SECTION 1.0 MATERIALS USED IN REVIEW

Table 1 MATERIALS UTILIZED IN REVIEW

ITEM	DATE	MATERIAL
Volumes 1,2,3	18 December 1998	Introductory Information Proposed Labeling Application Summary
Volumes 63-725	18 December 1998	Clinical Data Case Report Forms
Amendment	5 April 1999	Additional Information
Amendment	24 May 1999	Additional Information

SECTION 2.0 BACKGROUND

SECTION 2.1 INDICATION

Dexmedetomidine is an intravenous alpha-2 adrenoreceptor agonist indicated for sedation and analgesia in an Intensive Care Unit setting.

SECTION 2.2 RELATED NDA'S AND IND'S

All clinical studies were conducted ———— . No previous NDAs are applicable.

SECTION 2.3 PROPOSED DIRECTIONS FOR USE

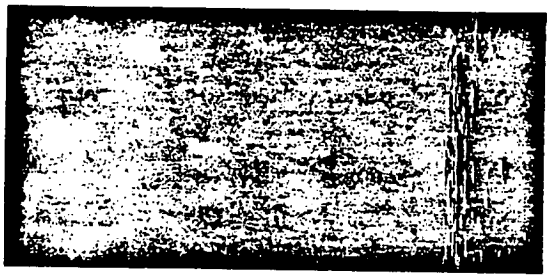
Dexmedetomidine is proposed for adults 18 years and older in an Intensive Care Setting who require sedation or potentiation of analgesia for up to 24 hours. The drug will be administered intravenously. Dosing is initiated with a loading dose of 1 µg/kg over 10 minutes followed by a maintenance dose of 0.2-0.7 µg/kg/hour; dosing is adjusted to achieve the desired level of sedation. The total daily dose will not exceed 20 µg/kg with a daily steady state plasma concentration exposure of less than 3.0 ng/ml.

SECTION 2.4. FOREIGN MARKETING

Dexmedetomidine is not marketed anywhere in the world.

SECTION 3.0 CHEMISTRY

[redacted]



Sponsor states the solution should be stored at room temperature (59 to 86 degree F).

SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The following is a summary of the pharmacology/toxicology provided by the sponsor:

"Alpha-2 adrenoceptor agonists have been in clinical use since the mid 1960s with the introduction of clonidine, the archetypal alpha-2 adrenoceptor agonist. Although clonidine has been used as an antihypertensive drug, it is also used as an adjunctive sedative in the intensive care setting.

Alpha-2 adrenoceptor activation is known to result in a variety of responses from several organs and tissues. A prominent effect is reduction in sympathetic nervous activity. Activation of presynaptic alpha-2 adrenoceptors located in sympathetic nerve endings inhibits the release of the neurotransmitter noradrenaline. Activation of postsynaptic alpha-2 adrenoceptors in the CNS leads to inhibition of sympathetic activity, causing decreases in blood pressure and heart rate, sedation, and relief of anxiety. Activation of alpha-2 adrenoceptors at the spinal cord results in analgesia. Peripheral alpha-2 adrenoceptors in blood vessels mediate vascular smooth muscle contraction.

Alpha-2 adrenoceptors agonists can decrease stress induced ACTH release and hence cortisol synthesis by a direct effect on the brain. Alpha-2 adrenergic agonists can inhibit insulin release by actions on pancreatic islet cells and have been shown to stimulate

growth hormone. Subcutaneous administration of Dexmedetomidine increased blood glucose, decreased insulin secretion, and inhibited lipolysis. Alpha-2 adrenoceptor agonists decrease circulating norepinephrine and epinephrine by central and peripheral mechanisms.

Dexmedetomidine is a specific alpha-2 adrenoceptor agonist as shown by both receptor binding and functional studies. Dexmedetomidine has very low affinity for alpha-1 adrenoceptors (1300 times less than for alpha-2 adrenoceptors in the rat membrane model) and negligible affinity for other receptors, including beta adrenergic, muscarinic, dopamine, serotonin, mu- and delta opiate, GABA, and benzodiazepine receptors. Dexmedetomidine is a lipophilic compound which is rapidly and extensively distributed to tissues and rapidly eliminated.

