New
Ventavis®
(iloprost) Inhalation Solution

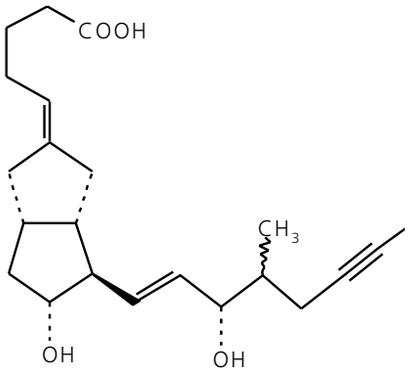
R_X Only

DESCRIPTION

Ventavis® (iloprost) Inhalation Solution is a clear, colorless, sterile solution containing 10 mcg/mL iloprost formulated for inhalation via the Prodose® AAD® (Adaptive Aerosol Delivery) System, a pulmonary drug delivery device. Each single-use glass ampule contains 2 mL (20 mcg) of the solution to be added to the Prodose® AAD® System medication chamber. Each mL of the aqueous solution contains 0.01 mg iloprost, 0.81 mg ethanol, 0.121 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.51 mg hydrochloric acid (for pH adjustment to 8.1) in water for injection. The solution contains no preservatives.

The chemical name for iloprost is (E)-(3aS,4R,5R,6aS)-hexahydro-5-hydroxy-4-[(E)-(3S,4RS)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Delta^{2(1H),\Delta}$-pentalenevaleric acid. Iloprost consists of a mixture of the 4R and 4S diastereomers at a ratio of approximately 53:47. Iloprost is an oily substance, which is soluble in methanol, ethanol, ethyl acetate, acetone and pH 7 buffer, sparingly soluble in buffer pH 9, and very slightly soluble in distilled water, buffer pH 3, and buffer pH 5.

The molecular formula of iloprost is $C_{22}H_{32}O_4$. Its relative molecular weight is 360.49. The structural formula is shown below:



CLINICAL PHARMACOLOGY

General

Iloprost is a synthetic analogue of prostacyclin PGI_2. Iloprost dilates systemic and pulmonary arterial vascular beds. It also affects platelet aggregation but the relevance of this effect to the treatment of pulmonary hypertension is unknown. The two diastereoisomers of iloprost differ in their potency in dilating blood vessels, with the 4S isomer substantially more potent than the 4R isomer.

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Pharmacokinetics

General

In pharmacokinetic studies in animals, there was no evidence of interconversion of the two diastereoisomers of iloprost. In human pharmacokinetic studies, the two diastereoisomers were not individually assayed.

Iloprost administered intravenously has linear pharmacokinetics over the dose range of 1 to 3 ng/kg/min. The half-life of iloprost is 20 to 30 minutes. Following inhalation of iloprost (5.0 mcg) patients with pulmonary hypertension have iloprost peak serum levels of approximately 150 pg/mL. Iloprost was generally not detectable in the plasma 30 minutes to 1 hour after inhalation.

Absorption and Distribution

The absolute bioavailability of inhaled iloprost has not been determined.

Following intravenous infusion, the apparent steady-state volume of distribution was 0.7 to 0.8 L/kg in healthy subjects. Iloprost is approximately 60% protein-bound, mainly to albumin, and this ratio is concentration-independent in the range of 30 to 3000 pg/mL.

Metabolism and Excretion

Clearance in normal subjects was approximately 20mL/min/kg. Iloprost is metabolized principally via ß-oxidation of the carboxyl side chain. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form. In animal experiments, tetranor-iloprost was pharmacologically inactive.

In vitro studies reveal that cytochrome P450-dependent metabolism plays only a minor role in the biotransformation of iloprost.

A mass-balance study using intravenously and orally administered [^{3}H]-iloprost in healthy subjects (n=8) showed recovery of total radioactivity over 14 hours post-dose was 81%, with 68% and 12% recoveries in urine and feces, respectively.

Special Populations

Liver Function Impairment

Inhaled iloprost has not been evaluated in subjects with impaired hepatic function. However, in an intravenous iloprost study in patients with liver cirrhosis, the mean clearance in Child Pugh Class B subjects (n=5) was approximately 10 mL/min/kg

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(half that of healthy subjects). Following oral administration, the mean $AUC_{0\text{-}8h}$ in Child Pugh Class B subjects (n=3) was 1725 pg*h/mL compared to 117 pg*h/mL in normal subjects (n=4) receiving the same oral iloprost dose. In Child Pugh Class A subjects (n=5), the mean $AUC_{0\text{-}8h}$ was 639 pg*h/mL. Although exposure increased with hepatic impairment, there was no effect on half-life.

