which melts over a wide range of temperatures with decomposition. It is readily soluble in water and ethanol, and sparingly soluble in acetonitrile.

14 CLINICAL TRIALS

Clinical Trials in Pulmonary Arterial Hypertension

***Acute Hemodynamic effects*:** Acute intravenous infusions of epoprostenol for up to 15 minutes in patients with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with connective tissue disease produced dose-related increases in cardiac index (CI) and stroke volume (SV), and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), and mean systemic arterial pressure (SAPm). The effects of epoprostenol on mean pulmonary arterial pressure (PAPm) were variable and minor.

Chronic Hemodynamic Effects in Idiopathic Pulmonary Arterial Hypertension (iPAH)

Chronic hemodynamic effects were generally similar to acute effects. CI, SV, and arterial oxygen saturation were increased, and PAPm, right atrial pressure (RAP), TPR, and systemic vascular resistance (SVR) were decreased in patients who received epoprostenol chronically, compared to those who did not.

Survival was improved in NYHA (New York Heart Association) functional Class III and Class IV iPAH patients treated with epoprostenol for 12 weeks in a multicenter, open, randomized, parallel, controlled study. At the end of the treatment period, 8 of 40 patients receiving standard therapy alone had died, whereas none of the 41 patients receiving epoprostenol had died (p=0.003).

Table 16 illustrates the treatment-related hemodynamic changes in these patients after 8 or 12 weeks of treatment.

Table 16: Hemodynamics During Chronic Administration of Epoprostenol in Patients with iPAH

Hemodynamic Parameter	Baseline		Mean change from baseline at end of treatment period*	
	Epoprostenol (n=52)	Conventional (n=54)	Epoprostenol (n=48)	Conventional (n=41)
CI ($L/min/m^2$)	2.0	2.0	0.3**	-0.1
PAPm (mm Hg)	60	60	-5**	1
PVR (Wood U)	16	17	-4**	1
SAPm (mm Hg)	89	91	-4	-3
SV (mL/beat)	44	43	6**	-1
TPR (Wood U)	20	21	-5**	1

*At 8 weeks: Epoprostenol n=10; Conventional Therapy n=11
(n is the number of patients with hemodynamic data).
At 12 weeks: Epoprostenol n=38; Conventional Therapy n=30
(n is the number of patients with hemodynamic data)
**Denotes statistically significant difference between Epoprostenol and Conventional Therapy groups
CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SAPm = mean systemic arterial pressure; SV = stroke volume ; TPR = total pulmonary resistance

Chronic Infusion in Pulmonary Arterial Hypertension (PAH) associated with connective tissue disease (CTD)

Hemodynamic effects: Chronic continuous infusions of epoprostenol in patients with PAH associated with CTD were studied in a prospective, open, randomized trial of 12 weeks duration comparing epoprostenol plus conventional therapy to conventional therapy alone. Except for the five New York Heart Association (NYHA) functional Class II patients, all patients were either functional Class III or Class IV. The patients principally had pulmonary vascular manifestations of the collagen-vascular disease, with minimal evidence of interstitial lung disease and with total lung capacities greater than 60% of the predicted normal. Dosage of epoprostenol was determined (see **DOSAGE AND ADMINISTRATION**) and averaged 11.2 ng/kg per minute at study end. Conventional therapy varied among patients and included oxygen and diuretics in two-thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. A statistically significant increase in CI, and statistically significant decreases in PAPm, RAP, PVR, and SAPm were observed in patients who received epoprostenol chronically compared to those who did not. Table 17 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of treatment.