Dexmedetomidine is an alpha-2 sedative in various animal species including the rat, dog, rabbit, and mouse producing dose dependent sedation/hypnosis when administered either intracerebroventricularly, subcutaneously, intraperitoneally, or intravenously. The sedative effect is biphasic: lower (10-300 µg/kg) doses cause maximal sedation and higher doses (≥ 1000 µg/kg) result in a reversal of the Dexmedetomidine sedative effect. The reversal of the sedative effect seen at higher doses of Dexmedetomidine is hypothesized to be due to the activation of alpha-1 adrenoceptors by Dexmedetomidine, as the reversal could also be blocked by the alpha-1 antagonist prazosin. At low doses (< 3 µg/kg) Dexmedetomidine is anxiolytic in mice and rats. It acts synergistically with midazolam, diazepam, or fentanyl to induce sedation/hypnosis and has potent volatile anesthetic sparing properties which are mediated via central alpha-2 adrenoceptors.

Dexmedetomidine administered both spinally and peripherally to rats, dogs, mice monkeys, and sheep produces dose dependent analgesia which is more potent than that caused by clonidine, ST-91, xylazine, epinephrine, or norepinephrine. The analgesia effect in animals lasts 1 to 8 hours depending on the route of administration. The analgesic effects of Dexmedetomidine are mediated by alpha-2 adrenoceptors.

Lower doses of Dexmedetomidine cause reduction in blood pressure and heart rate through a central effect whereas higher doses of Dexmedetomidine result in peripheral alpha-1 adrenoceptor activation and resultant higher blood pressure. The initial hypertensive effect of Dexmedetomidine seen with IV bolus injections is reduced with a slower rate of infusion. At doses causing increases in mean arterial pressure, Dexmedetomidine reduces heart rate and cardiac output in a dose dependent manner. Dexmedetomidine has no direct depressant effect on the myocardium except at a very high supra-clinical concentration. Through its sympatholytic action, Dexmedetomidine depresses cardiac function and contractility; the effect on cardiac function and contractility are dose dependent.

Dexmedetomidine produces no significant effect on respiratory function except for mild respiratory depression at high supra-clinical doses.

Other effects of Dexmedetomidine in animals include reduced seizure thresholds, modulation of body temperature, and induction of hypothermia. Dexmedetomidine acts in an additive manner with opioids in producing analgesia and counteracts opioid induced muscle rigidity.

Animal deaths have been reported only after the administration of doses of Dexmedetomidine exceeding the LD50. All adverse effects are extensions of alpha-2 adrenergic activity."

SECTION 5.0 SUMMARY OF HUMAN PHARMOKINETICS

The pharmacokinetic and pharmacodynamic profiles of Dexmedetomidine were based on data from 14 studies. The sponsor has summarized the human pharmacokinetic and bioavailability data as follows:

"Dexmedetomidine is extensively metabolized in humans. In a radiolabeled Dexmedetomidine study, there was virtually no penetration of radioactivity into the cellular fraction. The major circulating metabolites are the N-glucuronides of Dexmedetomidine. Other minor metabolites include the carboxy (COOH), N-methylated (N-meth), the glucuronide conjugate of hydroxylated Dexmedetomidine, and additional unidentified minor metabolites.

The pharmacokinetics of Dexmedetomidine are biphasic with rapid distribution ($t\ ½\ \alpha \cong 6$ min) and a mean terminal half life of approximately 2.0 to 2.5 hours. Following the loading infusion, venous plasma concentrations rise rapidly. Due to the rapid distribution pharmacokinetics, concentrations drop quickly when the loading infusion stops, after which the combined effects of the loading and maintenance infusions hold plasma concentrations stable until the infusion is terminated. Dexmedetomidine is almost exclusively eliminated by metabolism; 95% of a radioactive dose is excreted as conjugates in the urine, and the remainder in the feces.

The following were measured PK parameters in healthy human subjects:

Table 2 Dexmedetomidine Pharmacokinetic Parameters

Parameter	Mean Value (±SD)
Cmax (ng Eq/g)	3.12 ± 0.27
T ½ (h)	2.85 ±1.1
AUC (ng-h/g)	3.49 ±0.68
Clearance (L/hour)	42.6 ±7.1
Volume of distribution (L)	143.9 ±15.5

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