Renal Function Impairment

Inhaled iloprost has not been evaluated in subjects with impaired renal function. However, in a study with intravenous infusion of iloprost in patients with end-stage renal failure requiring intermittent dialysis treatment (n=7), the mean $AUC_{0\text{-}4h}$ was 230 pg*h/mL compared to 54 pg*h/mL in patients with renal failure (n=8) not requiring intermittent dialysis and 48 pg*h/mL in normals. The half-life was similar in both groups. The effect of dialysis on iloprost exposure has not been evaluated.

Clinical Trials

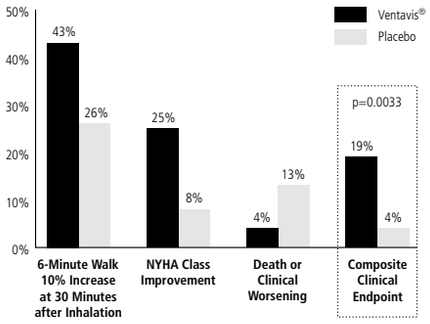
A randomized, double-blind, multi-center, placebo-controlled trial was conducted in 203 adult patients (inhaled iloprost: n=101; placebo: n=102) with NYHA Class III or IV pulmonary arterial hypertension (PAH, WHO Group I; idiopathic in 53%, associated with connective tissue disease, including CREST and scleroderma, in 17%, or associated with anorexigen use in 2%) or pulmonary hypertension related to chronic thromboembolic disease (WHO Group IV; 28%). Inhaled iloprost (or placebo) was added to patients' current therapy, which could have included anticoagulants, vasodilators (e.g. calcium channel blockers), diuretics, oxygen, and digitalis, but not PGI_2 (prostacyclin or its analogues) or endothelin receptor antagonists. Patients received 2.5 or 5.0 mcg of iloprost by repeated inhalations 6 to 9 times per day during waking hours. The mean age of the entire study population was 52 years and 68% of the patients were female. The majority of patients (59%) were NYHA Class III. The baseline 6-minute walk test values reflected a moderate exercise limitation (the mean was 332 meters for the iloprost group and 315 meters for the placebo group). In the iloprost group, the median daily inhaled dose was 30 mcg (range of 12.5 to 45 mcg/day). The mean number of inhalations per day was 7.3. Ninety percent of patients in the iloprost group never inhaled study medication during the nighttime.

The primary efficacy endpoint was clinical response at 12 weeks, a composite endpoint defined by:

a) improvement in exercise capacity (6-minute walk test) by at least 10% versus baseline evaluated 30 minutes after dosing, b) improvement by at least one NYHA class versus baseline, and c) no death or deterioration of pulmonary hypertension. Deterioration required two or more of the following criteria: 1) refractory systolic blood pressure < 85 mmHg, 2) worsening of right heart failure with cardiac edema, ascites, or pleural effusion despite adequate background therapy, 3) rapidly progressive cardiogenic hepatic failure (e.g. leading to an increase of GOT or GPT to > 100 U/L, or total bilirubin ≥ 5 mg/dL), 4) rapidly progressive cardiogenic renal failure (e.g. decrease of estimated creatinine clearance to ≤ 50% of baseline), 5) decrease in 6-minute walking distance by ≥ 30% of baseline value, 6) new long-term need for i.v. catecholamines or diuretics, 7) cardiac index ≤ 1.3 L/min/m^2, 8) CVP ≥ 22 mmHg despite adequate diuretic therapy, and 9) SVO_2 ≤ 45% despite nasal O_2 therapy.

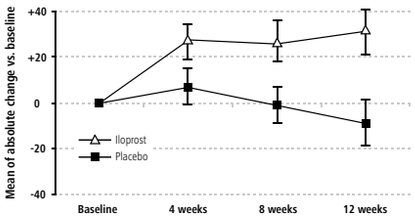
Although effectiveness was seen in the full population (response rates for the primary composite endpoint of 17% and 5%; p=0.007), there was inadequate evidence of benefit in patients with pulmonary hypertension associated with chronic thromboembolic disease (WHO Group IV); the results presented are therefore those related to patients with PAH (WHO Group I). The response rate for the primary efficacy endpoint among PAH patients was 19% for the iloprost group, compared with 4% for the placebo group (p=0.0033). All three components of the composite endpoint favored iloprost (Figure 1).

Figure 1: Composite Primary Endpoint for PAH Patients (WHO Group I)



The absolute change in 6-minute walk distance (Figure 2) measured (using all available data and no imputation) 30 minutes after inhalation among patients with PAH was greater in the iloprost group compared to the placebo group at all time points. At Week 12, the placebo-corrected difference was 40 meters (p<0.01). When walk distance was measured immediately prior to inhalation, the improvement compared to placebo was approximately 60% of the effect seen at 30 minutes after inhalation.