Table 17: Hemodynamics During Chronic Administration of Epoprostenol in Patients with PAH associated with CTD

Hemodynamic Parameter	Baseline		Mean Change from Baseline at 12 Weeks	
	Epoprostenol (n=56)	Conventional Therapy (n=55)	Epoprostenol (n=50)	Conventional Therapy (n=48)
PAPm (mm Hg)	51	49	-5*	1
RAP (mm Hg)	13	11	-1*	1
PVR (Wood U)	14	11	-5*	1
SAPm (mm Hg)	93	89	-8*	-1

* Denotes statistically significant difference between Epoprostenol and Conventional Therapy groups (n is the number of patients with hemodynamic data).
CI = cardiac index; PAPm = mean pulmonary arterial pressure; RAP = right atrial pressure; PVR = pulmonary vascular resistance; SAPm = mean systemic arterial pressure

Clinical Effects: Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk, in patients receiving continuous intravenous epoprostenol plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Improvements were apparent as early as the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as measured by the Borg Dyspnea Index and Dyspnea Fatigue Index. By week 12, NYHA Functional Class improved in 21 of 51 (41%) patients treated with epoprostenol compared to none of the 48 patients treated with conventional therapy alone.

No statistical difference in survival over 12 weeks was observed in PAH patients treated with epoprostenol. At the end of the treatment period, 4 of 56 (7%) patients receiving epoprostenol died, whereas 5 of 55 (9%) patients receiving conventional therapy died.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity Studies

Rodents: The acute toxicity of epoprostenol sodium was determined in rodents as follows:

Strain/Species	No. per Group	Dose (mg/kg)	Route	LD_{50} (mg/kg)
Evans-1 mouse	10M, 10F	0, 0.1, 0.3, 1, 10	I.V.	> 10
Evans-1 mouse	10M, 0F	0, 0.003, 0.03, 0.1, 0.3, 1	I.V.	-
Wistar rat	5M, 5F	0, 0.0001, 0.01, 1, 100 25, 35, 50, 70, 80, 100	I.V.	66.3

The LD_{50} in mice could not be estimated since the maximum dose level of 10 mg/kg epoprostenol was lethal in only 1 of 10 male and in none of 10 female mice.

Epoprostenol 0.0001 mg/kg was without effect. The effects of epoprostenol sodium were observed in mice given doses as low as 0.003 mg/kg. Flaccid paralysis, hypoactivity, ataxia, lost or weak righting reflex, slow and/or deep laboured breathing, ptosis and piloerection were observed following doses of epoprostenol greater than 0.01 mg/kg I.V. Signs of toxicity observed 2 to 5 minutes postdose with 0.03 to 10 mg/kg included decreased activity, bradypnea, hypothermia, ataxia, and skin flushing. These signs disappeared in 2 hours postdose. Dose-related hypothermia, which occurred slightly later than the other signs, was most prominent 10 minutes following dosing, but undetectable at 2 hours postdose. With the exception of pulmonary hemorrhage in one male mouse receiving 10 mg/kg, there were no gross lesions in any other animal. Rats given intravenous doses of 100 mg/kg developed respiratory distress, collapsed and died 1 to 10 minutes postdose.

Subacute and Subchronic Toxicity Studies

Strain/Species	No. per Group	Doses	Route	Duration (days)	Drug-related Findings
SD Rat	5M, 5F	0, 56, 180, 560 ng/kg/min	continuous I.V.	14	Weight loss, reddened skin, and decreased platelet counts.
Beagle Dog	2M, 2F	0, 12.5, 40, 125 ng/kg/min	continuous I.V.	30	Emesis, soft feces, decreased platelet counts, significantly decreased white blood cells.
Beagle Dog	2M, 2F	125 ng/kg/min	continuous I.V.	30	Platelet decreases and hematologic changes reversed.
Monkey *(Erythrocebus patas)*	2M, 2F	0, 0.01, 0.1, 1 µg/kg/min	I.V. (1 hr/day 3 X/wk)	14	Emesis, diarrhea, decreased blood pressure, tachycardia, focal necrosis in heart (1 monkey), bleeding time and blood glucose significantly increased.

Wistar Rat	0M, 2F	0, 1, 10, 30, 60 mg/kg	S.C.	7	Hypotension, EKG changes (myocardial ischemia), necrosis in heart.
Wistar Rat	15M, 15F	0, 1, 10, 100 µg/kg	S.C.	14	Red skin, hypotension, EKG changes (myocardial ischemia).
Monkey *(Erythrocebus patas)*	1M, 0F	Dose escalation 0, 1, 10, 30, 60, 60 mg/kg	S.C.	5	Red skin, hypotension (all doses); necrosis in heart.

