FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

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MEMORANDUM

to: John K. Jenkins, MD
Director,
Office of Drug Evaluation II

Division File: NDA # 21-038

from: Cynthia G. McCormick, MD /S/
Director, Division of Anesthetics, Critical Care and Addiction Drug Products

subject: Dexmedetomidine NDA

date: November 30, 1999

This memorandum summarizes for the file the basis for the approval action recommended by the Division of Anesthetics, Critical Care, and Addiction Drug Products for NDA #21-038, Dexmedetomedine HCl for Injection, a sedative/hypnotic agent intended for use in the intensive care setting.

Background

Dexmedetomidine is the dextro-enantiomer of the racemic mixture, medetomidine[1] and a selective α-2-adrenoreceptor agonist. It has been shown in standard animal models of efficacy to have anxiolytic activity (0.3-2.0 µg/kg IV), analgesic activity (3-6 µg/kg IV), and sedative properties (10-30 µg/kg IV) in a dose-related manner in mice, rats and dogs. Dexmedetomidine was developed in humans primarily for its sedative properties and was studied as a sedative in the intensive care setting, delivered by continuous intravenous infusion.

It was anticipated that dexmedetomidine would provide effects similar to those of clonidine, also an α-2-adrenergic agonist which has been used as an anesthetic adjuvant producing analgesia and sedation, and purported to decrease anesthetic requirements and

[1] Medetomidine is a veterinary sedative widely available in Europe and approved in the US in 1997.

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improve hemodynamic stability. The theoretical basis for the use of the α-2-adrenergic agonists as adjunctive medications is that they are thought to act as neuromodulators, regulating central (medullary) cardiovascular or peripheral vasomotor responses such as those to anesthetics, thus producing an anesthetic-sparing effect. These effects were not specifically characterized for approval purposes, although some exploratory studies were undertaken during early development.

A unique feature of dexmedetomidine as a sedative which was observed in phase I studies was its property of providing adequate sedation but with ease of alerting and without persisting central effects, once the patient is aroused.

Efficacy

The Sponsor submitted two adequate and well-controlled studies of similar design in support of the proposed indication for sedation. The studies were randomized, double blind, double-dummy parallel group multicenter trials comparing the effects of dexmedetomidine infusion with placebo. The trials evaluated the sedative properties of dexmedetomidine and control by inference, that is, they compared the amount of rescue medication (midazolam in one trial and propofol in the second) required to achieve a specified level of sedation (by the standardized Ramsay sedation scale) between the placebo and treatment group from onset to extubation. There were a number of potentially confounding variables that were assessed as secondary outcome measures, particularly time to extubation and amount of morphine used for analgesia.

In study W97-245, 175 patients were randomized to the placebo arm and 178 patients were randomized to receive dexmedetomidine by intravenous infusion at doses of 0.4 μ/kg/hr (with allowed adjustment between 0.2 and 0.7 μg/kg/hr) following an initial bolus of 6 μg/kg IV. Patients were allowed to receive midazolam as needed to maintain a Ramsay sedation score of ≥3. In addition, morphine sulfate could be administered as an analgesic as needed. The primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to maintain sedation as specified while intubated. There was a statistically significantly greater use of midazolam in patients randomized to placebo than to dexmedetomidine during treatment.

A second prospective primary analysis was undertaken at the request of the division to obtain a direct assessment of the sedative effects of dexmedetomidine, that is, a comparison of the percentage of patients who were able to achieve a Ramsay sedation score of ≥3 during intubation, without the use of additional rescue medication, between the dexmedetomidine and the placebo groups. It can be seen from the results reported in the table on the following page that a significantly greater number of patients in the dexmedetomidine group (61%) compared to the placebo group (25%) maintained a Ramsay sedation score of ≥3 without any additional midazolam rescue.

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Midazolam use as rescue medication during intubation (ITT) Study W97-245				
		PBO	Dexmedetomidine	p-value
		N=175	N=178	
Mean total dose (mg) of midazolam		18.6 mg	4.8 mg	0.0011*
Categorized midazolam use				
# pts used	0mg	43(25%)	108 (61%)	<0.001**
	0-4 mg	34 (19%)	36(20%)	
	>4 mg	98 (56%)	34 (19%)	

* ANOVA model with rx and ctr. **Chi-square (after J.Ma's table 3.2, review, p.5)

In study W97-246, 198 patients were randomized to the placebo arm and 203 patients were randomized to receive dexmedetomidine by intravenous infusion at doses of 0.4 µkg/hr (with allowed adjustment between 0.2 and 0.7 µg/kg/hr) following an initial bolus of 6 µg/kg IV. Patients were allowed to receive propofol as needed to maintain a Ramsay sedation score of ≥3. In addition, morphine sulfate could be administered as an analgesic as needed. The primary outcome measure for this study was the total amount of rescue medication (propofol) needed to maintain sedation as specified while intubated. There was a statistically significantly greater use of propofol in patients randomized to placebo than to dexmedetomidine during treatment.

The same prospective primary analysis that was performed in study W97-245 was also performed in this study. It can be seen from the results reported in the table below that a significantly greater number of patients in the dexmedetomidine group (60%) compared to the placebo group (24%) maintained a Ramsay sedation score of ≥3 without any additional propofol rescue.