Figure 2: Change (Mean ± SEM) in 6-Minute Walk Distance 30 Minutes post Inhalation in PAH Patients (WHO Group I)



The effect of Ventavis® in various subgroups is shown in Table 1.

Table 1: Treatment Effects by Subgroup among PAH Patients (WHO Group I)

	Composite Clinical Endpoint			
	n	**Ventavis**	**n**	**Placebo**
All Subjects with PAH	68	13 (19%)	78	3 (4%)
NYHA III	40	7 (18%)	47	2 (4%)
NYHA IV	28	6 (21%)	31	1 (3%)
Male	23	5 (22%)	24	0 (0%)
Female	45	8 (18%)	54	3 (6%)
Age ≤ 55	41	6 (15%)	40	2 (5%)
Age > 55	27	7 (26%)	38	1 (3%)
	6-Minute Walk*			
	n	**Ventavis (Mean ± SD)**	**n**	**Placebo (Mean ± SD)**
All Subjects with PAH	64	31 ± 76	65	-9 ± 79
NYHA III	39	24 ± 72	43	-16 ± 86
NYHA IV	25	43 ± 82	22	6 ± 63
Male	21	37 ± 81	21	-22 ± 77
Female	43	29 ± 74	44	-2 ± 81
Age ≤ 55	39	24 ± 79	32	-5 ± 78
Age > 55	25	42 ± 71	33	-13 ± 81

*Change from baseline to 12 Weeks with measurement 30 minutes after dosing, based on all available data.

Treatment-related effects on hemodynamic measures (e.g. PVR, mPAP, CO, SVO_2) have not been demonstrated.

INDICATIONS AND USAGE

Ventavis® is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms. In controlled trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration (see **CLINICAL PHARMACOLOGY, Clinical Trials**). Ventavis has not been adequately studied with concomitant use of other approved therapies for pulmonary arterial hypertension.

CONTRAINDICATIONS

There are no known contraindications.

WARNINGS

Ventavis is intended for inhalation administration only via the Prodose® AAD® System, a pulmonary drug delivery device (See **DOSAGE AND ADMINISTRATION**). It has not been studied with any other nebulizers.

Because of the risk of syncope, vital signs should be monitored while initiating Ventavis. In patients with low systemic blood pressure, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg. Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope. Syncope can also occur in association with pulmonary arterial hypertension, particularly in association with physical exertion. The occurrence of exertional syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.

Should signs of pulmonary edema occur when inhaled iloprost is administered in patients with pulmonary hypertension, the treatment should be stopped immediately. This may be a sign of pulmonary venous hypertension.

PRECAUTIONS

General

Ventavis® solution should not be allowed to come into contact with the skin or eyes; oral ingestion of Ventavis solution should be avoided.

Direct mixing of Ventavis with other medications in the Prodose® AAD® System has not been evaluated.

Ventavis has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections.

Information for Patients

Patients receiving Ventavis® should be advised to use the drug only as prescribed with the Prodose® AAD® System, a pulmonary drug delivery device, following the manufacturer's instructions (see **DOSAGE AND ADMINISTRATION**). Patients should be trained in proper administration techniques including dosing frequency, ampule dispensing, Prodose® AAD® System operation, and equipment cleaning.

Patients should be advised that they may have a fall in blood pressure with Ventavis, so they may become dizzy or even faint. They should stand up slowly when they get out of a chair or bed. If fainting gets worse, patients should consult their physicians about dose adjustment.

Patients should be advised that Ventavis should be inhaled at intervals of not less than 2 hours and that the acute benefits of Ventavis may not last 2 hours.

Drug Interactions

In studies in normal volunteers, there was no pharmacodynamic interaction between intravenous iloprost and either nifedipine, diltiazem, or captopril. However, iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. Since iloprost inhibits platelet function, there is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants. During clinical trials, iloprost was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, corticosteroids, and other medications. Intravenous infusion of iloprost had no effect on the pharmacokinetics of digoxin. Acetylsalicylic acid did not alter the clearance (pharmacokinetics) of iloprost. Although clinical studies have not been conducted, *in vitro* studies of iloprost indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Iloprost was not mutagenic in bacterial and mammalian cells in the presence or absence of extrinsic metabolic activation. Iloprost did not cause chromosomal aberrations *in vitro* in human lymphocytes and was not clastogenic *in vivo* in NMRI/SPF mice. There was no evidence of a tumorigenic effect of iloprost clathrate (13% iloprost by weight) in Sprague-Dawley rats dosed orally for up to 8 months at doses of up to 125 mg/kg/day (Cmax of 45 ng/mL serum), followed by 16 months at 100 mg/kg/day, or in Crl: CD-1®(ICR)BR albino mice dosed orally for up to 24 months at doses of up to 125 mg/kg/day (Cmax of 156 ng/mL serum).