Carcinogenicity

Carcinogenesis bioassays have not been performed with epoprostenol sodium.

Mutagenicity

Preliminary studies showed that epoprostenol sodium was non-mutagenic in the Ames Salmonella assay, non-clastogenic in the rat micronucleus assay, and did not damage DNA in the alkaline elution assay (see below).

Study	Species	No. per Group	Dose/Concentration	Duration
Ames assay	*Salmonella typhimurium*	NA[1]	Up to 2000 µg/plate	NA
Micronucleus assay	Rat	10M, 0F	0, 10, 20, 40 mg/kg i.p.	1 day
Alkaline Elution assay	*in vitro*	NA	Up to 3 mM concentration	NA

[1]Not Applicable

Reproduction and Teratology

In a Segment I reproduction study in rats, males were treated with 0, 10, 30, or 100 µg/kg/day subcutaneous epoprostenol sodium for 60 days prior to mating and during a 14-day mating period. Females were treated 14 days before mating and during mating, gestation and lactation. There were no signs of treatment-related effects on fertility of either the parental generation or the first filial generation rats. Estrus cycles of the F_o dams were normal. Pregnancies, developmental milestones and behavioural tests were all judged to be normal.

There was no teratogenic effect in fetuses from rats and rabbits given epoprostenol sodium by subcutaneous injection during critical periods of organogenesis at dose levels of 1, 10, and 100 µg/kg/day. Gestation, parturition, and the rearing of young were all normal in rats given subcutaneous doses of 0, 10, 30 and 100 µg/kg/day.

Study	Strain/ Species	No. per Group	Route	Dose and Frequency	Drug-related Findings
Segment I Fertility	SD Rat	12M, 24F	S.C.	0, 10, 30, 100 µg/kg/day (60 days)	Depression (all doses), ataxia (30 and 100 µg/kg); no effect on fertility.
Segment II Teratology	Wistar Rat	20F	S.C.	0, 1, 10, 100 µg/kg/day Gestational days 6-16	No teratogenic effects.
Segment III Peri-postnatal	SD Rat	24F	S.C.	0, 10, 30, 100 µg/kg/day Gestational day 15 through Postpartum day 21	Depression (all doses), ataxia (30 and 100 µg/kg); slightly delayed parturition; pup survival significantly decreased.
Segment II Teratology	DB Rabbit	15F	S.C.	0, 1, 10, 100 µg/kg/day Gestational days 6-18	No obvious teratogenic effects; technical difficulties with the study.
Segment II Teratology	DB Rabbit	44F	S.C.	0, 100 µg/kg/day Gestational days 6-18	Red skin, hypotension. No teratogenic effects.

Other Toxicity Studies

Dermal Irritation: Epoprostenol sodium at a dose of 0.1 mL (1 mg/mL concentration) applied three times in one day to abraded skin of CFLP mice produced no histopathologic alterations.

Toxicity of Hydrolysis Product: The subacute toxicity of 6-keto-$PGF_{1\alpha}$ an epoprostenol hydrolysis product, was investigated in patas monkeys. A dose of 1 µg/kg/min given as a 60-minute intravenous infusion 3 times per week for 2 weeks was devoid of toxic and pharmacodynamic activity.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr CARIPUL®
(epoprostenol sodium)
0.5 or 1.5 mg epoprostenol sodium per vial

Read this carefully before you start taking **CARIPUL®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CARIPUL®**.

CARIPUL® is a very complicated medication to administer. The drug must be prepared daily under rigorous conditions. You will need to learn about the medicine, the delivery system (the central venous catheter) and the pump. You will need to have a 'significant other' who is willing to learn along with you and to be available in case of need. Your doctor or nurse will teach you and your 'significant other' how to prepare the medication and use the pump for administering the medication.

What is CARIPUL® used for?

