Ventavis

(iloprost) Inhalation Solution

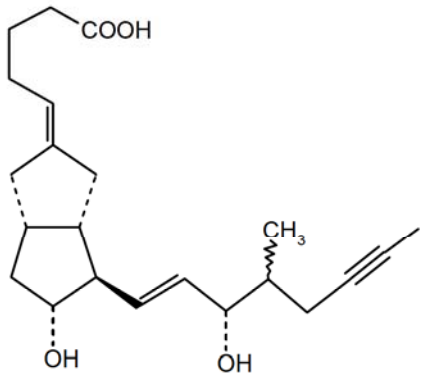
R_X Only

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*)-(3a*S*,4*R*,5*R*,6a*S*)-hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Lambda^{2(1H),\Delta}$-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.

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 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 20 mL/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 (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.

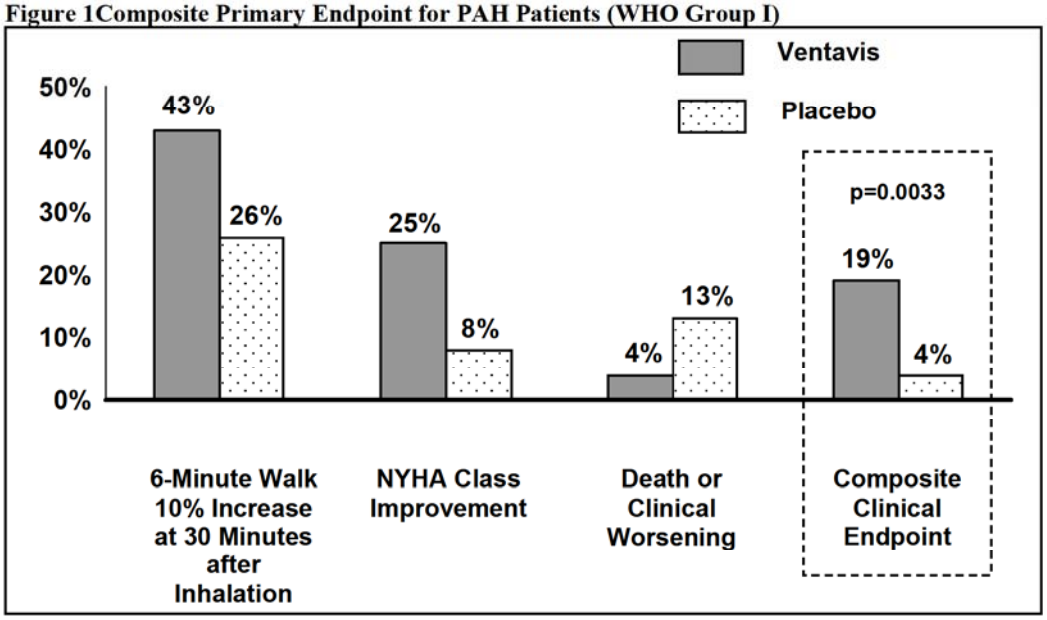
Clinical Trials

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 $\geq$ 5 mg/dL), 4) rapidly progressive cardiogenic renal failure (e.g. decrease of estimated creatinine clearance to $\leq$ 50% of baseline), 5) decrease in 6-minute walking distance by $\geq$ 30% of baseline value, 6) new long-term need for i.v. catecholamines or diuretics, 7) cardiac index $\leq$ 1.3 L/min/m^2, 8) CVP $\geq$ 22 mmHg despite adequate diuretic therapy, and 9) $SVO_2 \leq$ 45% despite nasal O_2 therapy.

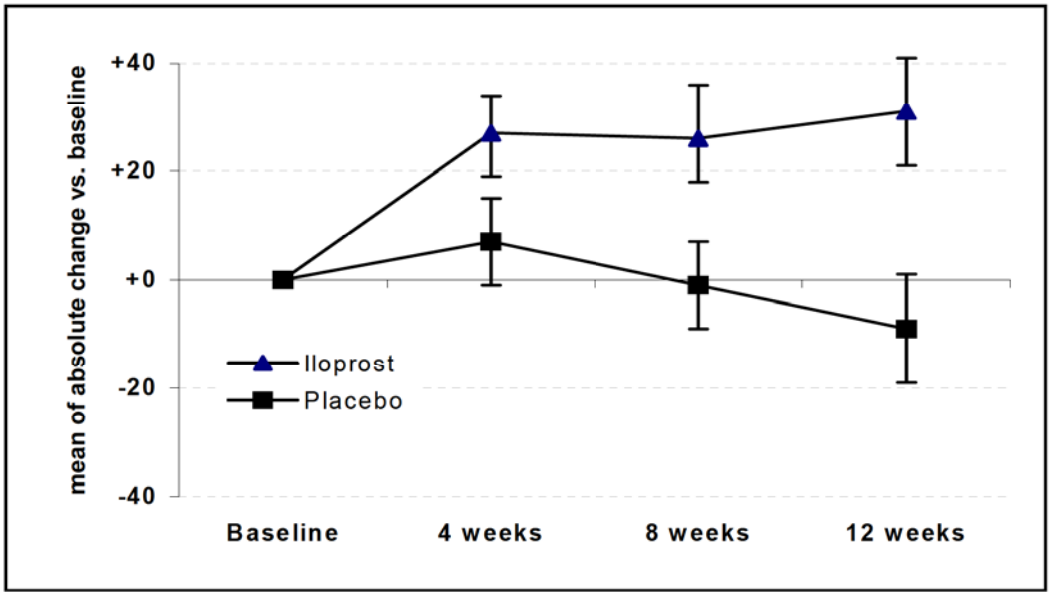
Although effectiveness was seen in the full population (response rates for the primary composite endpoint of 17% and 5%; p=0.007), there was inadequate evidence of benefit in patients with pulmonary hypertension associated with chronic thromboembolic disease (WHO Group IV); the results presented are 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 1Composite 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				6-Minute Walk*			
	n	Ventavis	n	Placebo	n	Ventavis (mean ± SD)	n	Placebo (mean ± SD)
All Subjects with PAH	68	13 (19%)	78	3 (4%)	64	31 ± 76	65	-9 ± 79
NYHA III	40	7 (18%)	47	2 (4%)	39	24 ± 72	43	-16±86
NYHA IV	28	6 (21%)	31	1 (3%)	25	43 ± 82	22	6±63
Male	23	5 (22%)	24	0 (0%)	21	37 ± 81	21	-22 ± 77
Female	45	8 (18%)	54	3 (6%)	43	29 ± 74	44	-2 ± 81
Age ≤ 55	41	6 (15%)	40	2 (5%)	39	24 ± 79	32	-5 ± 78
Age > 55	27	7 (26%)	38	1 (3%)	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

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