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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-779**

**Clinical Pharmacology and Biopharmaceutics  
Review**

## MEMORANDUM

**From:** B. Nhi Beasley, Pharm.D.

**To:** Division of Cardio-Renal Drug Products

**Subj:** Amendment to Clinical Pharmacology and Biopharmaceutics Review for  
NDA 21-779 (iloprost inhalation solution, Ventavis®)

**Date:** December 23, 2004

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The original review by Dr. Robert Kumi recommends using an initial dose of 1.25 ug in patients with Child Pugh Class B hepatic impairment, patients with a creatinine clearance (CLcr) less than or equal to 30 mL/min and in patients requiring dialysis. The actual effect of dialysis on iloprost was not studied. Because the 1.25 ug dose was not available, the Clinical Pharmacology Reviewers were asked to determine if increasing the dosing interval while maintaining the initial dose of 2.5 ug (sponsor recommended initial dose for all patients) would be acceptable.

Further analysis by Dr. Atul Bhattaram shows that in hepatic impairment patients, while the clearance of oral iloprost increases, the half-life remains similar in healthy volunteers ( $2.1 \pm 0.6$  min) compared to Child Pugh Class A ( $1.1 \pm 0.6$  min) and B ( $1.5 \pm 0.3$  min) patients. Thus, it is likely that there are volume changes that were not reported in addition to the reported clearance changes.

Further analysis of the renal impairment study shows that patients with impaired renal function (includes severe renal impairment,  $CLcr \leq 30$  mL/min) have similar exposure compared to subjects with normal renal function (As noted in Dr. Kumi's review on page 21). Since iloprost is extensively metabolized, it is also highly unlikely that renal impairment will affect iloprost pharmacokinetics. Interestingly, patients with  $CLcr \leq 30$  mL/min and requiring dialysis had three-fold higher concentrations than patients with moderate to severe renal impairment not requiring dialysis ( $CLcr$  around 10 - 40 mL/min). The effect of dialysis was not studied. Thus, although the effect of dialysis is unknown, patients requiring dialysis had higher exposure to iloprost than renal impairment patients not requiring dialysis.

The following changes are recommended for the iloprost label:

1. Under Pharmacokinetics / General:

"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."

*Rationale: The differences in reported half-life between the different routes of administration are a reflection of the assay sensitivity. To avoid confusion, only one half-life should be described in the label (e.g., the half-life with the most credibility).*

2. All “clearance” wording in the special populations section should be replaced with “mean AUC” and their corresponding values. Specifically,

#### **“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<sub>0-8h</sub> 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<sub>0-8h</sub> 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, patients with end-stage renal failure requiring intermittent dialysis treatment (n=7) the mean AUC<sub>0-4h</sub> was 230 pg\*h/mL compared to 54 pg\*h/mL in patients with renal failure (n=8) not requiring intermittent dialysis. The half-life was similar in both the groups. The effect of dialysis on iloprost exposure has not been evaluated.”

*Rationale: Avoid any confusion or an assumption that decreases in clearance mean that one can increase the dosing interval.*

3. Add the following to the precautions section:

##### **“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**).”

4. Change the Dosing and Administration section to the following:

##### **“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**).”

CC list: HFD-110: NDA 21-779; HFD-860: (Marroum, Mehta, Rahman, Gobburu, Bhattaram, KumiR); CDER Central Document Room

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