CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20845
IND: [redacted]

SUBMISSION DATES: May 24, 1999
August 13, 1999

DRUG NAME: Nitric Oxide gas for inhalation
INOmax™

FORMULATION: 100 & 800 parts per million (ppm)
DOSE: 20 ppm up to 14 days

INDICATION: hypoxemic respiratory failure in the term and near-term newborn in conjunction with mechanical ventilation

SPONSOR: INO Therapeutics, Inc.

REVIEWER: B. Nhi Nguyen, Pharm.D.

SUBMISSION: New Drug Application

SUMMARY

The sponsor is seeking the approval of inhaled nitric oxide (I-NO), 100 and 800 parts per million (ppm), for use in hypoxemic respiratory failure in the term and near-term newborn. The sponsor submitted a paper NDA that cites, for safety and efficacy, one large randomized, controlled, multicenter trial conducted in neonates with hypoxic respiratory failure, one large randomized, double-blind, placebo-controlled trial conducted in neonates with primary pulmonary hypertension (PPHN), and some other studies and case reports that include a total of 188 neonates in whom I-NO was used for PPHN. A randomized, double-blind, placebo-controlled study examining safety in 155 neonates with PPHN was also cited in the label. Additionally, eight studies were cited in the pharmacokinetic section of the label. One of these was the large randomized, double-blind, placebo-controlled trial conducted in neonates with PPHN. In this study, the investigators reported methemoglobin and nitrogen dioxide (NO_2) concentrations. The other seven studies included healthy adults in the treatment arm. One of these seven studies also included a severe heart failure patient treatment arm.

Inhaled NO (I-NO), a gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%), is a potent, local and selective pulmonary vasodilator. I-NO decreases pulmonary artery pressure and increases the partial pressure of arterial oxygen (PaO_2) leading to increased blood flow to the lungs. I-NO enhances V/Q matching by redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios towards regions with normal ratios.

Between 75-90% of I-NO is absorbed by the alveoli. After inhalation, NO immediately binds to hemoglobin. This subsequently produces methemoglobin and nitrate. These are the primary products that enter the systemic circulation. Methemoglobin is primarily metabolized by

methemoglobin reductase to form hemoglobin and nitrate. Thus, nitrate is the final metabolite formed from nitric oxide by all pathways. Nitrates are eliminated principally by the kidney.

RECOMMENDATION

The application does not completely fulfill the requirement of the Office of Clinical Pharmacology and Biopharmaceutics since the pharmacokinetic information in the target population was not submitted. Comments 1-8 and the labeling comment should be forwarded to the sponsor.

TABLE OF CONTENTS

BACKGROUND

The sponsor is seeking the approval of inhaled nitric oxide (I-NO), 100 and 800 parts per million (ppm), for use in hypoxemic respiratory failure in the term and near-term newborn. I-NO is a potent, local and selective pulmonary vasodilator that acts from the outer surface of the pulmonary vessels. I-NO decreases pulmonary artery pressure and increases the partial pressure of arterial oxygen (PaO_2) leading to increased blood flow to the lungs. I-NO enhances ventilation/perfusion (V/Q) matching, the appropriate contact between alveolar gas and pulmonary capillary blood, by redistributing pulmonary blood flow away from lung regions with low V/Q ratios towards regions with normal ratios.

Structure

$\cdot \bar{N}{=}\bar{O}:$ nitric oxide

The recommended safe and effective dose is 20 ppm of INOmax as a constant inhalation for up to 14 days until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

Formulation

I-NO is a gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%)

Deliver System

The sponsor recommends I-NO be delivered through an FDA approved NO delivery device, such as INOvent™ delivery device. Precise monitoring of inspired NO and NO_2 should be instituted, using a properly calibrated analysis device with alarms. This system should be calibrated using a precisely defined calibration mixture of NO and NO_2, such as INOcal™. Sample gas for analysis should be drawn before the Y-piece, proximal to the patient.

SUMMARY OF BIOAVAILABILITY / PHARMACOKINETICS

Bioavailability

Food effects

It is possible that foods rich in nitrates may interact with I-NO. However, this has not been studied and may not be relevant to the neonatal population. The effect of parenteral nutrition in neonates is unknown.

Pharmacokinetics

Absorption / Uptake and Distribution

Absorption of I-NO has ranged from 66% to 99% in healthy adult volunteers. The majority of I-NO traverses the pulmonary capillary bed where it binds with oxyhemoglobin (60-100% oxygen saturated) to form methemoglobin and nitrate (NO_{3-}). I-NO can also combine with deoxygenated hemoglobin to form nitrosylhemoglobin which is rapidly converted into nitrogen oxides and methemoglobin upon exposure to oxygen. NO also undergoes direct conversion to nitrite and

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