CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

PHARMACOLOGY REVIEW(S)

Z. McDONALD

OCT 10 1997

REVIEW AND EVALUATION OF PRECLINICAL PHARMACOLOGY AND TOXICOLOGY DATA

NITRIC OXIDE

Ohmeda Pharmaceutical Products Division Inc
110 Allen Road
Liberty Corner, NJ 07938-0804

Narendra B. Oza, PH. D.
October 9, 1997

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ORIGINAL NDA:	20,845
CENTER RECEIPT DATE:	June 17, 1997
REVIEWER RECEIPT DATE:	July 1, 1997
SPONSOR:	Ohmeda Inc.,Pharmaceutical Products Div. 110 Allen Road, PO Box 804, Liberty Corner, NJ 07938 (908) 604 7722
DRUG PROPRIETARY NAME:	I-NO™ (Nitric Oxide)
GENERIC NAME/CODE NAME:	N / A
STRUCTURE / NATURE:	N=O / Evanescent gas
MOLECULAR WEIGHT:	30
FORMULATION:	Formulated in 100, 400 and 1600 ppm nitric oxide with nitrogen (N_2) as the balance
RELEVANT IND'S:	NIH IND for respiratory hypoxia
PHARMACOLOGICAL CLASS:	Selective Pulmonary Vasodilator
INDICATION:	Respiratory Hypoxia of the newborn
DOSAGE:	5-80 ppm for up to 14 days
MODE OF ADMINISTRATION:	Inhalation

Pharmacodynamics:

A. Mechanism of Action:

NO is an endogenous, potent vasodilator substance. After its production , e.g., in vascular endothelial cells, the NO diffuses into smooth muscle cells, binds with the heme moiety of soluble guanylate cyclase and thus activates the enzyme. This enzyme increases intracellular cyclic guanosine 3',5'-monophosphate (cGMP) from its precursor, guanosine triphosphate (cGTP). The resulting increase in intracellular cGMP concentration leads to vasodilation.

B. Background:

NO, synonymous with EDRF (Endothelium Derived Relaxing Factor), is biosynthesized from L-Arginine by NO-Synthase primarily in endothelial cells. It is now becoming apparent that macrophages, neurons and many other cell types may also have a capability for local production of NO.

NO is an evanescent compound with half life of 41 seconds. NO is known not to be transported in the vascular bed and thus actions and interactions of NO are short term and local. NO has great affinity for hemoglobin. Following a very rapid binding with NO, haemoglobin is converted into methemoglobin (MHB) and the NO is inactivated. MHB is an abnormal, nonfunctioning ferric hemoglobin that is incapable of binding oxygen or carbon dioxide. Since MHB is unable to bind or release oxygen, any increase in its concentration can lower oxygen saturation in the blood and thus can become fatal. MHB level of 70% is usually fatal although a survival has been reported even after 81% level of MHB. The major enzyme responsible for the reduction of MHB is the NADPH dependent MHB reductase which is present in the erythrocytes. Spontaneous reduction of MHB is generally slow and methylene blue can serve as a cofactor by donating an electron and thereby increasing the amount of available NADPH. In vivo increase of NADPH can greatly accelerate the reduction of MHB.

The sponsors have proposed to monitor MHB levels and to terminate the inhalation of NO if the MHB level should exceed 5%.

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