CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

MEDICAL REVIEW(S)

McDonald

OCT 29 1999

Primary Medical Review of Inhaled Nitric Oxide (I-NO)

NDA 20-845

Food and Drug Administration
Division of Cardio-Renal Drug Products (HFD-110)

October 29, 1999

By
Douglas C. Throckmorton, M.D.

Table of Contents

Table of Contents (cont)

NDA: 20-845

NAME OF DRUG: Inhaled Nitric Oxide (I-NO)
TRADE NAME: INOmax
FORMULATION: Gas for inhalation
RELATED APPLICATION: None

DATE OF SUBMISSION: 5.25.99
DATE RECEIVED BY FDA: 5.26.99
DATE ASSIGNED TO CURRENT REVIEWER: 6.17.97(see below)
DATE REVIEW COMPLETED: 10.29.99

PROPOSED INDICATION: Treatment of hypoxic respiratory failure in newborns

SPONSOR/MONITORS: INO Therapeutics, Inc.

/S/ 10.29

Douglas C. Throckmorton, M.D.
Primary Medical Reviewer

0.0 Overall Summary of Efficacy and Safety for I-NO

Inhaled Nitric Oxide (I-NO) has been proposed as a treatment for hypoxic respiratory failure in neonates. Clinical support for this indication comes from four clinical trials conducted in this population and submitted as part of this NDA, as well as an extensive published literature on the use of I-NO in this setting. Three of these trials were previously reviewed as part of an earlier NDA submission by the sponsor. The fourth trial was completed more recently and is reviewed as part of the present document.

The data from three trials (NINOS, INO-01/ -02 and CINRGI) demonstrate that I-NO administration is associated with a significant decrease in the use of extra-corporeal membrane oxygenation (ECMO), an invasive method of oxygenating the blood. This effect of I-NO to decrease ECMO use may well be due to the acute effect of I-NO to improve oxygenation, rather than due to any other beneficial effect on the course of the disease causing the hypoxic respiratory failure. In support of this contention, no beneficial effect of I-NO on mortality or any other clinical endpoint was demonstrated by the available data. No effect of I-NO on mortality (beneficial or adverse) has been demonstrated by the data. The effect of I-NO to improve oxygenation is significant, however, and avoidance of ECMO is a clinically-desirable outcome. In the absence of hard clinical benefit (e.g., decreased mortality, fewer days of hospitalization) the safety of I-NO needs to be firmly established prior to allowing its non-investigational use.

The following safety issues have been raised during one or both of my reviews:

1) The safety database included small number of subjects, and for most adverse events, the INO-01/ -02 was the primary source of information. Given the baseline differences between the subjects in the INO-01/ -02 and the other trials, extrapolating between the two populations is also difficult, and open to serious errors of omission due to inadequate data. These difficulties have been alleviated to some extent by the addition of 97 additional patients who were exposed to I-NO, bringing the total number of children exposed to I-NO in the NDA database to 375. The difficulties with differences in baseline characteristics are again present in the CINRGI trial, complicating its interpretation. Another potentially confounding variable between the CINRGI trial and the previous trials is the lower dose of I-NO administered in CINRGI (20 ppm reduced to 5 ppm if possible), compared with the NINOS and INO-01/ -02 trials (20-80 ppm).

2) The available safety database in the original NDA raised several potential safety issues. The most troubling of the adverse events, raised in the original medical review, was the possible association of I-NO with acute and chronic pulmonary toxicities. This association, like all of the safety data, relied on small numbers of subjects, although the association was plausible, given the available data. The addition of the CINRGI trial data, along with additional long-term follow-up data from NINOS and INO-01/ -02 has allayed some of the concerns, especially regarding the occurrence of chronic injury. The existing database is inadequate, however, to exclude the occurrence of pulmonary toxicity in association with the use of I-NO.

3) There was a definite association of I-NO with the development of methemoglobinemia and elevated NO_2 concentrations, identified in the NINOS and INO-01/ -02 trials (especially at the 80 ppm dose). This concern is minimized with the use of the lower doses of I-NO in the CINRGI trial (and the proposed dose for the label).

4) Several other adverse events were also possibly linked to the administration of I-NO based on the data available in 1997, although the data were insufficient to determine the seriousness of these potential adverse events, or to determine their duration or dose-response. The addition of the CINRGI data has resolved some of these safety concerns, and no new safety concerns have arisen as a result of the CINRGI trial review. The available data does suggest that rapid discontinuation of I-NO is associated with rebound hypoxia in some patients.

5) For some adverse events of interest, no data were obtained at all. Most critical of these was the effect of I-NO on coagulation parameters. Other clinical events for which we have either scarce or no clinical data include: musculoskeletal injury; non-glomerular renal injury; effects on the cardiac conduction system, and effects on serum electrolytes.

6) The number of patients exposed to I-NO is too small to adequately assess the potential interactions of I-NO with disease states, patient demographics and concomitant medications. The potential interaction of I-NO with other drugs is of particular importance for drugs commonly used to treat this condition, such as steroids and vasodilators (with the exception of tolazoline).

7) Finally, an issue that cannot be resolved from the database is the potential genotoxicity and carcinogenicity of I-NO. The available data on the genotoxicity of I-NO are mixed (see section 4.1 in my 1997 review for details). It is true that the duration of exposure to I-NO is limited in these studies, and that I-NO is produced (at many-fold lower concentrations) intracellularly. However, the cumulative years of risk for a newborn who receives I-NO is appreciably longer than an adult.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.