CARIPUL® is used to treat a lung condition called pulmonary hypertension. This is where the pressure is high in the main blood vessels in the lungs.

How does CARIPUL® work?

CARIPUL® widens the blood vessels to lower the blood pressure in the lungs.

What are the ingredients in CARIPUL®?

Medicinal ingredients: epoprostenol sodium
Non-medicinal ingredients: L-arginine, sodium hydroxide and sucrose

CARIPUL® comes in the following dosage forms:

CARIPUL® comes as a dried powder in a glass vial, 0.5 mg and 1.5 mg epoprostenol.

Do not use CARIPUL® if:

- you are allergic (hypersensitive) to epoprostenol, the medicinal ingredient in CARIPUL®, to any other ingredient in the formulation (see "What are the ingredients in CARIPUL®"), or to similar medicines.
- you have heart failure.
- you had fluid in the lungs (pulmonary edema) when you were started on CARIPUL®.

If you think any of these apply to you, don't take CARIPUL® until you have checked with your doctor.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CARIPUL®. Talk about any health conditions or problems you may have, including if you:

- have any problems with bleeding.

- are pregnant, or think you could be, or if you are planning to become pregnant. Your doctor will consider the benefit to you and the risk to your baby of taking CARIPUL® while you're pregnant.

- are breast-feeding. It is not known whether the ingredients of CARIPUL® can pass into breast milk.

- are younger than 18 years of age.

Other warnings you should know about:
- Pulmonary hypertension and your treatment may have an effect on your ability to drive or use machinery. Don't drive or use machines unless you're feeling well.

- Stopping CARIPUL® treatment must be done gradually. If the treatment is stopped too quickly, you may get serious side effects, including dizziness, feeling weak and breathing difficulties.

- If you have problems with the infusion pump or injection line that stops, or prevents treatment with CARIPUL®, go to your hospital emergency department immediately.

- Infection of the blood (sepsis/septicemia) is a serious common side effect in people taking CARIPUL®. Symptoms of sepsis include chills, with or without shaking, and fever. If you get any of these symptoms, go to your hospital emergency department immediately.

- Avoid situations that can lower blood pressure, including saunas, sunbathing or hot baths.

- Your doctor will arrange regular blood tests to check how well your blood clots.

Tell your healthcare professional about all the medicines you take, including drugs prescribed by other doctors and including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CARIPUL®:
- medicines used to prevent blood clots
- medicines used to dissolve blood clots
- medicines used for heart failure
- medicines used for high blood pressure
- medicines used for angina (chest pain)
- other medicines used to treat pulmonary hypertension
- medicines to treat inflammation or pain (also called 'NSAIDs')
- digoxin (a medicine used to treat heart disease)
- diuretics (water pill)

How to take CARIPUL®:
Initial Treatment
Your first treatment will be given to you in a hospital. This is because your doctor needs to monitor you and find the best dose for you.

You will start with an infusion of CARIPUL®. The dose will be increased, until your symptoms are relieved, and any side effects are manageable. Once the best dose has been found, a

permanent tube (also referred to as a line or central venous catheter) will be fitted into one of the large veins in your upper chest called a central vein. This is done because CARIPUL® needs to be given by continuous controlled infusion.

Your doctor will decide which type of catheter is best suited for you. The catheter is a thin soft flexible tube that is inserted under a local anaesthetic in the operating room. Sterile conditions are maintained during this procedure to avoid the risk of infection. You will not feel it inside your body. The catheter has been tunnelled into place inside your chest. The catheter has a Dacron fibre cuff which is under the skin. This will hold the catheter in place and avoid infection. The catheter may also be sutured into position.

The tip of the catheter lies in a vein that leads to the entrance of your heart. You can then be treated using an infusion pump that will deliver a prescribed amount of the drug through the catheter directly to your heart.

Your nurse will teach you how to care for the catheter, how to keep the skin around the catheter exit site clean and free from infection. You will learn how to change the dressing and to protect your skin. Your physician and nurse will make sure that you are comfortable in caring for the catheter exit site. It is very important that you follow all of their instructions carefully (see "***Steps for Caring for the Central Venous Catheter***" below).

