CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

ADMINISTRATIVE DOCUMENTS

RHPM Overview of NDA 20-845
INOmax (nitric oxide) Inhaled
Update November 14, 1999

Type: 1P
Receipt Date: May 26, 1999
User Fee Goal Date: November 26, 1999
Approvable Letter Issued: November 19, 1999

Background
Ohmeda originally submitted this application on June 16, 1997 for the use of nitric oxide in the treatment of hypoxic respiratory failure of the newborn. Orphan Drug designation was granted for this use on June 13, 1993. The application was withdrawn on September 17, 1997 before an action was taken. There have been two Advisory Committee meetings, one before the application was submitted (August 28, 1995) and the other after the application was withdrawn (April 9, 1998).
INO Therapeutics. Inc. acquired the NDA and resubmitted the application on May 26, 1999

Medical Reviews
There were two medical reviews of the NINOS and INO-01/02 trials completed during the first review period:

In his review dated November 24, 1997, Dr. Throckmorton, Medical Officer, HFD-110, recommended that the application not be approved stating that there was not sufficient data suggesting a clear beneficial effect of I-NO on hard endpoints. This was coupled with the potential adverse events associated with I-NO administration and the inadequacy of the safety database for certain key adverse events.

In her review dated August 25, 1197, Dr. Pina, Medical Officer, HFD-570, stated that there were many outstanding issues that prevent us from recommending these trials as supportive of the safety and efficacy of NO for the treatment of hypoxic respiratory failure. See her review.

There was one medical review of the CINRGI trial during the second review period:

In his review dated October 29, 1999, Dr. Throckmorton concluded that beyond the statistically significant findings of improvement in oxygenation and decreased ECMO, no effect of I-NO on durable clinical efficacy (duration of hospitalization, neurologic status at discharge) was demonstrated. There was a trend towards less evidence of pulmonary injury at the time of discharge that is complicated by the baseline imbalance in pulmonary status. Using incomplete follow-up data through one year, no adverse or beneficial effects of I-NO on mortality of neurologic/pulmonary status were identified, again relative to the control group. He recommended approval with careful labeling to reflect limits of the data.

Medical Team Leader Memo
In his draft review, Dr. Stockbridge provided two options: 1) Not approve the application because of inadequacies in the design and implementation of the major studies and the lack of demonstrated long-term benefit. Doing so, however, would not likely create and environment wherein a better placebo-controlled study would be forthcoming. 2) Approve the use of nitric oxide with a label suitably circumspect with regard to the potential benefits and risks. Per Dr. Stockbridge, a safety update was not needed because all studies were completed before the application was submitted.

Statistical Review
In his review dated November 4, 1999, Dr. Cui came to essentially the same conclusions as the medical reviewer.

Pharmacology
In his review dated October 9, 1997, Dr. Oza was unable to completely assure safety because NO toxicity mechanisms are not known and the data did not prove beyond a reasonable doubt that NO can be

benefits, he favored the use of a very low dose. The dose should never exceed 10 ppm. There is support from the animal data on the efficacy for the low dose although risk cannot be excluded.

Biopharmaceutical Review
In her review dated November 10, 1999, Dr. Nguyen states that 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. The labeling should clearly state that the uptake, distribution and elimination were determined primarily in healthy adults.

Clinical Inspection
In his clinical inspection summary dated September 22, 1999, Dr. U stated that the data collected from the three sites can be used in support of the NDA claim.

Chemistry Review
In his review dated November 5, 1999, Dr. Advani stated that the NDA may be approved from a chemistry viewpoint. The action letter should state that the expiry date is 30 months for a drug product stored at 25^0 C. Container labels need to be provided.

Trade Name:
The trade name, INOmax, was found acceptable by the Labeling and Nomenclature Committee on November 3, 1997.

Establishment Inspection:
The establishment inspection was recommended acceptable on October 22, 1999.

Methods Validation:
The firm has submitted the validation package. It will be sent to our district laboratories for evaluation.

Environmental Assessment:
Nitric Oxide was found to have no significant impact on the environment on July 26, 1997.

DDMAC
The firm submitted promotional material, received December 9, 1999. DDMAC is reviewing it.

Cardiac and Renal Drugs Advisory Committee
There was no Advisory Committee held specifically for this application.

CSO Summary

Final printed labeling was received December 9, 1999 that incorporated all labeling recommendations in the NDA Action Letter Routing Record and the marked-up labeling that accompanied the approvable letter. To my knowledge, there are no issues that would prevent action on this application.

An approval letter will be drafted for Dr. Temple's signature.

/S/
Zelda McDonald, RHPM

cc: Orig. NDA
HFD-110
HFD-111/McDonald

RHPM Overview of NDA 20-845
INOmax (nitric oxide) Inhaled
November 4, 1999

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Background
This application was originally submitted by Ohmeda on June 16, 1997 for the use of nitric oxide in the treatment of hypoxic respiratory failure of the newborn. Orphan Drug designation was granted for this use on June 13, 1993. The application was withdrawn on September 17, 1997 before an action was taken. There have been two Advisory Committee meetings, one before the application was submitted (August 28, 1995) and the other after the application was withdrawn (April 9, 1998).
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Medical Team Leader Memo He recommended approval with careful labeling to reflect limits of data

Deputy Division Director Memo
In his draft review, Dr. Stockbridge provided two options: 1) Not approve the application because of inadequacies in the design and implementation of the major studies and the lack of demonstrated long-term benefit. Doing so, however, would not likely create and environment wherein a better placebo-controlled study would be forthcoming. 2) Approve the use of nitric oxide with a label suitably circumspect with regard to the potential benefits and risks. Per Dr. Stockbridge, no safety update was needed because all of the studies were completed before the submission - CLL 11/22/99

Statistical Review
In his review dated November 4, 1999, Dr. Cui came to essentially the same conclusions as the medical reviewer.

Pharmacology
In his review dated October 9, 1997, Dr. Oza was unable to completely assure safety because NO toxicity mechanisms are not known and the data did not prove beyond a reasonable doubt that NO can be administered at a safe dose that does not for methemoglobin. If the clinical data suggested distinct benefits, he favored the use of a very low dose. The dose should never exceed 10 ppm. there is support from the animal data on the efficacy for the low dose although risk cannot be excluded.

Biopharmaceutical Review
In her draft review, Dr. Nguyen states that 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. The labeling should clearly state that the uptake, distribution and elimination were determined primarily in healthy adults.

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Cardiac and Renal Drugs Advisory Committee
There was no Advisory Committee held specifically for this application.

CSO Summary
An approvable letter will be drafted for Dr. Temple.

The marked-up labeling in this package contains changes from all disciplines except Biopharm. I have requested container labeling from the firm.

To my knowledge, there are no issues that would prevent action on the goal date, November 26, 1999.

/S/
Zelda McDonald, RHPM

cc: Orig. NDA
HFD-110

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