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The recommended clinical dosage regimen for iloprost (5.0 mcg) affords a serum Cmax of 0.16 ng/mL. Fertility of males or females was not impaired in Han-Wistar rats at intravenous doses up to 1 mg/kg/day.

Pregnancy

Pregnancy Category C. In developmental toxicity studies in pregnant Han-Wistar rats, continuous intravenous administration of iloprost at a dosage of 0.01 mg/kg daily (serum levels not available) led to shortened digits of the thoracic extremity in fetuses and pups. In comparable studies in pregnant Sprague-Dawley rats which received iloprost clathrate (13% iloprost by weight) orally at dosages of up to 50 mg/kg/day (Cmax of 90 ng/mL), in pregnant rabbits at intravenous dosages of up to 0.5 mg/kg/day (Cmax of 86 ng/mL), and in pregnant monkeys at dosages of up to 0.04 mg/kg/day (serum levels of 1 ng/mL), no such digital anomalies or other gross-structural abnormalities were observed in the fetuses/pups. However, in gravid Sprague-Dawley rats, iloprost clathrate (13% iloprost) significantly increased the number of non-viable fetuses at a maternally toxic oral dosage of 250 mg/kg/day and in Han-Wistar rats was found to be embryolethal in 15 of 44 litters at an intravenous dosage of 1 mg/kg/day. There are no adequate and well-controlled studies in pregnant women. Ventavis® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Ventavis is excreted in human milk. In studies with Han-Wistar rats, higher mortality was observed in pups of lactating dams receiving iloprost intravenously at 1 mg/kg daily. In Sprague-Dawley rats, higher mortality was also observed in nursing pups at a maternally toxic oral dose of 250 mg/kg/day of iloprost clathrate (13% iloprost by weight). It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Ventavis, a decision to discontinue nursing should be made, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Ventavis did not include sufficient numbers of subjects age 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious,

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usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Hepatic or Renal Impairment

Ventavis has not been studied in patients with pulmonary hypertension and hepatic or renal impairment, both of which increase mean AUC in otherwise normal subjects (see **CLINICAL PHARMACOLOGY, Special Populations**).

ADVERSE REACTIONS

Safety data on Ventavis® were obtained from 215 patients with pulmonary arterial hypertension receiving iloprost in two 12-week clinical trials and two long-term extensions. Patients received inhaled Ventavis for periods from 1 day to more than 3 years. The median number of weeks of exposure was 15 weeks. Forty patients completed 12 months of open-label treatment with iloprost.

The following table shows adverse events reported by at least 4 iloprost patients and reported at least 3% more frequently for iloprost patients than placebo patients in the 12-week placebo-controlled study.

Table 2: Adverse Events in Phase 3 Clinical Trial

Adverse Events	Iloprost (n=101)	Placebo (n=102)	Placebo subtracted %
Vasodilation (flushing)	27	9	18
Cough increased	39	26	13
Headache	30	20	10
Trismus	12	3	9
Insomnia	8	2	6
Nausea	13	8	5
Hypotension	11	6	5
Vomiting	7	2	5
Alk phos increased	6	1	5
Flu syndrome	14	10	4
Back pain	7	3	4
Abnormal lab test	7	3	4
Tongue pain	4	0	4
Palpitations	7	4	3
Syncope	8	5	3
GGT increased	6	3	3
Muscle cramps	6	3	3
Hemoptysis	5	2	3
Pneumonia	4	1	3

Serious adverse events reported with the use of inhaled iloprost and not shown in Table 2 include congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure.

Adverse events with higher doses

In a study in healthy volunteers (n=160), inhaled doses of iloprost solution were given every 2 hours, beginning with 5.0 mcg and increasing up to 20 mcg for a total of 6 dose inhalations (total cumulative dose of 70 mcg) or up to the highest dose tolerated in a subgroup of 40 volunteers. There were 13 subjects (32%) who failed to reach the highest scheduled dose (20 mcg). Five were unable to increase the dose because of (mild to moderate) transient chest pain/discomfort/tightness, usually accompanied by headache, nausea, and dizziness. The remaining 8 subjects discontinued for other reasons.