Should you develop sudden fever, contact your doctor as soon as possible.

Continual Treatment
Your doctor or nurse will show you how to prepare and use CARIPUL® and will also advise you how to stop treatment if necessary. Stopping CARIPUL® must be done gradually. It is very important that you follow all their instructions carefully.

Steps for Reconstituting CARIPUL®
CARIPUL® comes as a powder in a glass vial. Before use, the powder must be:

- dissolved (reconstituted) in vial with only 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection.
- reconstituted product should be further diluted as directed with the same diluent used for reconstitution.
- CARIPUL® solution reconstituted with 5 mL Sterile Water for Injection or Sodium Chloride 0.9% Injection, and immediately diluted to the final concentration in the drug delivery reservoir can be administered per the conditions of use as outlined below:

Final concentration range	**Immediate administration**	**If stored for up to 8 days at 2° - 8°C**
≥3,000 ng/mL and <15,000 ng/mL	48 hours	24 hours
≥15,000 ng/mL	48 hours	48 hours

The following instructions explain how to reconstitute CARIPUL®. **They should supplement the instructions given to you by your doctor or nurse.**

CARIPUL® must be reconstituted with Sterile water for injection or 0.9% Sodium Chloride injection solution). Reconstituted CARIPUL® solution should not be mixed with other solutions or medicines prior to or during administration.

Your doctor will tell you how much CARIPUL® and Sterile Diluent you will need to use when making up your daily supply. The general procedures for reconstituting CARIPUL® solution are described below.

1. First, clean your worksite and gather your supplies. Wash your hands thoroughly and then open all the packages. Remove the vial caps from the vial containing Sterile Diluent and clean the tops of the vials with alcohol swabs.
2. Once you finish cleaning the tops of your vials and opening your supplies, attach a needle to the syringe. Now break the syringe seal by gently pulling the plunger out slightly and then pushing it back. Draw air into the syringe; the amount of air that you draw into the syringe should be equal to the amount of Sterile Diluent you've been instructed to withdraw from the vial. Insert the needle through the rubber seal of the vial and press the plunger down to inject the air into the vial. Once all the air has been injected, pull the plunger gently back up to withdraw the prescribed amount of Sterile Diluent. Without withdrawing the needle, invert the vial and syringe and tap the syringe gently so that any air bubbles trapped in the syringe rise towards the top. If necessary, depress the plunger gently to force the air bubbles out and then withdraw sufficient additional Sterile Diluent to restore the required volume in the syringe. Once the required volume has been drawn into the syringe, withdraw the needle.
3. Now insert the needle through the rubber seal of the CARIPUL® vial and inject the Sterile Diluent gently onto the side of the vial. Always direct the flow of Sterile Diluent towards the side of the vial and inject it gently so that the CARIPUL® doesn't foam. Allow the pressure to equalize and withdraw the needle from the vial. Now, mix the CARIPUL® by gently swirling the vial. Turn the vial upside down to catch any undissolved powder near the top. **Never shake the vials.** If you need to mix more than one vial of CARIPUL®, simply repeat this process.
4. Your doctor or nurse will advise you on the amount of reconstituted CARIPUL® to be withdrawn. First, by gently pulling the plunger back, fill the syringe with the amount of air that is equal to the amount of CARIPUL® to be withdrawn. Remember to wipe the tops of the vials with an alcohol swab. Now, insert the needle through the seal of the CARIPUL® vial and inject the air. Then pull the plunger gently back to withdraw the reconstituted CARIPUL® into the syringe. Remove any air that may be trapped in the syringe as described in step 2 above. Withdraw the needle and place the cap back on the syringe.
5. You are now ready to inject the CARIPUL® into your cassette. Remove the end cap from the cassette tubing; then carefully remove the needle from the syringe, discard in an appropriate manner and attach the syringe to the cassette tubing. Now, while holding the cassette in one hand, you can use the tabletop as a third hand while you push down on the syringe to inject the solution into the cassette. Once the syringe is empty, clamp the cassette tubing near the syringe, disconnect the syringe and cap the tubing with the red cap.
6. Now you will withdraw the contents of the Sterile Diluent vials and inject them into the cassette. Using a 60 cc syringe, attach a new needle to the syringe, break the seal on the syringe by pulling the plunger out and pushing it back in. Next, fill the syringe with the amount of air that is equal to the amount of Sterile Diluent you will remove from the first vial. Remember to wipe the top of the Sterile Diluent vial with an alcohol swab before you insert the needle. Once it is dry, insert the needle through the rubber seal, inject some of the air into the vial and allow the fluid to flow into the syringe. With the larger syringe, it may be easier to hold it in the vertical position. Push more air in as needed until you have withdrawn all of the contents of the vial. Remove any air that may be in the syringe as described in step 2 above. Once the vial is emptied, allow the pressure to equalize before