Midazolam use as rescue medication during intubation (ITT) Study W97-246				
		PBO	Dexmedetomidine	p-value
		N=198	N=203	
Mean total dose (mg) of propofol		513 mg	72 mg	<0.0001*
Categorized propofol use				
# pts used	0mg	47(24%)	122 (60%)	<0.001**
	0-50 mg	30 (15%)	43 (21%)	
	>50 mg	121 (61%)	38 (19%)	

* ANOVA model with rx and ctr. **Chi-square (after J.Ma's table 3.5, review, p.9)

For both studies, the time to extubation was measured and analyzed, and found to be, based on a very conservative approach, not significantly different between groups. For more detail, Dr. Jonathan Ma's analysis p.10-11 should be referenced. In addition the

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amount of morphine used for analgesia in both studies was found to be significantly greater in the control group. These are both important findings combined with the primary analysis, since they establish that the treatment group did not succeed based on the sedation afforded by morphine sulfate or because of a longer time and therefore greater access to more medication.

Dexmedetomidine is said to have been studied as adjunctive therapy insofar as rescue with a second agent was required in many cases to achieve the specified sedation, rather than increasing the infusion (and thus the dose) of dexmedetomidine as needed. Clearly it was the primary agent. The sponsor compared between the two randomized groups in both studies, the percentage of patients who received only dexmedetomidine and who required no rescue medication, confirming its efficacy as monotherapy in two trials.

The primary review team and Dr.Rappaport have carefully reviewed these trials. There is nothing to add to the Medical and Statistical analyses and I concur with their conclusions that these studies, while somewhat unique in their design, clearly establish that dexmedetomidine is an effective sedative when administered by intravenous infusion at doses of 0.4 μ/kg/hr (with allowed adjustment between 0.2 and 0.7 μg/kg/hr) following an initial bolus of 6 μg/kg IV.

Safety

Nonclinical

No significant animal toxicity was described in acute studies in rats or dogs. However, chronic dosing of up to 28 days in dogs and rats was associated with hepatic toxicity, specifically enlarged livers, eosinophilic inclusions in hepatocytes, and elevated LFTs. These changes were not observed in the acute studies. The genesis of the hepatotoxicity has not been characterized as to whether it is correlated with parent compound or any specific metabolite. While there appears to be an adequate safety margin in dosing, the contribution of a different human metabolic profile may theoretically alter the toxicity of this compound with chronic dosing in humans. This bears further evaluation.

Dexmedetomidine had no effect on ACTH-stimulated cortisol release in dogs given just a single dose of 80 μg/kg/dose S.C., but after one week of treatment with 3 μg/kg/hr, the ACTH-stimulated release of cortisol was reduced by 40%. This has implications on the hypothalamic-pituitary-adrenal axis with prolonged ICU treatment with this agent, and should be further elaborated concurrently with human trials evaluating the safety of long-term infusion.

The nonclinical pharmacokinetics of dexmedetomidine are similar to humans with the exception of metabolism, which differs by two major metabolites. The two major metabolites found in human (the 2 glucuronides of imidazole nitrogen) and absent in the rat and dog, were never studied in animals. Because it is projected that this product will be used in ICU for longer than 24 hrs of infusion, the potential toxicity of these human metabolites should be evaluated. This should be done as a Phase 4 study of long-term

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infusion in an appropriate animal species, either indirectly by administration to an animal species that does not produce these metabolites or in an animal species which produces the same metabolites.

Dexmedetomidine was not shown to be teratogenic in rats or rabbits. However fetal toxicity was observed in rats, evidenced by increased postimplantation losses and reduced number of live pups per litter. Prenatal and postnatal effects included reduced pup body weights during and after nursing and delayed motor development. Placental transfer of dexmedetomidine was observed in rats.

Dexmedetomidine was not mutagenic in the Ames test or the mouse lymphoma assay. It was shown to be clastogenic in both the *in vitro* human lymphocytes chromosomal aberration assay in the presence of metabolic activation and in *in vivo* mouse micronucleus assay.

Carcinogenicity testing was considered unnecessary due to the projected short-term use of this product.

Clinical

The safety data for this NDA was combined from two sources, -- [redacted] Japanese original development program, and subsequent Abbott Laboratories data from the more recent development. The safety database of dexmedetomidine exposure includes 3038 subjects, of whom 1473 were ICU patients who received the drug by continuous infusion. The bulk of exposure was in the range of 4-6 mg/kg and less than 16 hours. The dose and duration of exposure provide sufficient experience to be able to assess the safety of this product for the proposed duration of up to 24 hours infusion.

There was also limited exposure (78 patients) who received infusion longer than 24 hours with the longest infusion lasting between 30-40 hours in 2 patients.

The deaths and serious adverse events reported were not unexpected for the ICU population under study in this NDA either in quality or in quantity.

In the placebo-controlled infusion studies in Phase 2-3, the only commonly reported adverse events observed in more than 1% of patients treated with dexmedetomidine and occurring with a frequency more than 2-fold that of the placebo were predictably hypotension (22%) , hypertension (12%) , and bradycardia (5%).

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