OVERDOSAGE

In clinical trials of Ventavis®, no case of overdose was reported. Signs and symptoms to be anticipated are extensions of the dose-limiting pharmacological effects, including hypotension, headache, flushing, nausea, vomiting, and diarrhea. A specific antidote is not known. Interruption of the inhalation session, monitoring, and symptomatic measures are recommended.

DOSAGE AND ADMINISTRATION

Ventavis is intended to be inhaled using the Prodose® AAD® System, a pulmonary drug delivery device. The first inhaled dose should be 2.5 mcg (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 mcg and maintained at that dose. Ventavis should be taken 6 to 9 times per day (no more than every 2 hours) during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 mcg (5.0 mcg 9 times per day).

Direct mixing of Ventavis with other medications in the Prodose® AAD® System has not been evaluated. To avoid potential interruptions in drug delivery due to equipment malfunctions, the patient should have easy access to a back-up Prodose® AAD® System.

Each inhalation treatment requires one single-use ampule. Each single-use ampule delivers 20 mcg/2 mL to the medication chamber of the Prodose® AAD® System, and delivers a nominal dose of either 2.5 mcg or 5.0 mcg to the mouthpiece.

For each inhalation session, the entire contents of one opened ampule of Ventavis® should be transferred into the Prodose® AAD® System medication chamber immediately before use. After each inhalation session, any solution remaining in the medication chamber should be discarded. Use of the remaining solution will result in unpredictable dosing. Patients should follow the manufacturer's instructions for cleaning the Prodose® AAD® System components after each dose administration.

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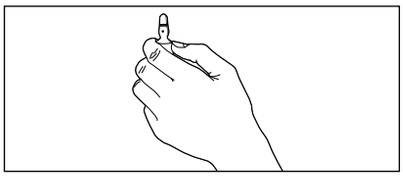
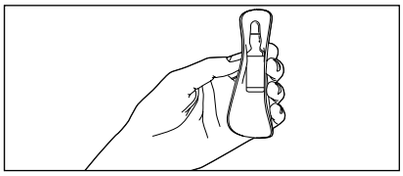
Preparation

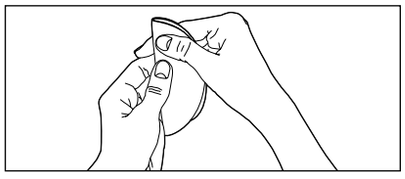
1. With one hand, hold the bottom of the ampule with the blue dot facing away from your body.



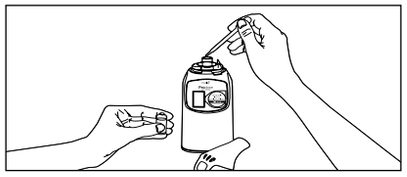
2. With the other hand, wrap the included rubber pad around the entire ampule.



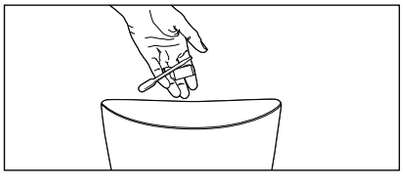
3. Using your thumbs, break open the neck of the ampule by snapping the top toward you.



4. Transfer the entire contents of the ampule into the medication chamber of the Prodose® AAD® System.



5. Safely dispose of the open ampule out of the reach of children and as instructed by your healthcare practitioner.



6. Follow the instructions provided by the drug manufacturer for administration of the Ventavis® dose and maintenance of the Prodose® AAD® System.

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Use of Ventavis with other approved treatments for pulmonary hypertension has not been studied. Should patients deteriorate on this treatment, alternative treatments should be considered. Several patients whose status deteriorated while on Ventavis were successfully switched to intravenous epoprostenol.

Dosage and Administration in Hepatic Impairment

Because iloprost elimination is reduced in patients with impaired liver function (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**), caution should be exercised during iloprost therapy in patients with at least Child Pugh Class B hepatic impairment.

Dosage and Administration in Renal Impairment

Dose adjustment is not required in patients not on dialysis. The effect of dialysis on iloprost is unknown. Use caution in treating patients on dialysis (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

HOW SUPPLIED

Ventavis® (iloprost) Inhalation Solution is supplied in cartons of 30 or 100 clear glass single-use ampules (20 mcg iloprost per 2 mL ampule):
30 ampule cartons: NDC 10148-101-30
100 ampule cartons: NDC 10148-101-01

STORAGE

Store at 20–25°C (68–77°F)
Excursions permitted to 15–30°C (59–86°F)
[See USP Controlled Room Temperature]

Distributed by:

CŌTHERIX™

5000 Shoreline Court, Ste. 101, South San Francisco, CA 94080