you pull the needle out. If you don't, you may lose fluid from the syringe or the vial and you would need to start the whole process over again. Withdraw the needle and place the cap back on the syringe.

7. Now you are ready to inject the first syringe full of Sterile Diluent into the cassette. To do this, first uncap the cassette tubing. Then carefully remove the needle from the syringe, discard in an appropriate manner and attach the syringe to the cassette tubing. Unclamp the cassette tubing and then carefully inject the solution into the cassette. When the syringe is empty, clamp the cassette tubing near the syringe, disconnect the syringe and cap the cassette tubing. You will repeat this same process to transfer the contents of the required Sterile Diluent vial as specified by your doctor or nurse into the cassette.
8. After you have completed the transfer of all the required Sterile Diluent, leave the syringe attached to the cassette tubing while you mix the solution. Gently invert the cassette at least 10 times, thoroughly mixing the CARIPUL®. Now you need to remove all the air from the cassette.
9. In order to remove the air inside the cassette, first you have to collect the air bubbles. Simply rotate the cassette around until all of the small bubbles join to form one big air pocket. Then tilt the cassette carefully so that the air pocket is in the corner where the tubing connects to the bag. To remove the air from the cassette, unclamp the tubing and pull back the plunger of the syringe until you see fluid fill the tubing. Then clamp the tubing near the connector, disconnect it and cap it with the red cap. To avoid any confusion, label the cassette with the date and time you made up the CARIPUL®.

Now put the cassette into the refrigerator until it is time to use it. Store it on the top shelf to avoid spilling any food or drink onto your cassette.

Steps for Administering CARIPUL® by a Continuous Infusion Pump

You will use a pump to receive medication by continuous delivery. The instructions for use may vary depending on the particular make and model of the pump you are using. To avoid any potential interruptions in CARIPUL® delivery, you should have access to a back-up infusion pump and intravenous infusion sets.

Infusion sets with an in-line 0.22 micron filter should be used.

Suitable ambulatory pumps to be used for the administration of CARIPUL® include:

- CADD-Solis VIP

Manufactured by Smiths Medical.

Pump accessories found compatible with the administration of CARIPUL® include:

- CADD disposable Medication Cassette Reservoir 100 mL from Smiths Medical.
- CADD extension set with in-line 0.2 micron filter (CADD extension set with male luer, 0.2-micron air-eliminating filter, clamp, and integral anti-siphon valve with male luer) from Smiths Medical.

Your doctor or nurse will give detailed instructions on how to use and care for the specific pump and accessories that you will use for administering the medicine (including changing the pump battery, cassette and tubing).

Steps for Caring for the Central Venous Catheter

Change the dressing on the catheter exit site 1 to 2 times per week or more frequently if needed. You will need the following equipment: dressing set, 2 sterile containers, povidone-

iodine antiseptic solution, gauze swabs, 70% alcohol, povidone-iodine antiseptic ointment, sterile cotton swabs, adhesive tape (nonallergenic), transparent dressing 10 cm x 12 cm or 6 cm x 7 cm.

Maintain sterile technique at all times. If you suspect that you have contaminated anything, discard the equipment and begin again.

1. Assemble equipment.
2. Stabilize catheter while removing old transparent dressing.
3. Open sterile dressing kit.
4. Pour alcohol into sterile container.
5. Pour povidone-iodine antiseptic solution into sterile container.
6. Squeeze povidone-iodine antiseptic ointment onto sterile field.
7. Open transparent dressings onto sterile field.
8. Remove old transparent dressing.
9. Clean the catheter exit site with povidone-iodine antiseptic solution soaked 2” x 2” gauze swabs, starting at the catheter exit site. Work outward in a circular extending motion extending to an 8 cm radius.
10. Repeat step 9 three times.
11. **Never return to the catheter exit site using the same swab.**
12. Repeat steps 9 and 10 using an alcohol soaked 2” x 2” gauze swab.
13. Apply povidone-iodine antiseptic ointment to the catheter exit site with a sterile cotton swab.
14. Apply new sterile transparent dressing.
15. Tape catheter to skin using ‘stress loop’.

Usual dose:
Your doctor will decide how much (i.e. dose) and the duration of CARIPUL® therapy that is right for you. The amount you are given is based on your body weight, and your type of illness. Your dose may be increased or decreased depending on how well you respond to treatment.

CARIPUL® is given by slow continuous infusion (drip) into a vein.

Overdose:
Seek urgent medical attention if you think you have used too much CARIPUL®. Symptoms of overdose may include headache, nausea, vomiting, diarrhea, fast heart rate, warmth or tingling, or feeling like you might pass out (feeling faint/dizziness), unconsciousness, or collapse.

If you think you have taken too much CARIPUL®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using CARIPUL®?

These are not all the possible side effects you may feel when taking CARIPUL®. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, CARIPUL® can cause side effects, but not everybody gets them.

Very common side effects
- headache
- jaw pain
- pain
- being sick (vomiting)
- feeling sick (nausea)
- diarrhea
- redness of your face (flushing)

Common side effects
- stomach discomfort or pain
- joint pain
- feeling anxious, feeling nervous
- rash
- pain at the injection site

Uncommon side effects
- sweating
- dry mouth

Very rare side effects
- feeling tired, weak
- feeling agitated
- pale skin
- redness at the injection site
- overactive thyroid gland

Tell your doctor or pharmacist if any of the side effects become severe or troublesome.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		**Go to the hospital immediately**
	Only if severe	In all cases	
COMMON Bleeding that lasts longer than usual or which cannot be stopped, bruising more easily than normal		✓	
Unusually slow or fast heartbeats, or feeling dizzy or faint, which can be signs of low blood pressure (hypotension)			✓
Blood infection (sepsis/ septicemia): chills, with or without shaking, and fever			✓
Chest pain			✓
UNCOMMON Build up of fluid in the lungs (pulmonary edema): swelling or difficulty breathing			✓

RARE Injection site infection: redness, tenderness, swelling or pus at infusion site		✓	
VERY RARE Injection site reaction: tenderness, burning, stinging, swelling, redness, blistering or peeling		✓	
Injection line blockage: dizziness, weakness and breathing difficulties			✓
Feeling of tightness around the chest			✓
Too much pumping of blood from the heart (high cardiac output failure): Leading to persistent cough, shortness of breath, fatigue, swelling of the legs and abdomen due to fluid build-up			✓
Ascites: Swelling due to build up of fluid around the stomach		✓	
Enlarged spleen: upper left abdominal discomfort, fullness or pain, problems digesting a large meal.		✓	
Heart attack: Feeling of tightness around the chest; pain radiating into the arm or jaw combined with shortness of breath, nausea and lightheadedness.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use CARIPUL® after the expiry date on the label.

Store the vials of CARIPUL® between 15-30°C. Protect from freezing.

Follow hospital rules when throwing away unused drug and other waste.

Keep out of reach and sight of children.

If you want more information about CARIPUL®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (www.janssen.com/canada) or by calling 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc., Toronto, Ontario, M3C 1L9

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